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Meta-Analysis

Meta-analysis on the Association Between Thyroid Hormone Disorders and Arterial Stiffness

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Abstract

Context: Aortic stiffness is an emerging predictor of cardiovascular morbidity and mortality. Current data about the effect of subclinical and overt thyroid hormone disorders on aortic stiffness are often conflicting.

Objective: Primary outcome was to investigate if subclinical and overt thyroid hormone disorders were associated with aortic stiffness. Secondary outcome was to identify disease effect modifiers.

Methods: Data sources were PubMed, Google Scholar, SCOPUS, Web of Sciences, and the Cochrane Library. Eligible studies included reports of pulse wave velocity (PWV), which is the gold standard method for measuring aortic stiffness, in patients with subclinical and overt thyroid disorders. Two investigators independently identified eligible studies and extracted data. Pooled mean difference was the summary effect measure. Data were presented in forest plots with outlier and influential case diagnostics. Univariate meta-regression analysis was used to identify effect modifiers.

Results: Eleven observational studies were selected, including 1239 patients with subclinical hypothyroidism, 81 patients with overt hypothyroidism, 338 patients with thyrotoxicosis, and 12 715 controls. PWV was significantly higher in subclinical ($P < .001$) and overt hypothyroidism ($P < .001$), as well as in patients with thyrotoxicosis ($P = .027$) compared with controls. Age was an effect modifier in hypothyroid patients.

Conclusion: This study shows that both overt and subclinical hypothyroidism as well as thyrotoxicosis were associated with an increase of aortic stiffness. The impact of treatment of these conditions on aortic stiffness should be assessed in clinical trials.

Key Words: meta-analysis, hypothyroidism, thyrotoxicosis, hyperthyroidism, arterial stiffness, pulse wave velocity

Abbreviations: BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; MD, mean difference; PWV, pulse wave velocity; TSH, thyrotropin.

The cardiovascular system is one of the main targets of thyroid hormone actions [1, 2]. Overt changes in circulating thyroid hormones can significantly affect cardiovascular function and homeostasis, as thyroid hormone excess or deficiency can induce or exacerbate atrial and ventricular arrhythmias, cardiomyopathy [3, 4], heart failure, arteriosclerosis, and atheroma formation. Consistent with these actions, both hypothyroidism and/or thyrotoxicosis are regarded as a cardiovascular risk factor in the general population [2]. Also subclinical hypothyroidism, which affects >10% of European and American postmenopausal women [5, 6], as shown in the Rotterdam or Colorado cohort studies, has been associated with an increased risk of cardiovascular morbidity [5] and mortality [7, 8], particularly in those with a thyrotropin (TSH) concentration of 10 mIU/L [8].

Arteriosclerosis, which corresponds to an age-related stiffening of the vessels, is a process consisting of a gradual fatigue fracture of elastic fibers within the arterial wall, with a resultant transfer of wall stress to collagen fibers over time, leading to the development of arterial stiffness [9]. This process should not be confused with atherosclerosis, which is characterized by vascular wall inflammation and plaque formation [10], although they can be associated. Arterial stiffness determines the rate at which the pulse pressure wave travels along the vessels (the higher is the stiffness the higher is the pulse wave velocity [PWV]), such that the measurement of PWV represents the gold standard method for its assessment [11, 12]. The pulse wave has 2 components: a forward travelling wave and a reflected wave, which travels from the periphery to the aortic root in diastole. In case of an increase in arterial stiffness, the reflected wave returns earlier, which raises aortic pressure during systole, systolic and pulse pressure, and it promotes left ventricular hypertrophy as well as subendocardial ischemia [9, 13] with other hemodynamic consequences [9, 14]. Aortic stiffness is an important emerging predictor of all-cause mortality in the general population [15, 16]. A meta-analysis on 17 635 subjects demonstrated that aortic stiffness could predict future fatal and nonfatal coronary and stroke events, with a hazard ratio of 1.3 after adjustments for established cardiovascular risk factors [17].

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During the last decades, several works have evaluated the impact of hypothyroidism and/or thyrotoxicosis on arterial stiffness, with different methods and conflicting results [18-21], such as in patients with subclinical hypothyroidism [18, 19] and thyrotoxicosis [20, 21]. The aim of this study was to evaluate the association between thyroid hormone deficiency and excess (be it overt or subclinical) and central arterial stiffness, as assessed by PWV, and to identify potential effect modifiers.

Materials and Methods

Data Sources and Search Strategy

This systematic review and meta-analysis were conducted following the PRISMA checklist [22]. We conducted a systematic literature search in 5 electronic bibliographic databases, to select all the studies evaluating PWV in patients with hypothyroidism and/or thyrotoxicosis compared with controls or evaluating PWV in patients with thyroid dysfunction before and after thyroid function normalization. The electronic bibliographic databases included PubMed, Google Scholar, SCOPUS, Web of Science, and the Cochrane Library. The query string included the terms "arterial stiffness" or "aortic stiffness" or "arterial compliance" or "pulse wave velocity" or "pwv" or "arterial elasticity" or "augmentation index" or "AIx" combined with any of the following: "hypothyroidism" or "thyroid hormones" or "thyrotoxicosis" or "levothyroxine" or "Hashimoto" or "Graves" or "Basedow" or "dysthyroidism." The search was performed from database inception to October 8, 2021.

Study Selection

Studies were examined and selected for inclusion independently by 2 investigators (R.M.A. and M.F.C.) and a third investigator (S.B.) was consulted in case of controversy. Inclusion criteria were as follows: (1) original studies; (2) adult population; (3) patients with thyroid disease (hypothyroidism or thyrotoxicosis); (4) report of PWV as assessed by validated methods, reviewed in [23]. Overt hypothyroidism was defined by high TSH with low free triiodothyronine (FT3) and free thyroxine (FT4) levels, while subclinical hypothyroidism was defined by high TSH with normal FT3 and FT4 levels. Overt thyrotoxicosis was defined by low TSH with high FT3 and FT4 levels, while subclinical thyrotoxicosis was defined by low TSH with normal FT3 and FT4 levels. Exclusion criteria of studies were as follows: (1) studies not written in English; (2) other publication types, such as reviews, meta-analysis, study protocols, case reports, letters, errata, conference proceedings, book chapters; (3) patients without hypothyroidism or thyrotoxicosis; (4) absence of PWV or PWV reported as quartiles or different study design; (5) overlapping populations [24, 25]. Figure 1 shows the stepwise procedure for study selection.

