Published in final edited form as:

Clin Endocrinol (Oxf). 2015 April ; 82(4): 592–597. doi:10.1111/cen.12532.

Serum free thyroxine levels are positively associated with arterial stiffness in the SardiNIA study

Alessandro P. Delitala¹, Marco Orrù², Fabiana Filigheddu¹, Maria Grazia Pilia², Giuseppe Delitala¹, Antonello Ganau¹, Pier Sergio Saba¹, Federica Decandia¹, Angelo Scuteri², Michele Marongiu², Edward G. Lakatta³, James Strait³, and Francesco Cucca^{2,4}

¹Department of Clinical and Experimental Medicine, Azienda Ospedaliero-Universitaria di Sassari, Italy

²Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Cagliari, Italy

³Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute of Aging, Baltimore, MD, USA

⁴Department of Biochemical Science, Azienda Ospedaliero-Universitaria di Sassari, Italy

Abstract

Objective—Thyroid dysfunction may accelerate atherosclerosis. Aortic pulse wave velocity is an early index of arterial stiffness and an important risk factor for cardiovascular disease, and might therefore be linked to changes in thyroid activity. We investigated the relationship between thyroid function and carotid-femoral pulse wave velocity, as an index of arterial stiffness.

Design—Cross-sectional cohort study.

Patients—Participants from the SardiNIA study. Those being treated for thyroid diseases were excluded, yielding a sample of 5,875 ages 14–102.

Measurements—Clinical parameters, blood tests including serum TSH and serum FT4, and carotid-femoral pulse wave velocity were measured.

Results—After adjusting for confounders, a direct and linear association between FT4 and pulse wave velocity was shown (multiple regression analysis). The model containing age, mean blood pressure, body mass index, heart rate, FT4, hypertension, diabetes and dyslipidaemia accounted for 55% of the variation in pulse wave velocity.

Conclusions—Like several other known risk factors, serum FT4 levels are associated with carotid-femoral pulse wave velocity, suggesting that high FT4 levels have a detrimental effect on aortic stiffness and may contribute to aging process of the vascular system. This finding may help

Correspondence: Dr. Alessandro P. Delitala, Department of Clinical and Experimental Medicine, Azienda Ospedaliero-Universitaria di Sassari, Italy. Viale San Pietro 8, 07100 Sassari, Italy. Mobile: +39 3477057777, Fax number: +39 079228207, aledelitala@tiscali.it.

Conflicting interests: Nothing to declare.

Financial disclosure: The SardiNIA team was supported by Contract NO1-AG-1-2109 from the NIA.

to understand the pathogenesis of cardiovascular disease and contribute to improve prevention therapy.

Keywords

free thyroxine; pulse wave velocity; arterial stiffness; thyroid function; cardiovascular disease

Introduction

Thyroid disorders are associated with increased prevalence of cardiovascular disease, dyslipidaemia, and atherosclerosis.^{1,2} In particular, overt and subclinical hypothyroidism is associated with hypercholesterolemia³ and high risk of coronary heart disease,⁴ while overt hyperthyroidism is a risk factor for atrial fibrillation, stroke, all-cause mortality, and cardiovascular mortality.⁵⁻⁷ Recent evidence suggests that even levels of thyroid hormones within the normal reference range are associated with cardiovascular risk.⁸ Although the upper limit of the TSH reference range has not been universally accepted, clinical observations have led to a lowering to 2.5 $\mu\text{UI/ml}$, because circulating TSH levels above this limit increase the probability of developing metabolic syndrome in the general population.⁹

