The impact of diabetes and subclinical hypothyroidism association with coronary artery calcium: results from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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ABSTRACT

Objective: We aimed to analyze the association of diabetes and subclinical hypothyroidism with subclinical atherosclerosis measured by coronary artery calcium (CAC) in the baseline of the ELSA-Brasil study. **Materials and methods:** CAC was measured using a 64-detector computed tomographic scanner. The association of CAC > 0 was presented as an odds ratio (OR) and 95% confidence intervals (95%CI) in logistic models and as β (95%CI) in linear models after multivariable adjustment for confounders. **Results:** We analyzed 3,809 participants (mean-age (SD) 50.5 (8.8); 51.7% women). In the main analysis, we did not find an association of diabetes and subclinical hypothyroidism with CAC. However, in stratified analysis according to age strata, we found no significative interaction terms, an important heterogeneity between the groups, with the younger age strata showing an association of the group with both diseases and CAC > 0 (OR 7.16; 95%CI, 1.14; 44.89) with a wide but significative 95%CI, suggesting that the smaller number of participants in the younger group may influence the results. Our findings also showed an association of CAC > 0 and log (CAC+1) with diabetes in logistic (OR, 1.31; 95%CI, 1.05-1.63) and linear models (β, 0.24, 0.16, 0.40), respectively. Diabetes was independently associated with CAC > 0 in linear models. **Discussion:** In conclusion, our results showed a great heterogeneity in stratified analysis based on age in the younger age strata. Although we found no significant interaction factors, the smaller sample size for the analysis may influence the negative findings.

Keywords

Coronary artery calcium; diabetes mellitus; subclinical hypothyroidism; subclinical atherosclerosis; cardiovascular disease

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INTRODUCTION

The International Diabetes Federation Atlas reported that 537 million adults around the world are living with diabetes, a 16% increase since the previous IDF estimates in 2019 (1). However, some data suggest that these numbers are underestimated and the real numbers may be worse in the following years (2). Thyroid dysfunction is also very frequent, with a high prevalence worldwide, especially considering subclinical thyroid diseases (3,4). Subclinical thyroid diseases are less symptomatic, and a great majority of patients remain undiagnosed in clinical practice (5).

Several authors have recognized the possible association of diabetes and subclinical hypothyroidism (6,7). Some studies have shown that patients with type 2 diabetes and subclinical hypothyroidism are more likely to have microvascular complications, such as diabetic nephropathy (8-10), retinopathy (11) and peripheral neuropathy, than individuals with only diabetes (12). However, these findings were not confirmed in other studies (13-15).

Researchers have conducted few studies to evaluate the synergic effect of diabetes and subclinical hypothyroidism with macrovascular complications of diabetes, such as coronary heart disease (7,9). Han and cols. (2015), in a systematic review and meta-analysis, reported a non-significant association of diabetes and subclinical hypothyroidism with coronary heart disease [OR of 1.59, 95%CI, 0.92-2.76] (7). Contrasting with these findings, Jia and cols. (2015) reported an association of diabetes and subclinical hypothyroidism with coronary heart disease (9). Therefore, there is conflicting data about the possible synergic association of diabetes and subclinical hypothyroidism in microvascular and macrovascular complications of diabetes in individuals with both diseases.

Coronary artery calcium (CAC) scores are a surrogate marker of subclinical atherosclerosis and a predictor of future cardiovascular events (16,17). Although some studies showed an association of diabetes with CAC (18,19), subclinical hypothyroidism with CAC (20) or even high-normal TSH levels with CAC (21), researchers have conducted few other studies to analyze the associations among subclinical hypothyroidism, diabetes and CAC. Posadas-Romero and cols. (2014) reported an association of subclinical hypothyroidism, metabolic syndrome and its components with subclinical atherosclerosis measured by CAC and fat liver disease (22). In addition, a cross-sectional study in Brazil reported a strong positive association between CAC > 100 and subclinical hypothyroidism in older men with a Framingham risk score ≥ 10% and having diabetes as one of the cardiovascular risk factors evaluated (23). Recently an association with higher CAC score values was reported in patients in hemodialysis, high TSH levels and a high prevalence of diabetes (24). Subclinical hypothyroidism in high-risk groups may represent an additional risk factor for coronary artery calcification in individuals with intermediate and high cardiovascular risk scores. It is important to note that all these studies showed possible associations among subclinical hypothyroidism, diabetes and CAC in subgroup analyses.

We aimed to analyze the association of diabetes, subclinical hypothyroidism or both diseases with subclinical atherosclerosis measured by CAC using data from the baseline examination of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Our hypothesis is that the subgroup of subjects with diabetes and subclinical hypothyroidism would be associated with higher CAC scores compared to other subgroups with only diabetes or subclinical hypothyroidism, using the group of participants without diabetes and subclinical hypothyroidism as the reference.