Data Extraction and Risk of Bias Assessment

Data on study design, patient characteristics, and PWV measurement were extracted independently by 2 investigators (S.B. and B.F.). In order to assess the risk of bias of the included studies, we used the ROBINS-I tool [26]. The ROBINS-I assesses 7 domains: D1, bias due to confounding; D2, bias due to selection of participants; D3, bias in classification of interventions; D4, bias due to deviation from intended intervention; D5, bias due to missing data; D6, bias in measurement of outcomes; and D7, bias in selection of the reported result. For each of these risk domains of bias, the studies were categorized as having a low, moderate, high, or critical risk. If the domains were not applicable, the risk of bias assessment was reported as not applicable. Risk of bias was independently assessed by S.B. and B.F. Traffic-light plots of risk-of-bias assessment (Fig. 2) were designed using "robvis" R-package [27].

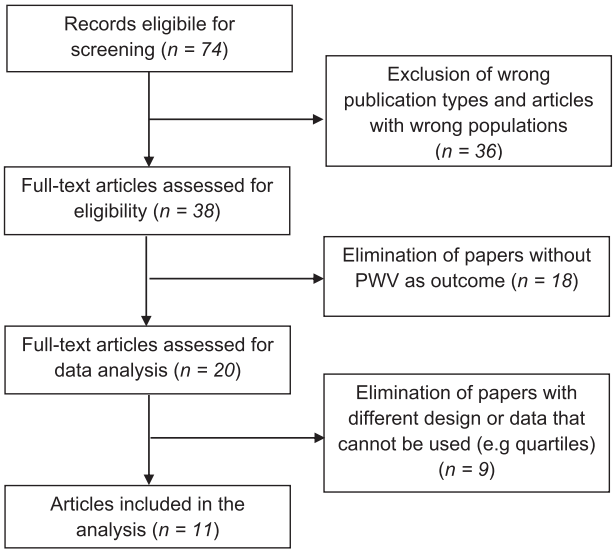

Figure 1. Stepwise procedure for study selection.

Statistical Analysis

To investigate the difference of PWV between patients with hypothyroidism or thyrotoxicosis and controls, pooled mean difference (MD), which we chose as the summary effect measure, was generated using the inverse-variance weighting method. Given that most of the studies reported data as mean ± SD, when data were reported as mean ± SE [28, 29], we computed SD, and when data were reported as median (min-max) or median (IQR) [30, 31], they were converted based on the method described by McGrath et al [32]. Pooled data of our meta-analysis are presented in forest plots.

A Cochran's Q test for heterogeneity was performed reporting the I^2 statistic and its 95% CI [33], which indicates the percentage of variation across studies because of heterogeneity rather than chance [34]. Heterogeneity values of <30%, 30% to 60%, 61% to 75%, and >75% were classified as low, moderate, substantial, and considerable [35]. The pooled MD and corresponding 95% CI were calculated according to the random effects models of DerSimonian and Laird [36], which incorporate both within- and between-study variability as a weighted average of the estimated MDs by giving each study a weight proportional to its precision.

In order to identify potential outliers and influential cases that might distort and affect the validity of the meta-analysis, we explored effect sizes and heterogeneity with the outlier and influential case diagnostics, which includes the Baujat plot, the influence analysis, and the leave-one-out method [37]. When the number of studies/comparisons was ≥10 entries, heterogeneity was evaluated with the Baujat plot, which is a graphical method to describe heterogeneity [38]. Otherwise, outliers and influential cases were identified with