As an early index of vascular damage, the favoured measure of arterial stiffness, aortic pulse-wave-velocity (PWV), has emerged as an independent risk indicator for cardiovascular morbidity and mortality.¹⁰ Higher PWV values are positively associated with arterial stiffness and directly related to cardiovascular disease. Investigations of the vascular effects of thyroid hormones have been limited, but previous studies have reported increased arterial stiffness in patients with hypothyroidism,¹¹ even at a subclinical stage.¹² Moreover, a decrease in arterial stiffness has been described after normalization of thyroid biochemical parameters by levothyroxine replacement therapy in hypothyroid patients.¹³ By contrast, both overt hyperthyroidism and long-term TSH-suppressive therapy with levothyroxine have been reported to impair vascular elasticity and -- despite normal blood pressure values -- to be associated with increased arterial stiffness.^{14, 15} Moreover, recent data demonstrated that the risk of cardiovascular and all cause mortality is increased in patients with differentiated thyroid carcinoma treated with a TSH suppressive levothyroxine supplement, independent of age, sex and cardiovascular risk factors.¹⁶ Taken together, these data suggest a complex involvement of thyroid hormones in the development of arterial stiffness. To extend analyses, we have evaluated levels of thyroid hormones and their correlation with measured PWV in a large and relatively homogeneous Sardinian population.

Materials and Methods

Participants and data recorded

The cohort is from the SardiNIA study, a population-based survey that investigates more than 300 genetic and phenotypic traits associated with aging.^{17,18} Briefly, from 2001-2004, all residents in four towns of Lanusei valley (Lanusei, Arzana, Ilbono, and Elini) aged 14 years and older were invited to participate. In all, 6,148 subjects were recruited, approximately 62% of the eligible population. For the purpose of this study, subjects who reported taking thyroid medications (thyroid hormone replacement or thyrostatics) or drugs

that alter thyroid function tests (amiodarone, lithium, and corticosteroids) were excluded. A final group of 5,875 (age 14-102 years) all had routine medical examinations including i) measurements of height, weight, systolic (SBP) and diastolic blood pressure (DBP); ii) medical history including therapy; iii) blood sampling (see below); and iv) measurement of carotid-femoral PWV (see below). Body mass index (BMI) was calculated as weight (kg) / height² (m²). Mean blood pressure (MBP) was computed as DBP + [(SBP – DBP)/3]. Heart rate was calculated from electrocardiograms.

Each participant signed an Informed Consent. All study methods were conducted according to the principles expressed in the Declaration of Helsinki and were approved by the governing Ethics Committee, ASL4.

Biochemical and hormone assays

Blood venous samples were drawn between 7 and 8 a.m. after an overnight fast. Serum samples were stored at -80°C until use. Plasma triglycerides and total cholesterol were determined by an enzymatic method (Abbott Laboratories ABA-200 ATC Biochromatic Analyzer, Irving, TX, USA). High-density lipoprotein (HDL) cholesterol was determined by dextran sulphate–magnesium precipitation. Low-density lipoprotein (LDL) cholesterol was estimated by the Friedewald formula, calculated as follow: LDL cholesterol = total cholesterol - [HDL cholesterol + (triglycerides/5)]. Fasting plasma glucose concentration was measured by the glucose oxidase method (Beckman Instruments Inc., Fullerton, CA, USA).

Thyroid hormones were evaluated on stored samples in 2007-2008. Samples were thawed and serum TSH assessed with the Siemens TSH assay (Immulite 2000) according to manufacturer's instructions. The method is a solid-phase, two-site chemiluminescent immunometric assay (normal range 0.4 – 4.0 µIU/ml).

FT4 was measured with the Siemens FT4 assay (Immulite 2000). The method is a solid-phase, enzyme labelled chemiluminescent competitive immunoassay (normal range 0.89 – 1.76 ng/dl, [11.5 – 22.7 pmo/L]).

The iodine status at the time of evaluation was not assessed, although a mild to moderate iodine deficiency may be assumed from previous data.¹⁹

Overt hypothyroidism was defined as serum TSH level above the upper limit of reference range and serum FT4 level below the lower limit. Overt hyperthyroidism was diagnosed in subjects who had serum TSH level below the lower limit of reference range and serum FT4 level above the upper limit. We defined subclinical thyroid dysfunction as the presence of serum FT4 level in the normal reference range together with high serum TSH (subclinical hypothyroidism) or low serum TSH (subclinical hyperthyroidism).