MATERIALS AND METHODS

The ELSA-Brasil is a prospective cohort study that enrolled 15,105 civil servants age 35 to 74 from five public universities and research institutes located in 6 state capitals: Salvador (BA), Belo Horizonte (MG), Vitória (ES), Rio de Janeiro (RJ), São Paulo (SP) and Porto Alegre (RS) (25-27). Inclusion criteria are being a 35-to 74-year-old active or retired employee of one of the six institutions. Exclusion criteria included not having severe communication or cognitive problems; the near-future possibility of stopping working in the institutions soon after the enrollment in the study and intention to move to neighborhoods outside the metropolitan area in which the institution was localized, compromising participation in the study and being pregnant (25). The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethic Board of all six centers. All participants provided an informed consent.

This is a cross-sectional analysis using data from the baseline of the ELSA-Brasil conducted between 2008-2010, and it was registered with Brazil Platform with a CAAE number of 42178221.8.0000.0076. The present analysis is a cross-sectional study using a subsample of participants from ELSA-Brasil of the research center of São Paulo (N = 5,061). From those, we excluded 104 participants with no data regarding thyroid diseases and 499 without information about CAC at baseline, 130 using drugs that may alter thyroid function and 141 with previous cardiovascular diseases. We also excluded 378 participants with overt or subclinical hyperthyroidism and overt hypothyroidism, leaving 3,809 participants for this analysis: 2,885 with no disease, 297 with only subclinical hypothyroidism, 572 with only diabetes and 55 with both diseases (Figure 1).

Definition of diabetes

The definition of diabetes included a self-reported medical diagnosis of diabetes, use of drugs to treat diabetes, fasting plasma glucose levels ≥ 7.0 mmol/L, 2-h glucose levels ≥ 11.1 mmol/L or HbA1c ≥ 6.5% (28).

A 12-hour fasting blood sample was drawn in the morning following study procedures (28-30). A standardized 75-g oral glucose tolerance test (OGTT) was conducted with all participants without a previous diagnosis of diabetes based on the above criteria. Glucose levels were measured following the hexokinase method (ADVIA Chemistry; Siemens, Deerfield, Illinois), and HbA1c was measured using high pressure liquid chromatography (Bio-Rad Laboratories, Hercules, California).

Thyroid function

TSH (normal range: 0.4-4.0 mIU/L), FT4 (0.93-1.7 ng/dL) and FT3 (0.20-0.44 ng/dL) were determined using a third-generation immunoenzymatic assay (Roche Diagnostic, Manheim, Germany) (28). The analysis included euthyroid participants (TSH levels 0.4-4.0 mIU/L with no use of levothyroxine/anti-thyroid drugs) and subclinical hypothyroidism (TSH > 4.0 mIU/L with FT4 0.93-1.7 ng/dL). We excluded participants with overt thyroid diseases, with subclinical hyperthyroidism or using medication that alter thyroid

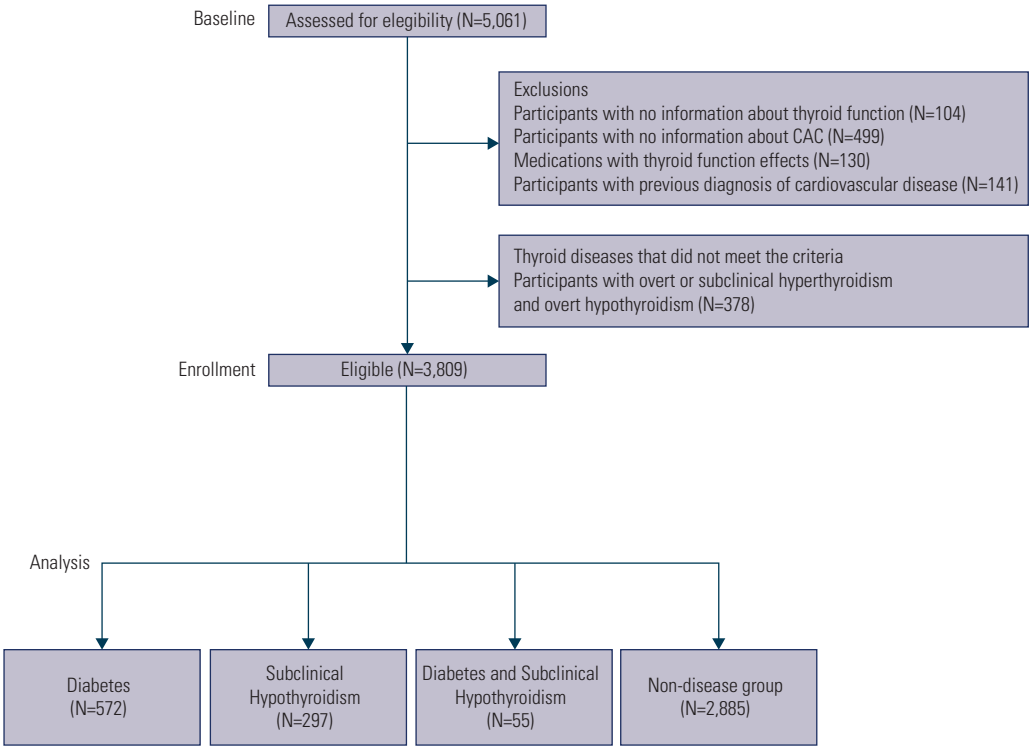

Figure 1. Description of the sample included in the analysis.

function (amiodarone, carbamazepine, carbidopa, furosemide, haloperidol, heparin, levodopa, lithium, metoclopramide, phenytoin, propranolol, primidone, rifampicin, steroids and valproic acid) (Figure 1) (31,32).