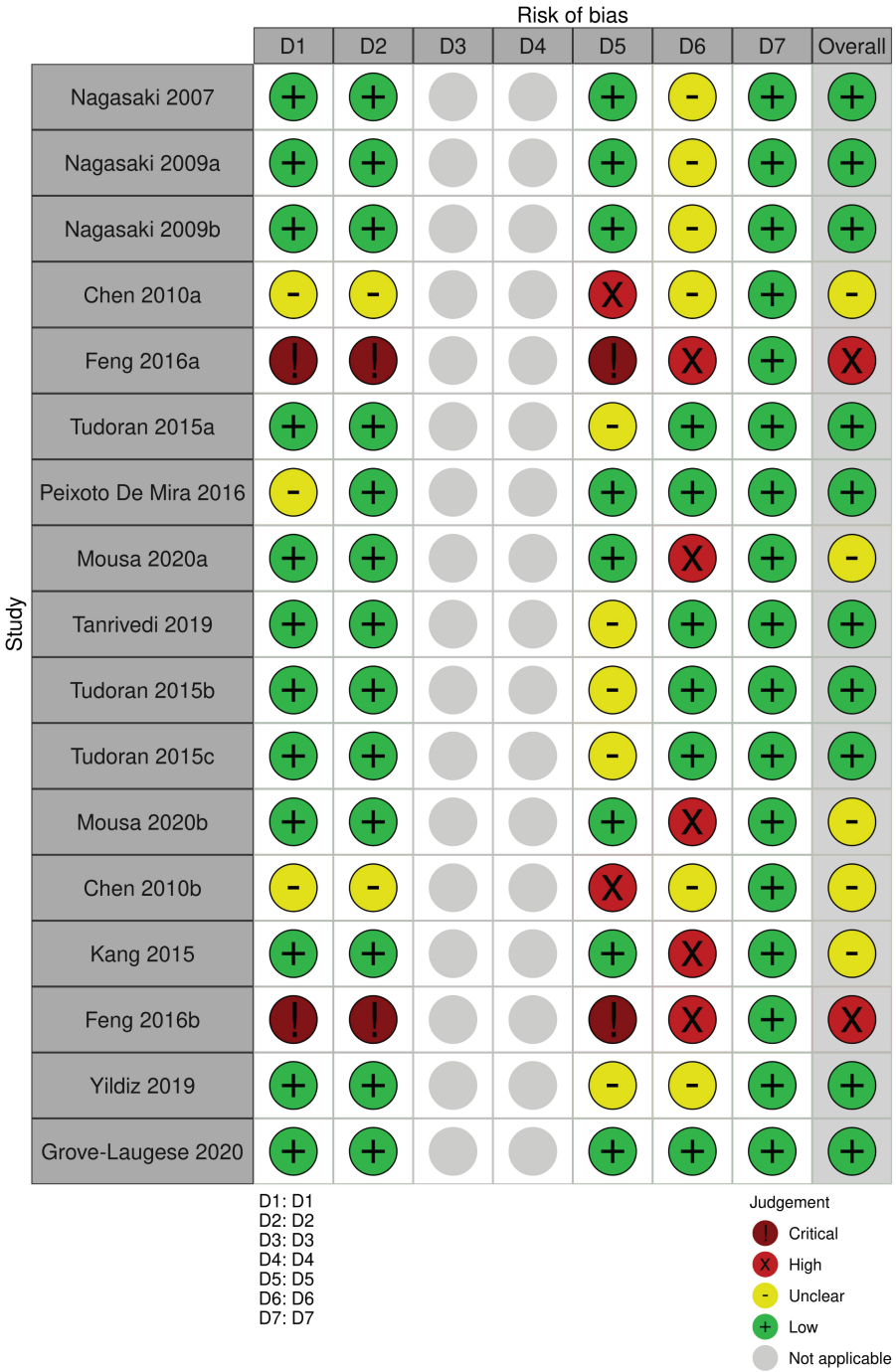

Figure 2. Bias assessment of selected studies. Risk of bias was classified as low (green), moderate (yellow), high (red), or critical (brown). Risk of bias was based on the judgement of domains D1-D7. Risk of bias in D1 was judged moderate for Chen et al and Peixoto de Miranda et al as they included patients with hypertension and diabetes, and critical for Feng et al. because of all the missing data. Risk of bias in D2 was judged moderate for Chen et al, because free thyroxine levels were not specified, and Feng et al. because the exact mean value of TSH and free thyroxine were not specified. Risk of bias in D5 was judged moderate for Tudoran et al and Tanriverdi et al (both did not report blood pressure), as well as Yildiz et al (not reporting cholesterol). Risk of bias in D5 was judged high for Chen et al not reporting the exact proportion of females and mean free thyroxine levels, and critical for Feng et al not reporting almost all variables linked to cardiovascular risk profile. It has to be noted that even if Kang et al did not report mean cholesterol levels, they stated that patients with hyperlipidemia were excluded. Risk of bias in D6 was judged moderate when PWV was assessed at the brachial and ankle sites and high when it was assessed with ultrasonography. Chen et al [18]; Peixoto de Miranda et al [19]; Feng et al [20]; Tudoran et al [41]; Tanriverdi et al [43]; Yildiz et al [30]; Kang et al [44].

the influence analysis and the influence diagnostic plots [39]. This analysis is based on the impact of excluding studies on various statistics such as the summary externally standardized residuals, DFFITS value, Cook's distance, and covariance ratio. Then, to assess the stability of the pooled results, we performed a sensitivity analysis by sequential omission of individual studies (leave-one-out method), which allows one to detect the studies that influence and might distort the overall estimate of a meta-analysis [39]. Then, based on the outlier and influential case diagnostics, the meta-analytic

models were run both with and without outliers/influential studies.

In order to identify potential disease effect modifiers, we conducted univariate meta-regression analyses to investigate the role of continuous (age, body mass index [BMI], cholesterol, TSH, and FT4) and categorical moderators (method of PWV assessment), when there were at least 10 studies reporting these values.

Publication bias was visually described by funnel plot while Egger's test and Begg's test were performed to evaluate the symmetry of funnel plots [40]: this analysis was not performed when there were less than 10 comparisons because of insufficient power to distinguish chance from real asymmetry. Data were analyzed using the R statistical software (version 4.0.2 packages: meta, metafor, dmetar). A 2-tailed $P < .05$ was considered statistically significant.

Results

Study Characteristics

At the end of our qualitative analysis, we identified 11 studies to include in our meta-analysis [18-20, 28-31, 41-44]. These studies were published between 2007 and 2020 and they were nonrandomized observational studies, reporting PWV mean results (m/s) in patients with hypothyroidism (overt and/or subclinical) or in patients with overt thyrotoxicosis compared with controls. Overall, as shown in Table 1, 9 groups of patients with subclinical hypothyroidism (n = 1239), 3 groups of patients with overt hypothyroidism (n = 81), and 5 groups of patients with overt thyrotoxicosis (n = 338) were compared with respective controls (n = 12 715).

We did not analyze the association between subclinical thyrotoxicosis and arterial stiffness, as there was only 1 study reporting PWV in patients with subclinical thyrotoxicosis [30]. As for the effect of interventions/medication, there were only 3 studies reporting PWV in patients with hypothyroidism before and after thyroid function normalization [28, 29, 45], and only 1 study reporting it in patients with thyrotoxicosis [44]. Consequently, we did not perform a meta-analysis of the effect of thyroid function normalization on arterial stiffness as there were not enough studies.

Going back to the data of the included studies, mean age of study participants ranged from 31 to 66 years. They were predominantly female (52-100%). Looking at participant selection, in case–control comparisons, patients were generally matched by age, sex, BMI, and other cardiovascular risk factors, such as smoking habit, blood pressure, glycemia, lipid profile, and creatinine levels. Some studies included patients who were overweight [19, 41, 42], some included patients with hypertension [19, 41], and some included patients with diabetes [18, 19].

Aortic stiffness was evaluated by carotid-femoral [19, 31, 43], heart-femoral [42], carotid-radial [30, 41] PWV, as well as by brachial-ankle recordings [18, 28, 29]. In 2 studies, PWV was assessed automatically with Doppler ultrasonography on the carotid site [20, 44]. Figure 2 shows the risk of bias assessment. Overall, the majority of the studies that were evaluated showed a low risk of bias.

Meta-analysis

First, we compared PWV between patients with hypothyroidism and controls. The pooled MD of PWV was 1.65 (0.98-2.32), $P < .001$, indicating that hypothyroid patients had significantly higher arterial stiffness than controls (Fig. 3A). The I^2 statistic showed considerable heterogeneity ($I^2 = 92.4\%$, uncertainty range 88.5-94.9%, $P < .0001$). The Baujat plot showed that the studies with the highest influence on the overall results was that by Peixoto de Miranda et al [19] and on the overall heterogeneity were those by Nagasaki et al [28, 29]. Nevertheless, the leave-one-out method demonstrated that even when these studies were removed, the pooled MD remained significant (Fig. 3B).