Arterial function

As described elsewhere,¹⁸ carotid-femoral PWV was calculated as the ratio between the distance travelled by the flow wave (i.e. the distance in meters from the sternal manubrium to the right femoral sampling site minus the distance from the right carotid sampling site to

the sternal notch) and the transit time (i.e., the time delay in seconds between the feet simultaneously recorded carotid and femoral flow waves). A minimum of 10 pulse waves were recorded and stored using nondirectional transcutaneous Doppler probes (Model 810A, 9 to 10-Mhz probes, Parks Medical Electronics, Inc, Aloha, OR). The foot of the flow was identified off-line by a custom-designed computer algorithm, and verified or manually adjusted by the reader after visual review. The observer of PWV was blinded to thyroid function.

Definition of cardiovascular risk factors

Hypertension was defined as systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg, and/or self-reported use of antihypertensive drugs.

Diabetes mellitus was defined as self-reported diagnosis of diabetes and/or self-reported use of antidiabetic drugs or elevated fasting glycated haemoglobin or fasting glycaemia, according to the American Diabetes Association guidelines.²⁰

Dyslipidaemia was defined as a) self-reported use of lipid-lowering medications or b) the finding of LDL cholesterol levels ≥ 140 mg/dl or c) Triglycerides ≥ 400 mg/dl. Smokers were defined as current consumers of at least one cigarette per day.

We defined “cardiovascular event” as a documented history of myocardial infarction or stroke.

Statistical analysis

Normality was tested by the Shapiro-Wilk test for all the continuous variables under study. Because all of them had non-normal distributions and only one (SBP) could be transformed mathematically, nonparametric tests were used. Accordingly, median and interquartile range (IQR) were utilized as summary measures. On the basis of the results of univariate analysis (Wilcoxon rank sum test and Spearman's correlation), variables were tested in a multiple regression model (purposeful selection). FT4 and TSH were considered as continuous traits, while the thyroid state as a categorical variable (see below). Standardized coefficients were used as a measure of the contribution of each predictor to the final model. Polynomial and interaction terms were included as covariates. For simplicity and in order to avoid collinearity, blood pressure was represented by MBP in the multivariate analysis.

Collinearity was tested by assessing the variance inflation factor (VIF); values greater than 10 were considered as indicative of collinearity. Tests of significance were two-sided, and a $p < 0.05$ was assumed as statistically significant; Stata 11.1 for Windows was used for the analyses.

Results

The characteristics of the subjects are shown in Table 1. The distribution of sex, age, BMI, blood pressure, heart rate, lipids, and PWV was similar to that already reported by Scuteri et al. for the entire cohort.¹⁸

Overt hyperthyroidism and hypothyroidism were diagnosed in 25 (0.4%) and 35 (0.6%) participants, respectively, while subclinical hyperthyroidism and hypothyroidism were detected in 143 (2.4%) and 287 (4.9%) individuals, respectively.

Table 2 shows the distribution of PWV, TSH, and FT4 among age categories. FT4 and TSH progressively reduced in advancing age groups, consistent with previous findings in area with mild-moderate iodine deficiency.¹⁹ The age-specific increase in PWV is consistent with that reported in a large European population.²¹ Significant trends for changes were seen for all the variables.

Table 3 shows the results of multiple regression analysis. After adjusting for confounders, age, BMI, MBP, heart rate, FT4, the presence or absence of hypertension, diabetes and dyslipidaemia were associated with PWV, while sex, smoking, TSH, and the history of previous cardiovascular events were excluded. In particular, PWV was directly related to age, BMI, MBP, heart rate, and FT4, and was higher among hypertensive, diabetic and dyslipidemic subjects. The full model accounted for 55% of the variation in PWV. Among all the predictors, age was the one that contributed most (52%) to the explanation of the entire model (Table 3, standardized coefficients). The effect of FT4 was similar to that of dyslipidaemia and diabetes (4%, 2% and 6%, respectively). Interaction terms had no predictive value for PWV variability. Collinearity was excluded in the final model (VIF = 2.35 or lower).