Measurement of coronary artery calcium (CAC)

All participants underwent a CAC examination performed with a 64-detector computed tomographic scanner (Brilliance 64; Philips Healthcare, Best, The Netherlands). After the scout images were taken, each patient underwent an electrocardiogram-gated prospective calcium score examination with a tube potential of 120 kV and a tube current adjusted to body habitus. Images were reconstructed in 2.5-mm-thick slices using standard filtered back projection. The CAC was expressed in Agatston units, and an experienced cardiologist evaluated the percentile in a blinded fashion using semiautomatic software (Calcium Scoring, Philips Workstation). CAC severity was further categorized according to an Agatston score of 0 or >0 (33-35) or log transformed (log CAC+1).

Other variables

We evaluated sociodemographic characteristics, such as sex, age as continuous and stratified (35-44; 45-54; 55-64; 65-74 strata), educational attainment (less than high school, high school and some college and at least complete college), mean average family monthly income (≤US$ 1245, US$ 1246 to US$ 3319 and ≥ US$ 3320) and self-reported race/skin color (White, Mixed, Black, Asian and Indigenous). BMI was stratified as < 30 kg/m^2 and ≥ 30 kg/m^2. Smoking and alcohol use were categorized as never, past or current. Blood pressure (BP) was measured using a validated Omron HEM 705CPINT oscillometric device. Three blood pressure measurements were taken at 1-minute intervals, and the average of the last two measurements was considered the value for casual systolic and diastolic blood pressure. The definition of hypertension was based on current use of medication to treat hypertension or systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg . The definition of dyslipidemia was based on LDL-cholesterol levels > 130 mg/dL or the use of any type of lipid-lowering medication. Leisure time physical activity was classified according to the World Health Organization criteria using the long version of the International Physical Activity Questionnaire (IPAQ), in which being physically active meant at least 150 min of moderate-intensity, 75 min of high-intensity leisure-time aerobic physical activity or the combined equivalent of both each week. Any weekly activity below the previous threshold was classified as partly active, and the remaining participants were classified as inactive (36).

Statistical analysis

Categorical variables are expressed as absolute numbers with the respective frequencies and analyzed using the chi-square test. Continuous variables are presented as mean (standard deviations) and compared using ANOVA of normal distributions, and they are presented as medians (interquartile range) and analyzed using nonparametric tests if they show non-normal distribution.

Logistic regressions models were built to evaluate the association between diabetes, subclinical hypothyroidism and both diseases combined as independent variables and CAC > 0 Agatston units as the dependent variable considered in all models. ORs are presented without adjustment and after adjustment for sociodemographic variables (age, sex, self-reported race and education – Model 1), and multivariable adjustment for all variables included in Model 1, more smoking, alcohol intake and dyslipidemia (Model 2). Linear regression models using log (CAC+1) were presented as β coefficients (95%CI) using the same multivariable adjustments of the logistic models. We performed some sensitivity analyses according to age strata, excluding obese individuals (BMI ≥ 30 kg/m^2), and sex. The interaction between diabetes and subclinical hypothyroidism was tested using interaction terms in Model 2 of the logistic and linear regression models.

We considered p values < 0.05 significant. Data were analyzed using the Statistical Packages for Social Sciences SPSS version 25.0.

RESULTS

Table 1 shows baseline characteristics according to the presence of diabetes, subclinical hypothyroidism, both conditions and no diseases (reference group). Age, BMI and WC are higher in individuals with both diseases than in the other subgroups. The frequency of women was lower in the subgroup

of participants with diabetes than in the other subgroups. Frequencies of Whites and participants who completed college or more were lower in the group of patients with only diabetes than in the other subgroups ($P < 0.0001$). Current smoking was less common in participants with subclinical hypothyroidism ($P < 0.0001$). The frequency of some cardiovascular risk factors, such as hypertension and dyslipidemia, were higher in the group of patients with diabetes and both diseases. Participants with diabetes presented a higher frequency of CAC > 0 than the other subgroups.

Table 2 presents the ORs for the associations between subclinical hypothyroidism, diabetes and both diseases with CAC according to age strata and in the entire sample.