Then, patients with hypothyroidism were divided into 2 subgroups (subclinical and overt), as shown in Fig. 3C. The pooled MD of PWV in patients with overt hypothyroidism was 1.74 (0.87-2.62), $P < .001$, and the pooled MD in patients with subclinical hypothyroidism was 1.61 (0.84-2.37), $P < .001$. There were no subgroup differences ($P = .82$). The I^2 statistic indicated considerable heterogeneity in the subclinical group only (I^2 56.4% vs I^2 93.3%).

Given this significant heterogeneity, we conducted exploratory univariate meta-regression analyses to identify covariates that might influence the effect of hypothyroidism on arterial stiffness increase. Our meta-regression showed that age significantly influenced the association between hypothyroidism and arterial stiffness (Table 2). The regression coefficient for age was 0.068, indicating that every 1 year of age corresponded to a PWV increase of 0.068 m/s (Fig. 4A). To look for a possible influence of the method of PWV assessment on arterial stiffness increase in hypothyroid patients, we divided the studies into 3 subgroups: studies assessing central PWV (group A); studies assessing central/peripheral PWV (group B), and studies assessing PWV with ultrasonography (group C). The test for subgroup differences (random effects model) indicated $P = .14$, as represented in Fig. 4B.

The funnel plot for the effect of hypothyroidism on PWV suggested a publication bias, which was confirmed by Egger's ($t = 4.67$; $P < .001$) and Begg's ($z = 1.79$, $P = .07$) tests (Fig. 5). Looking at the funnel plot, the publication bias seems to be due to 3 small studies with very high effect sizes in the bottom-right corner of the plot, which had no equivalent on the bottom-left corner of the plot.

Second, we compared PWV between patients with thyrotoxicosis and controls. The pooled MD of PWV was -0.12 (-1.25 to 1.01), $P = .838$ (Fig. 6A). The I^2 statistic indicated considerable heterogeneity ($I^2 = 96.7\%$, uncertainty range 94.5-98.0%, $P < .0001$). The visual inspection of the forest plot and the influence analysis showed that the study by Feng et al [20] could potentially distort the overall estimate of our meta-analysis and should be removed (Fig. 6B). This was consistent with the fact that this study had a critical risk of bias, based on our bias assessment analysis, given that the authors did not report patient age, BMI, blood pressure, and total cholesterol (Table 1 and Fig. 2). The leave-one-out method indicated that the overall MD changed by omitting this study, confirming that this study was affecting our pooled results and it should be removed (Fig. 6C). A new random effects model showed that the pooled MD was 0.42 (0.05-0.79), $P = .027$, with moderate heterogeneity ($I^2 = 58\%$, uncertainty range 0-86%, $P = .07$), indicating that thyrotoxicosis was also associated with a significant increase of PWV (Fig. 6D).

Discussion

This is the first meta-analysis evaluating the association of subclinical and overt thyroid hormone disorders (deficiency

Table 1. Characteristics of patients recruited

Study	No. of patients		Age (years)		Sex (%F)		BMI (kg/m²)		SBP (mmHg)		TSH (μU/mL)		FT4 (pmol/L)		Cholesterol (mmol/L)		PWV (m/s)	
	Case	CNT	Case	CNT	Case	CNT	Case	CNT	Case	CNT	Case	CNT	Case	CNT	Case	CNT	Case	CNT
Subclinical hypothyroidism																		
Nagasaki 2007	42	42	66 ± 3	65 ± 3.2	81	81	22 ± 0.5	22 ± 0.5	133 ± 4	131 ± 4	7 ± 0.8	2.3 ± 0.5	15 ± 0.7	15 ± 0.7	5.5 ± 0.3	5.4 ± 0.25	18.5 ± 0.9	13.9 ± 0.4
Nagasaki 2009a	48	48	64 ± 3	64 ± 3	100	100	22 ± 0.5	22 ± 0.4	133 ± 4	131 ± 4	7 ± 0.6	2.5 ± 0.3	14.5 ± 0.7	15 ± 0.4	5.6 ± 0.3	5.6 ± 0.2	17.8 ± 0.9	14.2 ± 0.6
Nagasaki 2009b	47	48	66 ± 3	64 ± 3	100	100	22 ± 0.5	22 ± 0.4	133 ± 3	131 ± 4	7 ± 0.7	2.5 ± 0.3	14 ± 0.7	15 ± 0.4	5.5 ± 0.25	5.6 ± 0.2	17.4 ± 1	14.2 ± 0.6
Chen 2010a	491	4465	46 ± 14	47 ± 12	—	—	23 ± 3.5	23 ± 3	135 ± 26	134 ± 23	3.9 (3.3-51)	1.4 (1-2)	—	—	5.0 ± 1.1	4.95 ± 1.4	14.7 ± 3.9	14.5 ± 3.9
Feng 2016a	61	60	—	—	100	100	—	—	—	—	>4.8	0.4-4.5	—	—	—	—	8.9 ± 1.35	6.8 ± 1.3
Tudoran 2015a	15	15	37 ± 5	42 ± 7	100	100	26 ± 3	27.5 ± 7	—	—	12 ± 3	2.8 ± 0.6	6.5 ± 4	8.5 ± 3	6.0 ± 0.8	5.65 ± 0.7	6.9 ± 1.5	6.2 ± 1.4
Peixoto De Miranda 2016	463	7878	52 (45-58)	50 (44-56)	57	52	27 ± 5	27 ± 4.5	126 ± 16	119 ± 13	5 (4.4-6.4)	1.5 (1-2.2)	14 (12-16)	14 (13-15)	5.6 ± 1.1	5.55 ± 1.1	9.15 ± 1.7	9.1 ± 1.7
Mousa 2020a	40	20	35 ± 8	36 ± 5.5	100	100	31 ± 4	30 ± 2	114 ± 11	114 ± 9	7.6 (5.5-10)	2.5 (1-4)	15 (12-19)	19 (16-21)	5.7 ± 0.3	5.0 ± 0.4	9.3 ± 1.3	7.8 ± 2.1
Tanriverdi 2019	32	28	43 ± 10	43 ± 9	100	100	26.5 ± 4	26 ± 3.5	—	—	11 ± 7	2 ± 1	9 ± 1	10 ± 1	5.5 ± 1.3	5.1 ± 0.9	7.2 ± 1.5	6 ± 1.3
Overt hypothyroidism																		
Tudoran 2015b	26	15	43 ± 2	42 ± 7	100	100	28 ± 2.5	27.5 ± 7	—	—	51 ± 14	2.8 ± 0.6	5 ± 2	8.5 ± 3	6.9 ± 1.1	5.65 ± 0.7	8.7 ± 1.9	6.2 ± 1.4
Tudoran 2015c	15	15	40 ± 6	42 ± 7	100	100	27 ± 3	27.5 ± 7	—	—	31 ± 14.5 (4.4-6.4)	2.8 ± 0.6	5 ± 3	8.5 ± 3	6.5 ± 1.0	5.65 ± 0.7	7.25 ± 1	6.2 ± 1.4
Mousa 2020b	40	20	35 ± 6	36 ± 5.5	100	100	31.5 ± 6	30 ± 2	115 ± 6	114 ± 9	30.5 (21-49)	2.5 (1-4)	7.6 (5.5-10)	19 (16-21)	6.4 ± 0.6	5.0 ± 0.4	9.55 ± 1.8	7.8 ± 2.1
Thyrotoxicosis																		
Chen 2010b	124	4465	48 ± 11.5	47 ± 12	—	—	22 ± 3	23 ± 3	137 ± 25	134 ± 23	0.01 (0.01-0.17)	1.4 (1-2)	—	—	4.65 ± 1.2	4.95 ± 1.4	14.9 ± 3.8	14.5 ± 3.9
Kang 2015	70	74	37 ± 12.1	34 ± 10	68	70	20 ± 4	22.5 ± 2	121 ± 13	114 ± 11	0.07 ± 0.1	1.8 ± 1.05	66.5 ± 33	16 ± 4	—	—	6.3 ± 1.1	5.6 ± 0.98
Feng 2016b	59	60	—	—	100	100	—	—	—	—	<0.3	0.4-4.5	>25	9-23	—	—	4.5 ± 1.2	6.8 ± 1.3
Yildiz 2019	30	30	32.5 (19-65)	31 (19-64)	73	73	24 (16-40)	24 (18-44)	120 (102-140)	114 (101-138)	<0.01 (<0.01-0.02)	1.5 (0.55-3.6)	28 (19-55)	13 (11-17)	—	—	5.6 (4.8-9.7)	5.2 (4.5-8.5)
Grove-Laugesen 2020	55	55	40 ± 14	40 ± 14	82	82	25 (20-27)	23.5 (22-26)	124 ± 14	120 ± 13	0.00 (0-0)	2.2 (1.5-3)	32 (25-42)	15 (14-17)	4.1 ± 0.8	4.7 ± 0.9	8.4 (7.6-8.2)	8.1 (7.2-8.9)