Table 4 presents the data of PWV across thyroid states. When adjusted for covariates (multivariate analysis), only subjects with overt hyperthyroidism showed significantly higher PWV values compared to euthyroid individuals (reference). Although subjects with subclinical hyperthyroidism showed even higher PWV values, this difference did not reach the statistical significance after adjusting for confounders.

In order to explore the existence of biases related to sex or age, we analysed two further regression models, dividing the population by sex or by the median age (41.7 years), respectively. The association of FT4 with PWV was confirmed ($p < 0.05$) in all groups.

Discussion

We found a direct association of aortic PWV with serum FT4 level independent of other covariates.

Although an association between thyroid disease and changes in cardiovascular haemodynamics has been recognized for many years,²² few studies have considered possible effects of thyroid hormones on arterial stiffness. It has been demonstrated that overt and subclinical hypothyroidism are associated with increased PWV compared to normal euthyroid controls,^{11-13, 23} and clinical evidence also showed that increased arterial stiffness can be reversed by appropriate levothyroxine treatment.¹³ However, the association between hypothyroidism and increased arterial stiffness, which can be related to the presence of hypercholesterolemia, had been obtained from a limited number of studies with relatively few patients, possibly insufficient to reach conclusive evidence.

The association between hyperthyroidism and PWV is less clear. While some authors found increased arterial stiffness in overt hyperthyroidism,^{14, 24, 25} Obuobie et al. showed a reduced augmentation index in patients with thyrotoxicosis, which increased after treatment.²⁶ Like PWV, the augmentation index may be a surrogate measure of arterial stiffness, and it is directly related to the arterial stiffness.

The possible effect of thyroid hormone excess on arterial stiffening was also studied by Shargorodsky et al., who found decreased arterial elasticity in patients receiving long term TSH-suppressive therapy with levothyroxine, which is an iatrogenic subclinical thyrotoxicosis state.¹⁵

Although the interpretation of these divergent results is not clear, it should be taken into account that the methods used to estimate arterial stiffness were different in the various studies. Indeed, augmentation index is influenced by other parameters like sex, heart rate, height, left ventricular ejection, absolute systole duration, and vascular tone.

Overall, previous reports thus suggest a possible U-shaped relation between PWV and thyroid hormone levels, with PWV higher both in hypothyroid and hyperthyroid patients. However, in our analysis, the relationship between PWV and FT4 was linear and direct. In particular, after adjusting for the confounding effect of other covariates, patients with greater serum FT4 level recorded higher PWV. These results were substantially confirmed when the thyroid state was considered as a categorical trait, although the low numbers in some categories may have reduced the strength of the association.

One reason for disparate results is suggested by our multivariate analysis, in which the relationship between FT4 and PWV persisted after adjusting for heart rate, suggesting that additional mechanisms affect the role of thyroid hormones on vascular stiffness. This would be in line with complex and multiple actions of thyroid hormones on the heart, including genomic and non-genomic effects that influence myocardial contractility and excitability.^{27, 28}

Nevertheless, the primary association between heart rate and PWV is consistently supported in cross sectional studies, both in normal and hypertensive subjects.^{29, 30} This relation was confirmed for individual variability as well by Lantelme et al., who evaluated arterial stiffness in patients with pacemaker implantation by testing 5 different heart rate levels.³¹ Moreover, patients with hyperthyroidism treated with acute β -adrenergic blockade showed heart rate reduction, a process that is associated with normalization of total arterial stiffness.¹⁴ Thus, the authors suggested that the increased total artery stiffness may be a dynamic adaptation to the hypermetabolic state, promoting blood distribution into the peripheral vascular system.