Table 1. General and clinical characteristics of the sample according to the presence or not of subclinical hypothyroidism or diabetes

	Diagnosis of diabetes or subclinical hypothyroidism			
	No	**Only subclinical hypothyroidism**	**Only diabetes**	**Both**
	N = 2,885	**N = 297**	**N = 572**	**N = 55**
Age (years)	49.5 (49.2-49.9)	51.0 (50.0-52.0)	54.4 (53.7-55.1)	54.5 (52.0-57.0)
Women (%)	1,548 53.7 (51.8-55.5)	155 52.2 (46.3-58.0)	233 40.7 (36.7-44.9)	35 63.6 (49.5-75.9)
Self-reported race (%)				
White	1,677 58.8 (57.0-60.7)	187 63.2 (57.4-68.6)	276 49.1 (44.9-53.3)	33 62.3 (47.9-74.9)
Mixed	632 22.2 (20.7-23.8)	66 22.3 (17.8-27.6)	135 24.0 (20.6-27.8)	10 18.9 (9.9-32.4)
Black	399 14.0 (12.8-15.3)	29 9.8 (6.8-13.9)	102 18.1 (15.1-21.6)	7 13.2 (5.9-26.0)
Asian	112 3.9 (3.3-4.7)	10 3.4 (1.7-6.3)	43 7.7 (5.7-10.2)	2 3.8 (0.7-14.1)
Indigenous	30 1.1 (0.7-1.5)	4 1.4 (0.4-3.7)	6 1.1 (0.4-2.4)	1 1.9 (0.1-11.4)
Education				
Less than high-school	384 13.3 (12.1-14.6)	49 16.5 (12.6-21.3)	136 23.8 (20.4-27.5)	13 23.6 (13.7-37.3)
High-school and some college	1,231 42.7 (40.9-44.5)	116 39.1 (33.5-44.9)	228 39.9 (35.8-44.0)	24 43.6 (30.6-57.6)
Complete college or more	1,270 44.0 (42.2-45.9)	132 44.4 (38.7-50.3)	208 36.4 (32.4-40.5)	18 32.7 (21.0-46.8)
Body mass index (BMI) kg/m^2	26.7 (26.5-26.9)	27.5 (26.9-28.1)	29.5 (29.1-29.9)	30.6 (28.9-32.3)
Waist measurement (cm)	88.3 (87.9-88.7)	89.8 (88.4-91.2)	96.8 (95.8-97.9)	97.3 (93.4-101.2)
Hypertension (%)	676 23.4 (21.9-25.0)	77 25.9 (21.1-31.4)	329 57.5 (53.3-61.6)	31 56.4 (42.4-69.4)
Dyslipidemia (%)	1,156 40.1 (38.3-41.9)	113 38.0 (32.5-43.9)	299 52.3 (48.1-56.4)	27 49.1 (35.5-62.8)
Smoking (%)				
Never	1,559 54.0 (52.2-55.9)	170 57.2 (51.4-62.9)	279 48.8 (44.6-53.0)	34 61.8 (47.7-74.3)
Past	827 28.7 (27.0-30.4)	105 35.4 (30.0-41.1)	197 34.4 (30.6-38.5)	15 27.3 (16.5-41.2)
Current	499 17.3 (15.9-18.7)	22 7.4 (4.8-11.2)	96 16.8 (13.9-20.2)	6 10.9 (4.5-22.9)
Alcohol use (%)				
Never	332 11.5 (10.4-12.7)	38 12.8 (9.3-17.3)	69 12.1 (9.6-15.1)	10 18.2 (9.5-31.4)
Past	538 18.6 (17.3-20.1)	54 18.2 (14.1-23.1)	122 21.3 (18.1-25.0)	11 20.0 (10.9-33.4)
Current	2,015 69.8 (68.1-71.5)	205 69.0 (63.4-74.2)	381 66.6 (62.6-70.4)	34 61.8 (47.7-74.3)
Physical activity (%)				
Inactive	2,184 78.7 (77.1-80.2)	214 75.6 (70.1-80.4)	447 79.7 (76.1-82.9)	41 80.4 (66.5-89.7)
Insufficiently active	364 13.1 (11.9-14.4)	40 14.1 (10.4-18.9)	68 12.1 (9.6-15.2)	8 15.7 (7.5-29.1)
Active	228 8.2 (7.2-9.3)	29 10.2 (7.1-14.5)	46 8.2 (6.1-10.9)	2 3.9 (0.7-14.6)
CAC > 0	273 19.3 (17.3-21.5)	23 14.8 (9.8-21.6)	62 33.3 (26.7-40.7)	7 26.9 (12.4-48.1)
CAC (Agatston) median (IQR)	0 (0-0)	0 (0-1)	0 (0-56)	0 (0-26)

IQR: interquartile range.