Nagasaki 2007 [28]; Nagasaki 2009a and Nagasaki 2009b [29]; Chen 2010a [18]; Feng 2016a [20]; Tudoran 2015a [41]; Peixoto de Miranda 2016 [19]; Mousa 2020a [42]; Tanriverdi 2019 [43]; Tudoran 2015b and Tudoran 2015c [41]; Mousa 2020b [42]; Chen 2010b [18]; Kang 2015 [44]; Feng 2016b [20]; Yildiz 2019 [30]; Grove-Laugesen 2020 [31].
Abbreviations: CNT, control; BMI, body mass index; SBP, systolic blood pressure; PWV, pulse wave velocity; TSH, thyrotropin.

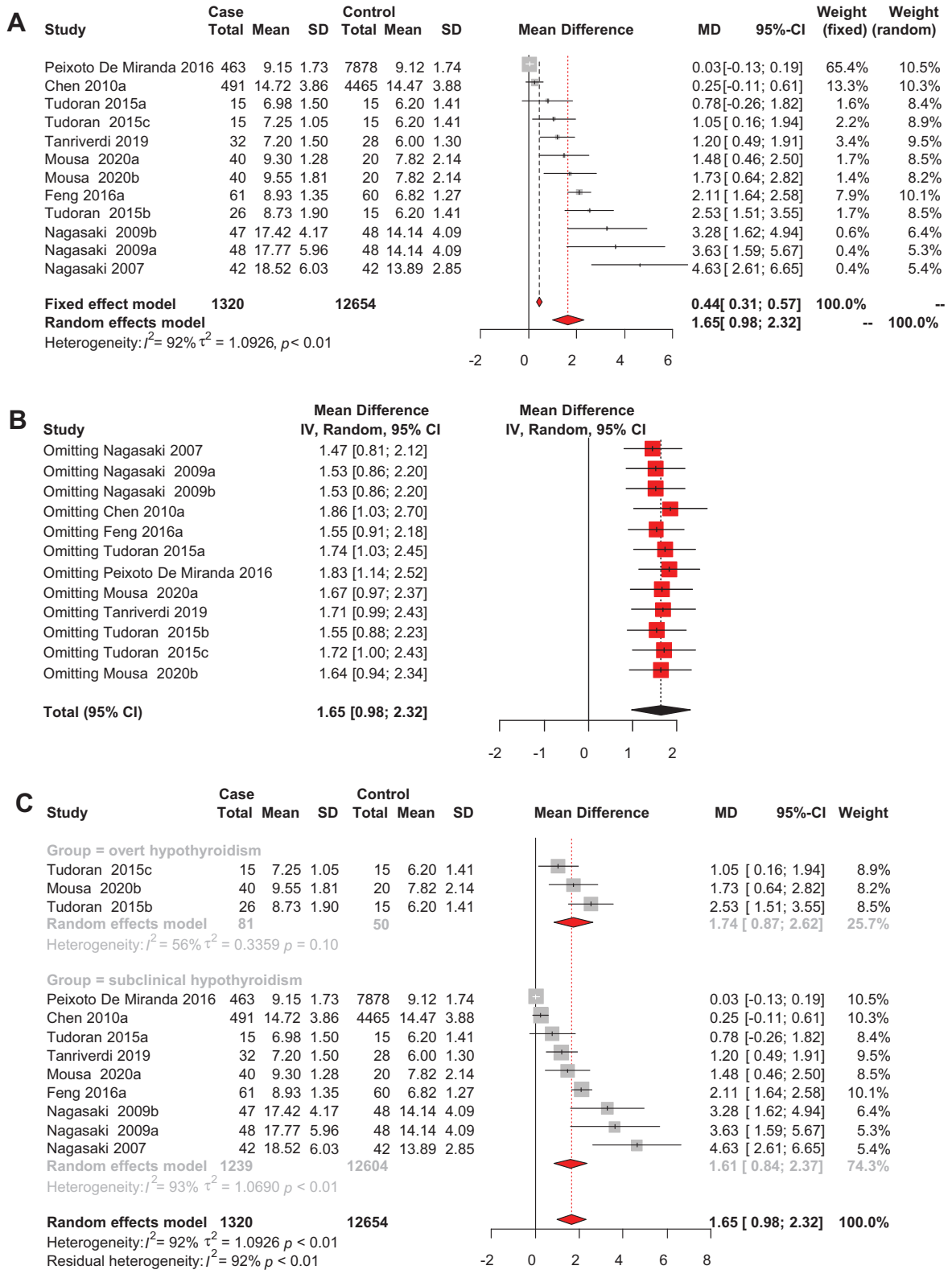

Figure 3. Arterial stiffness in patients with hypothyroidism. (A) Forest plot indicating the effect of hypothyroidism on PWV compared with controls. (B) Leave-one-out method showing the effect of sequential omission of individual studies on pooled MD. (C) Forest plot with subgroup analysis indicating the effect of overt hypothyroidism and subclinical hypothyroidism on PWV as compared to controls. Peixoto de Miranda 2016 [19]; Chen 2010a [18]; Tudoran 2015a and Tudoran 2015c [41]; Tanriverdi 2019 [43]; Mousa 2020a and Mousa 2020b [42]; Feng 2016a [20]; Tudoran 2015b [41]; Nagasaki 2009b and Nagasaki 2009a [29]; Nagasaki 2007 [28].

and excess) with aortic stiffness, as assessed by PWV, which is an emerging predictor of cardiovascular morbidity and mortality [15, 16]. Our meta-analysis shows that both overt and subclinical hypothyroidism, as well as overt thyrotoxicosis, were associated with an increase of aortic stiffness. In addition, age had a significant impact on the association between hypothyroidism and aortic stiffness increase.

Table 2. Summary of the output of univariate meta-regression

Moderator variable	K	Beta	SE	*P* value
Continuous moderator				
Age	11	0.0683	0.0343	.046
BMI	11	–0.1506	0.1179	.201
Cholesterol	11	0.4372	0.5901	.459
TSH	11	0.0053	0.0201	.794
FT4	10	0.0965	0.1095	.378
Categorical moderator				
Method				
A (central stiffness)	5	Reference		
B (central–peripheral stiffness)	4	1.4444	0.8638	.094
C (central stiffness by ultrasound)	3	0.7149	0.8744	.414

Abbreviations: BMI, body mass index; FT4, free thyroxine; K, number of studies; SE, standard error of meta-regression beta coefficient; TSH, thyrotropin.