In addition, thyroid hormones exert effects on the vascular system, decreasing systemic vascular resistance by vasodilation of the peripheral circulation,³² possibly as a direct action on vascular smooth muscle cells or through stimulation of vasodilatory endothelium-derived substances such as nitric oxide. Therefore, experimental and clinical findings can rationalize much of our findings: higher FT4 level could result in higher conversion to triiodothyronine, thus determining peripheral vasodilation and reflex cardiac effects such as increase in stroke

volume and heart rate. A direct thyroid effect enhancing sinoatrial node activity could also contribute to the increase in heart rate.³³

Because the measurement of carotid-femoral PWV is an early marker of atherosclerosis and independently associated with cardiovascular disease, the ESH/ESC Guidelines for the management for arterial hypertension recommend its measurement to detect subclinical organ damage.³⁴ In our study, in addition to FT4, also age, BMI, MBP, heart rate, hypertension, diabetes, and dyslipidaemia affected PWV values, with age showing the largest effect. The 'variable importance' of FT4 was of the same extent of other well-known cardiovascular risk factors, such as dyslipidaemia and diabetes. Altogether, the full model accounted for 55% of the variation in PWV suggesting that other sources of variability remain to be ascertained.

Our results also bear on the relative utility of TSH and FT4 determinations. TSH secretion from the pituitary gland is mainly regulated by thyroxine and triiodothyronine blood levels, as well as a variety of other factors such as drug therapies and chronic illnesses³⁵ and because it is more sensitive and specific, TSH level is commonly used to diagnose thyroid dysfunction. However, we found a direct relationship between PWV and FT4, but no association of TSH with PWV. In keeping with our results Gammage et al. found an association between FT4 concentration, but not TSH, and atrial fibrillation.³⁶ These findings taken together, would suggest that circulating FT4 levels are a more sensitive index of the effects of thyroid function on the cardiovascular system.

A major strength of our study is the size and homogeneity of the population studied. However this study has some limitations, some of which are commonly found in population surveys. All the subjects had only one assessment of TSH and FT4, thus potentially including individuals with non thyroidal illness or transient abnormality. In addition, thyroid hormone profile is not completed, as we did not assess serum FT3 level. Finally, because this is a cross sectional study, we can not discern any cause-and-effect relationship. Longitudinal data from the study should help to assess whether the increased PWV related to thyroid activity could be a physiological adaptation to vascular dynamics or could represent a risk factor for cardiovascular disease.

Our study included a large number of young individuals, who are not prone to develop arterial stiffness, but we excluded possible age bias by repeating the analysis with the cohort split according to the median age 41.7 years. Results were the same for both age groups.

In summary, we have shown that subjects with higher serum FT4 level have increased carotid-femoral PWV. The results suggest that high FT4 levels have a detrimental effect on aortic stiffness and may contribute to aging process of the vascular system. If these findings prove to be generalizable to other populations, need for treatment of subclinical hyperthyroidism should be reassessed.