Table 2. Logistic models (Odds ratio [OR] and 95% Confidence Interval [95%CI]) and linear regression models (β coefficient [β] (95%CI) for the association of subclinical hypothyroidism, diabetes and both diseases with CAC > 0 according to age-strata and the entire sample

Age-strata 35 to 44 years N =1009	**Crude**	**Model 1**	**Model 2**
Logistic regression models	OR (95%CI)	OR (95%CI)	OR (95%CI)
CAC > 0			
Subclinical hypothyroidism	1.74 (0.79; 3.79)	1.82 (0.80; 4.13)	1.73 (0.72; 4.15)
Only diabetes	4.41 (2.40; 8.10)	3.40 (1.78; 6.52)	2.96 (1.43; 6.14)
Both diseases	5.81 (1.10; 30.64)	4.54 (0.78; 26.61)	7.16 (1.14; 44.89)
Linear regression models			
Log CAC + 1	β (95%CI)	β (95%CI)	β (95%CI)
Subclinical hypothyroidism	0.17 (-0.012; 0.47)	0.14 (-0,14; 0,43)	0.19 (-0,11; 0,49)
Only diabetes	0.26 (0.17; 0.36)*	0.23 (0.14; 0.33)*	0.22 (0.12; 0.31)*
Both diseases	0.04 (-0,05; 0.14)	0.04 (-0.05; 0.13)	0.03 (-0.06; 0.12)
Age-strata 45 to 54 years N = 1636	**Crude**	**Model 1**	**Model 2**
Logistic regression models	OR (95%CI)	OR (95%CI)	OR (95%CI)
CAC > 0			
Subclinical hypothyroidism	0.93 (0.59; 1.49)	0.82 (0.50; 1.34)	0.81 (0.49; 1.36)
Only diabetes	1.74 (1.28; -2.37)	1.44 (1.03; 2.01)	1.07 (0.75; 1.52)
Both diseases	0.63 (0.18; 2.13)	0.49 (0.14; 1.77)	0.26 (0.06; 1.18)
Linear regression models			
Log CAC + 1	β (95%CI)	β (95%CI)	β (95%CI)
Subclinical hypothyroidism	0.04 (-0.33; 0.26)	-0.06 (-0.35; 0.22)	-0.17 (-0.45; 0.12)
Only diabetes	0.22 (0.12; 0.31)*	0.16 (0.07; 0.26)*	0.08 (-0.02; 0.18)*
Both diseases	-0.001 (-0.13; 0.13)	-0.02 (-0.15; 0.10)	-0.04 (-0.17; 0.08)
Age-strata 55 to 64 years N = 866	**Crude**	**Model 1**	**Model 2**
Logistic regression models	OR (95%CI)	OR (95%CI)	OR (95%CI)
CAC > 0			
Subclinical hypothyroidism	0.98 (0.60; 1.60)	1.11 (0.66; 1.87)	1.08 (0.63; 1.85)
Only diabetes	1.94 (1.38; 2.74)	1.87 (1.28; 2.74)	1.48 (1.00; 2.19)
Both diseases	0.69 (0.25; 1.93)	0.96 (0.32; 2.93)	0.94 (0.29; 3.03)
Linear regression models			
Log CAC+1	β (95%CI)	β (95%CI)	β (95%CI)
Subclinical hypothyroidism	-0.09 (-0.58; 0.40)	-0.11 (-0.38; 0.22)	-0.00 (-0.51; 0.51)
Only diabetes	0.39 (0.22; 0.55)*	0.34 (0.18; 0.50)*	0.23 (0.02; 0.39)*
Both diseases	0.07 (-0.17; 0.31)	0.14 (-0.09; 0.37)	-0.14 (-0.09; 0.37)
Age-strata 65 to 74 years N=298	**Crude**	**Model 1**	**Model 2**
Logistic regression models	OR (95%CI)	OR (95%CI)	OR (95%CI)
CAC > 0			
Subclinical hypothyroidism	0.55 (0.23; 1.30)	0.41 (0.16; 1.06)	0.46 (018; 1.18)
Only diabetes	1.27 (0.72; 2.25)	1.17 (0.63; 2.18)	0.99 (0.51; 1.91)
Both diseases	0.69 (0.19; 2.56)	1.32 (0.30;5.98)	0.89 (0.22; 3.59)
Linear regression models			
Log CAC + 1	β (95%CI)	β (95%CI)	β (95%CI)
Subclinical hypothyroidism	-0.11 (-0.80; 0.57)	0.36 (-0.34; 1.06)	0.39 (-0.34; 1.11)
Only diabetes	0.18 (-0.10; 0.46)*	0.17 (-0.10; 0.45)*	0.05 (-0.24; 0.34)*
Both diseases	-0.17 (-0.10; 0.46)	-0.23 (-0.68; 0.22)	-0.16 (-0.62; 0.29)