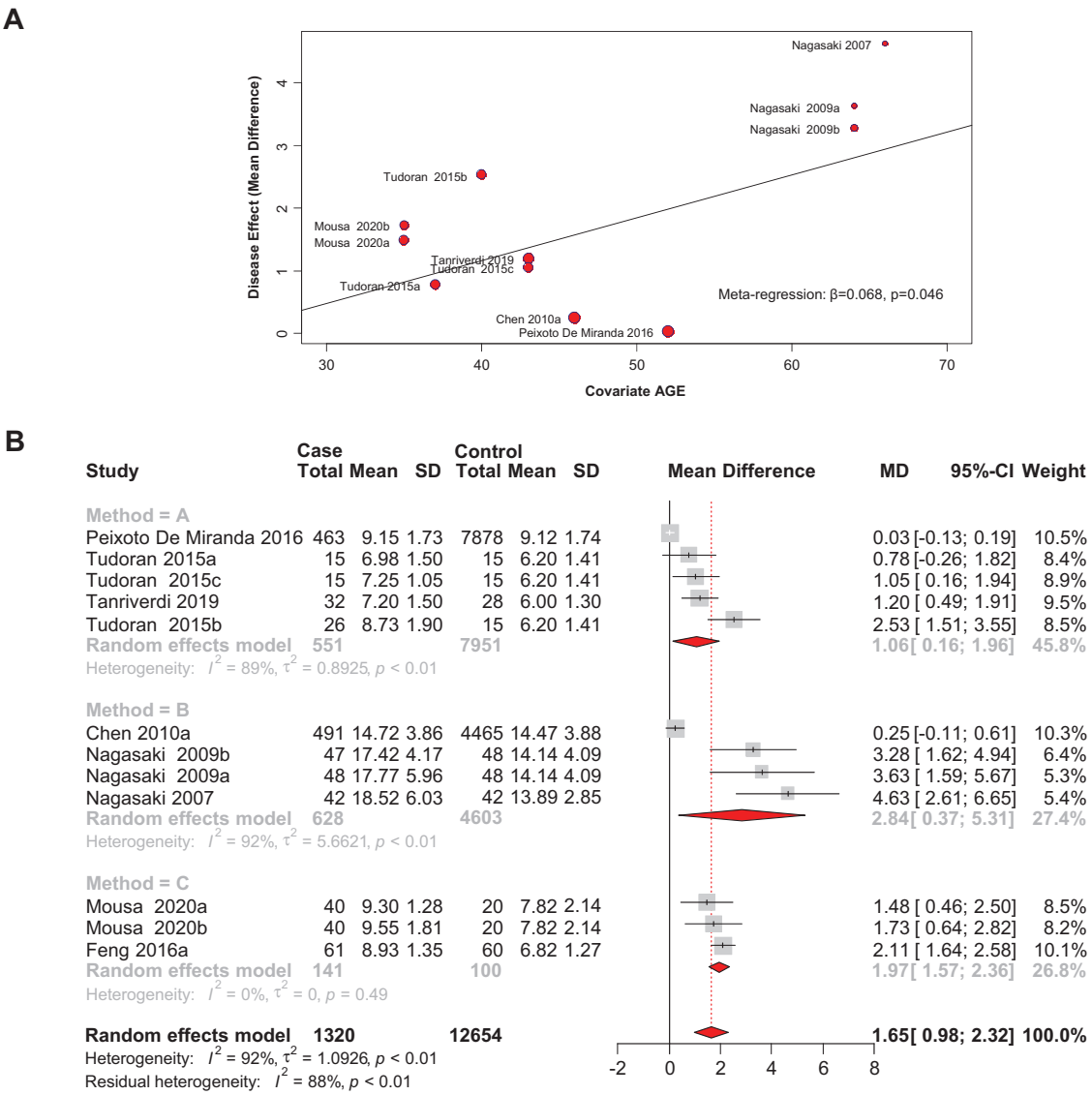

Figure 4. Meta-regression analysis in patients with hypothyroidism. (A) Bubble plot representing the correlation between age and mean difference of PWV. (B) Forest plot with subgroup analysis indicating the effect of hypothyroidism on PWV, as assessed by carotid-femoral or carotid-radial PWV (group A = central stiffness), brachial-ankle PWV (group B = central-peripheral stiffness), ultrasonography (group C = central stiffness by ultrasound). Peixoto de Miranda 2016 [19]; Tudoran 2015a and Tudoran 2015c [41]; Tanriverdi 2019 [43]; Tudoran 2015b [41]; Chen 2010a [18]; Nagasaki 2009b and Nagasaki 2009a [29]; Nagasaki 2007 [28]; Mousa 2020a and Mousa 2020b [42]; Feng 2016a [20].

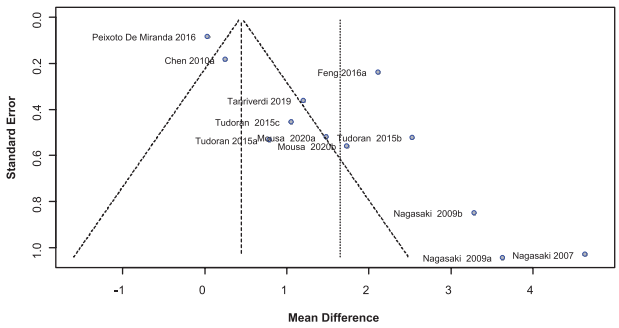

Figure 5. Funnel plot of the studies evaluating PWV in patients with hypothyroidism.

Thyroid hormones influence vascular homeostasis in 3 ways: by direct genomic actions through binding to nuclear receptors [46]; by direct extranuclear nongenomic actions [47, 48]; and by increasing vascular sensitivity to catecholamines as well as the expression of renin angiotensin system components [49]. When looking at thyroid hormone deficiency, overt hypothyroidism has been associated with impaired vascular function and impaired endothelial dependent vasodilation [50], partly because of the lack of vasodilatory triiodothyronine, which promotes NO production by endothelial and smooth muscle cells with subsequent myocyte vasodilation [13, 47, 51]. Previous works have shown that overt hypothyroid states were associated with a significant increase of central arterial stiffness, which was reduced by levothyroxine therapy [45, 52].

By contrast, the relationship between subclinical hypothyroidism and arterial stiffness has been recently challenged by 2 studies on large cohorts of patients, reporting the lack of an association between subclinical hypothyroidism and arterial stiffness increase, as assessed by brachial-ankle [18] or carotid-femoral PWV recordings [19]. Our meta-analysis shows that not only overt but also subclinical hypothyroidism was associated with increased arterial stiffness compared with controls. This is in line with the reports that this condition seemed to be associated with a higher risk of cardiovascular events and death [8], and that patients with this condition had fewer cardiovascular events after levothyroxine treatment [53]. Interestingly, the studies evaluating the effect of levothyroxine on arterial stiffness, in patients with subclinical hypothyroidism, have shown an improvement of vascular elasticity after thyroid function normalization [29, 54, 55].

Nevertheless, given that the association between subclinical hypothyroidism and arterial stiffness was heterogeneous across the studies, we conducted a meta-regression to identify potential moderators, which showed that patient age significantly influenced disease effect. By contrast, BMI, total cholesterol, TSH, and FT4 were not correlated with it. The fact that age influenced the increase of arterial stiffness in patients with hypothyroidism is consistent with the fact that arterial stiffening is mostly an age-related process of the arterial wall [9]. In particular, every 1 year of age corresponded to a PWV increase of 0.068 m/s. To translate this change of PWV into a clinical outcome, it has been demonstrated that any increase in aortic PWV by 1 m/s corresponds to an age-, sex-, and risk factor–adjusted risk increase of 14%, 15%, and 15% in total cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively [56].

In addition to the meta-regression, to understand if the methods used to measure PWV could justify the heterogeneity of the association between subclinical hypothyroidism and arterial stiffness increase, we performed a subgroup analysis dividing the studies into 3 categories: studies assessing central PWV, studies assessing central/peripheral PWV, and studies assessing PWV with ultrasonography. This analysis showed that when arterial stiffness was assessed with brachial-ankle PWV, there was a tendency to a greater MD in hypothyroid patients than in controls. This might be because central/peripheral vascular stiffness (which is measured by brachial-ankle PWV) tends to be higher than the central one (which is measured by carotid-femoral PWV), given that peripheral muscular arteries are inherently stiffer than the central elastic ones [9]. Nevertheless, it has to be noted that also brachial-ankle PWV can be considered a validated marker of cardiovascular risk [9], given that it is associated with cardiovascular events and mortality [57], it is correlated with aortic PWV [58], and it displays a similar accuracy to carotid-femoral PWV to predict the presence of stroke and coronary artery disease [59].

Besides hypothyroidism, thyroid hormone excess can also affect vascular homeostasis [49, 60]. Animal studies show that triiodothyronine administration significantly impairs vascular contraction and relaxation responses [61], while clinical studies show that hyperthyroidism increases NO production and vasodilation as well as the vascular reactivity, due to an exaggerated sensitivity to catecholamines (which is reversed by restoring euthyroidism) [60]. There are not many studies evaluating the effect of thyrotoxicosis on vascular stiffness, and their findings are conflicting, as some studies reported a reduction of vascular stiffness in case of thyroid hormone excess, while other authors found opposite changes [20, 21]. In this setting, our meta-analysis showed that overt thyrotoxicosis was associated with increased arterial stiffness, as assessed by PWV. Interestingly, consistent with our findings, subclinical thyrotoxicosis also seems to be associated with impaired vascular elasticity and higher arterial stiffness [30, 49].