Entire sample	Crude	Model 1	Model 2
Logistic regression models			
CAC > 0	OR (95%CI)	OR (95%CI)	OR (95%CI)
Subclinical hypothyroidism	1.03 (0.66-1.63)	0.87 (0.53-1.43)	0.87 (0.57-1.33)
Only diabetes	2.68 (1.97-3.65)	1.71 (1.20-2.44)	1.23 (0.92-1.66)
Both diseases	1.67 (0.75-3.73)	0.67 (0.27-1.68)	1.12 (0.38-3.23)
Linear regression models			
Log CAC + 1	β (95%CI)	β (95%CI)	β (95%CI)
Subclinical hypothyroidism	0.21 (-0.01; 0.42)	0.21 (-0.006; 0.42)	0.07 (0.15; 0.28)
Only diabetes	0.26 (0.17; 0.36)*	0.27 (0.18; 0.36)*	0.17 (0.08; 0.26)*
Both diseases	0.15 (-0.66; 0.37)	0.04 (-0.07; 0.14)	-0.06; 0.14)

*P < 0.05; CAC = coronary artery calcium; Model 1 adjusted for age, sex, race and education attainment; Model 2 = Model 1 plus smoking, alcohol intake, and dyslipidemia.

In the stratified analysis, we found great heterogeneity among the groups. In the younger age strata, we found an OR = 7.16; 95%CI: 1.14-44.89. Although the interactions terms of diabetes and subclinical hypothyroidism were not statistically significant for logistic (P = 0.97) or linear models (P = 0.50) in stratified analysis, the wide confidence interval suggests an effect of the smaller sample size in each group compared to the main analysis in the entire sample (Table 2). In the analysis, considering the entire sample, we found no addictive or multiplicative effect in the association of diabetes and subclinical hypothyroidism with CAC. The interaction terms of diabetes and subclinical hypothyroidism are not statistically significant in logistic (P = 0.29) or linear models (P = 0.11).

In logistic models, there was an association between diabetes and CAC > 0 even after a multivariable adjustment for age, sex, education, smoking, hypertension, dyslipidemia, alcohol intake and physical activity (OR: 1.31; 95%CI: 1.05-1.63). However, we found no association among the participants with only subclinical hypothyroidism (OR: 0.94; 95%CI: 0.69-1.29) or both diseases (OR: 0.63; 95%CI: 0.32-1.23). In the linear models with the same multivariable adjustment, we also confirmed an association with diabetes with log (CAC+1) (β: 0.236; 95%CI: 0.163 to 0.403). We found no other significant associations considering only subclinical hypothyroidism, diabetes or both diseases.

Supplementary Table 1 describes the association of subclinical hypothyroidism diabetes and both diseases with CAC > 0 according to BMI < 30 kg/m^2 and ≥ 30 kg/m^2. Although in linear regression models participants with diabetes in both BMI categories were associated with log CAC+1, patients with both diseases were not. Interaction terms between diabetes and subclinical hypothyroidism for the association with CAC values in logistic and linear models were non-significant. Supplementary Table 2 shows the results of the analysis according to sex. Only diabetes was associated with CAC in linear models for men and women. The results remained non-significant.

DISCUSSION

In the main analysis, we found no association of diabetes and subclinical hypothyroidism with CAC. However, in stratified analysis according to age, we found an association of patients with subclinical hypothyroidism and diabetes with CAC in the younger age strata group. Given the magnitude of point OR estimates, there may be some kind of interaction in the multiplicative and additive scales even though the interaction terms were not statistically significant in the youngest age stratum because of the small sample size in each group in the stratified analysis. We also found an association of logistic and linear regression models of diabetes with CAC.

Some points may be highlighted to explain our results. The number of participants with both diseases was only 55, which may not be enough to detect a positive association, especially if the strength of the association was not very high, which is the case in this analysis. The mean age of participants in the ELSA-Brasil at baseline examination was around 50 years. The prevalence of diabetes and subclinical hypothyroidism increases with age, as well as the presence of subclinical atherosclerosis. Therefore, the sample may be too

young to test our hypothesis considering all age strata together. Some imbalance in the distribution of diabetes according to sex shows more male patients with diabetes whereas subclinical hypothyroidism is more frequent in women. The possible interaction effects of having subclinical hypothyroidism and diabetes are also likely not homogeneous considering their different outcomes.

We hypothesized that the association of diabetes with subclinical hypothyroidism in the same patients would result in more subclinical atherosclerosis, reflected by a stronger association with CAC in this subgroup compared only to patients with diabetes. However, our results are not as clear as in a previous analysis of the ELSA-Brasil study, which revealed a clear additive effect between diabetes and subclinical hypothyroidism impacting the lower cardiac autonomic control in the subgroup of participants with both diseases compared to other subgroups. In addition, in the same analysis, a borderline-significant interaction occurred between diabetes and subclinical hypothyroidism on heart rate compared to patients with only diabetes (37).

In relation to the negative results in the main analysis, it is possible to say that when we analyze together all age strata, some differences related to age disappear and may be hidden, showing negative results. In addition, although the adoption of a single cutoff value for SCH classification for all ages enhances comparability, it may have led to some misclassification, which may have contributed to our negative results when we analyzed data from older participants.

The plausibility of our hypothesis of an association of diabetes and subclinical hypothyroidism may be supported by scientific evidence. Some studies, including one meta-analysis (7), have shown that subclinical hypothyroidism was associated with a higher prevalence of overall risk of diabetes and its complications (7-9,11). However, other studies did not confirm these associations. Sharma and cols. (2020) reported that patients with diabetes and subclinical hypothyroidism have similar glycemic control as patients with only diabetes (38), and Mehalingam and cols. (2020) reported that patients with both diseases did not present more severe complications of diabetes compared to patients with only diabetes (39). In addition, overt and subclinical hypothyroidism are associated with higher peripheral glucose levels (40,41), decreased glucose use (42) and insulin resistance (43,44). However, there is also evidence that overt and subclinical hyperthyroidism have been associated with increased hepatic gluconeogenesis (45), increased insulin clearance (46) and resistance (47), providing a plausible justification for a U-shaped curve. The original idea in the present analysis was to evaluate both subclinical thyroid diseases. However, the number of patients with diabetes and subclinical hyperthyroidism was very small in the sample (N = 3).

We also found an association with diabetes and CAC in logistic and linear models in the younger age strata. We conducted two sensitivity analyses according to BMI categories and sex. In the group of BMI < 30 kg/m^2 and in the group ≥ 30 kg/m^2, diabetes was associated with CAC > 0. In the analysis according to sex, we also found an association between diabetes and CAC in linear regression models for men and women. However, we found no association considering the subgroup with both diseases, and we detected no significant interaction between diabetes and subclinical hypothyroidism.

Some studies have shown an association of low TSH levels with CAC (20,21). In fact, Peixoto de Miranda and cols. (2017) found that lower and higher TSH levels were associated with CAC showing a U-shaped curve in women but not in men (20,21). The association between diabetes and atherosclerosis as we report it here is well known (48-50). The CAC score in patients with diabetes help in risk stratification of patients with diabetes and intermediary risk (50,51). Coronary artery calcium is also a predictor of cardiovascular events in asymptomatic patients with type 2 diabetes. Contrasting with these positive results for subclinical hypothyroidism and even for diabetes (18,19,51), studies showed no association with subclinical atherosclerosis measured by CAC. Researchers conducted few studies to evaluate an association of subclinical hypothyroidism, diabetes or metabolic syndrome with CAC in high-risk subgroups. Posadas-Romero and cols. (2014) reported an association of subclinical hypothyroidism, metabolic syndrome and its components with subclinical atherosclerosis measured by CAC and fat-liver disease (22). In addition, a cross-sectional study in Brazil reported a strong positive association between CAC >100 and subclinical hypothyroidism in older men with a Framingham risk score ≥ 10%

and having diabetes as one of the cardiovascular risk factors evaluated (23). Recently, patients with higher TSH levels and diabetes were associated with high CAC in hemodialysis (24). It is important to note that all these studies showed possible associations among subclinical hypothyroidism, diabetes and CAC in high-risk groups. One challenge is to find studies that include information about subclinical hypothyroidism, diabetes and CAC because most studies to evaluate this association included only euthyroid participants.

Our study must, however, be read considering the limitations and context of its cross-sectional design, which does not permit the evaluation of causal associations. The number of cases of diabetes and subclinical hypothyroidism is not so high, limiting our power to conduct the sensitivity analysis. Another limitation is the small number of high TSH values in the sample. The CAC score was measured at baseline when the participants were younger, with a mean age around 50 years, with a small number of participants with higher CAC values. In addition, some kind of misclassification in the diagnosis of subclinical hypothyroidism that was defined by the entire sample and not according to age may have contributed to our negative results. The analysis also has some strength. The ELSA-Brasil used centralized protocols to train the research team under strict quality control. The diagnosis of diabetes was very comprehensive and included previous medical history of diabetes, use of medication to treat diabetes, fasting plasma glucose and an oral glucose tolerant test as well as HbA1c. The study also describes a highly admixed sample from a middle-income country with different characteristics compared to samples analyzed in previous studies.

In conclusion, our results showed no association between the group with both diseases and CAC in the main analysis. However, the findings showed a great heterogeneity in stratified analysis according to age, with a strong association in the younger age strata. Although we found no significant interaction factors, the smaller sample size in stratified analysis may influence the negative findings.