The limitations of this meta-analysis include the fact that the majority of the studies were small and nonrandomized, subjects were young adults and mostly women, and PWV was assessed at different sites (carotid-femoral vs brachial-ankle). Nevertheless, only validated methods able to provide reliable PWV values were considered, and the strengths of our meta-analysis include the choice of PWV to assess arterial stiffness, which is in line with current recommendations, as well as the use of outlier and influential case diagnostics.

Another issue is the considerable heterogeneity between the studies investigating the association between subclinical hypothyroidism and arterial stiffness, as the smaller studies reported an association, whereas the largest studies reported a weak or no association. Our meta-analysis aimed to resolve this uncertainty by combining all available evidence and investigating reasons for between-study heterogeneity. Small research studies are generally a concern, because they are unstable and thus prone to being underpowered considered individually, and they tend to show more treatment effects than larger studies [62]. However, including small studies along with larger ones in a meta-analysis should not be a concern because none of them individually is given much weight, and the presence of 2 large well-powered studies avoids the problem to perform a meta-analysis with only small underpowered studies, and gives more consistent results.

In conclusion, this is the first meta-analysis on the association between thyroid hormone deficiency and excess and arterial

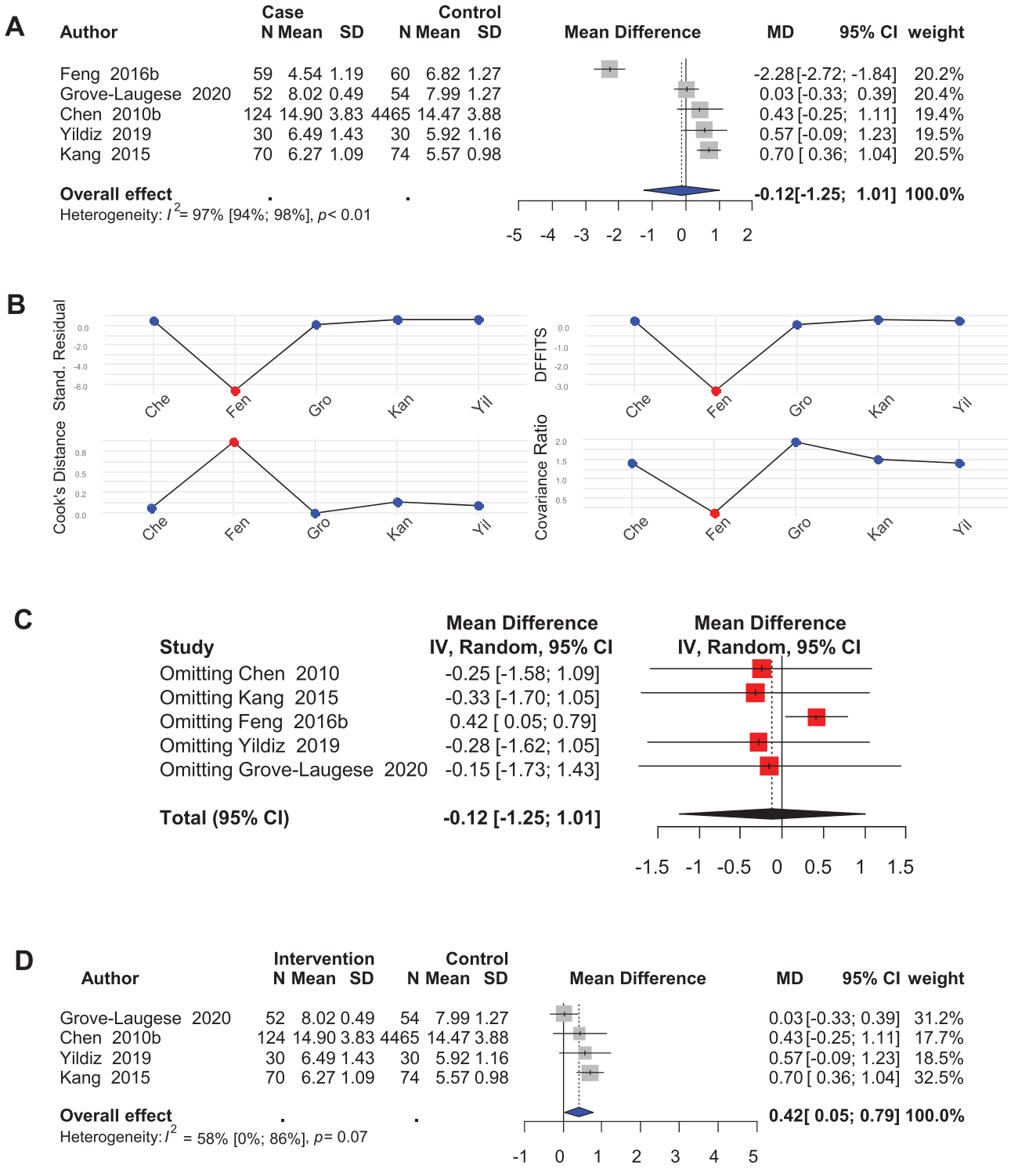

Figure 6. Arterial stiffness in patients with thyrotoxicosis. (A) Forest plot indicating the effect of thyrotoxicosis on PWV compared with controls. (B) Influence analysis of the studies evaluating the effects of thyrotoxicosis on PWV. Outliers and influential cases are displayed in red color. Che is for Chen et al, Fen is for Feng et al, Gro is for Grove-Laugese et al, Kan is for Kang et al, Yil is for Yildiz et al. (C) Leave-one-out method showing the effect of sequential omission of individual studies on pooled MD. (D) Forest plot indicating the effect of thyrotoxicosis on PWV after omitting influential studies.

stiffness, as assessed by PWV. Here we show that both overt and subclinical hypothyroidism are associated with higher arterial stiffness, and that this association increased with age. Likewise, also thyrotoxicosis was associated with higher arterial stiffness. These findings support the notion that both deficiency and excess of thyroid hormones might negatively impact on vascular homeostasis and that both overt and subclinical hypothyroidism deserve to be treated. Nevertheless, the impact of treatment of these conditions on aortic stiffness should be assessed and confirmed by clinical trials.

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Data Availability Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request

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