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Supplementary Table 1. Logistic models (Odds ratio [OR] and 95% Confidence Interval [95% CI]) and linear regression models (β coefficient [β] (95%CI) for the association of subclinical hypothyroidism, diabetes and both diseases with CAC >0 according to BMI < 30 kg/m² or BMI ≥30 kg/m² (obesity)

BMI < 30 kg/m²	**Logistic regression models (OR, 95%CI)**		
	Crude	**Model 1**	**Model 2**
CAC>0			
Only subclinical hypothyroidism	1.03 (0.75; 1.41)	0.87 (0.60; 1.24)	0.83 (0.57; 1.21)
Only diabetes	2.93 (2.32; 3.70)	1.68 (1.27; 2.22)	1.28 (0.95; 1.72)
Both diabetes and subclinical hypothyroidism	1.83 (0.83; 4.02)	1.24 (0.50; 3.06)	0.99 (0.38; 2.56)
Log CAC+1	**Linear regression models (β; 95% CI)**		
	Crude	**Model 1**	**Model 2**
Only subclinical hypothyroidism	0.30 (-0.009; 0.61)	0.32 (0.02; 0.61)	0.13 (-0.17; 0.43)
Only diabetes	0.49 (0.40; 0.58)*	0.41 (0.32; 0.50)	0.25 (0.16; 0.34)*
Both diabetes and subclinical hypothyroidism	0.01 (-0.10; 0.12)	-0.04 (-0.11; 0.10)	-0.02 (-0.12; 0.09)
BMI ≥30 kg/m²	**Logistic regression models (OR; 95% CI)**		
	Crude	**Model 1**	**Model 2**
CAC>0			
Only subclinical hypothyroidism	1.34 (0.76; 2.35)	1.08 (0.57; 2.06)	1.07 (0.55; 2.09)
Only diabetes	2.17 (1.58; 2.98)	1.37 (0.94; 2.00)	1.32 (0.89; 1.97)
Both diabetes and subclinical hypothyroidism	0.98 (0.41; 2.36)	0.65 (0.24; 1.79)	0.63 (0.22; 1.86)
	Linear regression models (β 95% CI)		
	Crude	**Model 1**	**Model 2**
Log CAC + 1			
Only subclinical hypothyroidism	0.02 (-0.31; 0.34)	0.02 (-0.31; 0.35)	-0.08 (-0.41; 0.26)
Only diabetes	0.37 (0.24; 0.50)*	0.31 (0.18; 0.44)*	0.22 (0.09; 0.35)*
Both diabetes and subclinical hypothyroidism	0.22 (0.002; 0.45)	0.20 (-0.02; 0.41)	0.14 (-0.07; 0.36)

*P < 0.05; CAC = coronary artery calcium; Model 1 adjusted for age, sex, race and education attainment; Model 2 = Model 1 plus smoking, alcohol intake, and dyslipidemia.

Supplementary Table 2. Odds ratio (95% Confidence Interval) of the association of subclinical thyroid disorders, diabetes and both diseases with coronary artery calcium CAC > 0 according to sex

	Logistic regression models (OR; 95% CI)		
	Crude	**Model 1**	**Model 2**
Women			
CAC > 0			
Only subclinical hypothyroidism	1.03 (0.66; 1.63)	0.87 (0.53; 1.43)	0.91 (0.54; 1.53)
Only diabetes	2.68 (1.97; 3.65)	1.71 (1.20; 2.44)	1.44 (0.98; 2.13)
Both diabetes and subclinical hypothyroidism	1.67 (0.75; 3.73)	0.67 (0.27; 1.68)	0.58 (0.22; 1.50)
Log CAC + 1	**Linear regression models (β, 95% CI)**		
	Crude	**Model 1**	**Model 2**
Only subclinical hypothyroidism	0.21 (-0.001; 0.42)	0,21 (-0,006; 0,42)	0.07 (-0.15; 0.28)
Only diabetes	0.28 (0.19; 0.36)*	0.27 (0.18; 0,36)*	0.17 (0.08; 0.26)*
Both diabetes and subclinical hypothyroidism	0.04 (-0.07; 0.14)	0.04 (-0,07; 0.14)	0.04 (-0,06; 0,14)
	Logistic regression models (OR, 95% CI)		
	Crude	**Model 1**	**Model 2**
Men			
CAC > 0			
Only subclinical hypothyroidism	1.11 (0.78; 1.59)	0.95 (0.63; 1.42)	0.87 (0.57; 1.33)
Only diabetes	2.26 (1.77; 2.88)*	1.59 (1.21; 2.10)*	1.23 (0.92; 1.66)*
Both diabetes and subclinical hypothyroidism	1.49 (0.61; 3.61)	1.40 (0.52; 3.75)	1.12 (0.38; 3.25)
Log CAC + 1	**Linear regression models (β, 95% CI)**		
	Crude	**Model 1**	**Model 2**
Only subclinical hypothyroidism	0.16 (-0.26; 0.58)	0.14 (-0.34; 0.37)	0.08 (-0.34; 0.50)
Only diabetes	0.47 (0.36; 0.58)*	0.45 (0.34; 0.56)*	0.28 (0.17; 0.39)*
Both diabetes and subclinical hypothyroidism	0.07 (-0.09; 0.24)	0.03 (-0.13; 0.20)	(-0.16; 0.16)

*P < 0.05; CAC = coronary artery calcium; Model 1 adjusted for age, sex, race and education attainment; Model 2 = Model 1 plus smoking, alcohol intake, and dyslipidemia.