Acknowledgments

This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

References

1. Nyirenda MJ, Clark DN, Finlayson AR, et al. Thyroid disease and increased cardiovascular risk. *Thyroid*. 2005; 15:718–724. [PubMed: 16053389]
2. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. *Journal of Clinical Endocrinology and Metabolism*. 2003; 88:2438–2444. [PubMed: 12788839]
3. O'Brien T, Dinneen SF, O'Brien PC, et al. Hyperlipidemia in patients with primary and secondary hypothyroidism. *Mayo Clinic Proceedings*. 1993; 68:860–866. [PubMed: 8371604]
4. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *Journal of the American Medical Association*. 2010; 304:1365–1374. [PubMed: 20858880]
5. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *New England Journal of Medicine*. 1994; 331:1249–1252. [PubMed: 7935681]
6. Sheu JJ, Kang JH, Lin HC, et al. Hyperthyroidism and risk of ischemic stroke in young adults: a 5-year follow-up study. *Stroke*. 2010; 41:961–966. [PubMed: 20360542]
7. Parle JV, Maisonneuve P, Sheppard MC, et al. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet*. 2001; 358:861–865. [PubMed: 11567699]
8. Takamura N, Akilzhanova A, Hayashida N, et al. Thyroid function is associated with carotid intima-media thickness in euthyroid subjects. *Atherosclerosis*. 2009; 204:e77–81. [PubMed: 18977482]
9. Ruhla S, Weickert MO, Arafat AM, et al. A high normal TSH is associated with the metabolic syndrome. *Clinical Endocrinology (Oxf)*. 2010; 72:696–701.
10. Najjar SS, Scuteri A, Shetty V, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *Journal of the American College of Cardiology*. 2008; 51:1377–1383. [PubMed: 18387440]
11. Obuobie K, Smith J, Evans LM, et al. Increased central arterial stiffness in hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*. 2002; 87:4662–4666. [PubMed: 12364455]
12. Dague AG, Lekakis JP, Papaioannou TG, et al. Arterial stiffness is increased in subjects with hypothyroidism. *International Journal of Cardiology*. 2005; 103:1–6. [PubMed: 16061115]
13. Nagasaki T, Inaba M, Kumeda Y, et al. Decrease of arterial stiffness at common carotid artery in hypothyroid patients by normalization of thyroid function. *Biomedicine and Pharmacotherapy*. 2005; 59:8–14. [PubMed: 15740929]
14. Palmieri EA, Fazio S, Palmieri V, et al. Myocardial contractility and total arterial stiffness in patients with overt hyperthyroidism: acute effects of beta1-adrenergic blockade. *European Journal of Endocrinology*. 2004; 150:757–762. [PubMed: 15191344]
15. Shargorodsky M, Serov S, Gavish D, et al. Long-term thyrotropin-suppressive therapy with levothyroxine impairs small and large artery elasticity and increases left ventricular mass in patients with thyroid carcinoma. *Thyroid*. 2006; 16:381–386. [PubMed: 16646685]
16. Klein Hesselink EN, Klein Hesselink MS, de Bock GH, et al. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. *Journal of Clinical Oncology*. 2013; 31:4046–4053. [PubMed: 24101052]
17. Pilia G, Chen WM, Scuteri A, et al. Heritability of cardiovascular and personality traits in 6,148 Sardinians. *PLoS Genetics*. 2006; 2:e132. [PubMed: 16934002]
18. Scuteri A, Najjar SS, Orru' M, et al. Age- and gender-specific awareness, treatment, and control of cardiovascular risk factors and subclinical vascular lesions in a founder population: the SardiNIA Study. *Nutrition, Metabolism and Cardiovascular Diseases*. 2009; 19:532–541.
19. Martino E, Loviselli A, Velluzzi F, et al. Endemic goiter and thyroid function in central-southern Sardinia. Report on an extensive epidemiological survey. *Journal of Endocrinological Investigation*. 1994; 17:653–657. [PubMed: 7868805]
20. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010; 32:S62–69.

21. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *European Heart Journal*. 2010; 31:2338–2350. [PubMed: 20530030]
22. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *New England Journal of Medicine*. 2001; 344:501–509. [PubMed: 11172193]
23. Nagasaki T, Inaba M, Kumeda Y, et al. Increased pulse wave velocity in subclinical hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*. 2006; 91:154–158.
24. Inaba M, Henmi Y, Kumeda Y, et al. Increased stiffness in common carotid artery in hyperthyroid Graves' disease patients. *Biomedicine and Pharmacotherapy*. 2002; 56:241–246. [PubMed: 12199623]
25. Czarkowski M, Hilgertner L, Powalowski T, et al. The stiffness of the common carotid artery in patients with Graves' disease. *International Angiology*. 2002; 21:152–157. [PubMed: 12110776]
26. Obuobie K, Smith J, John R, et al. The effects of thyrotoxicosis and its treatment on central arterial stiffness. *European Journal of Endocrinology*. 2002; 147:35–40. [PubMed: 12088917]
27. Dillmann WH. Biochemical basis of thyroid hormone action in the heart. *American Journal of Medicine*. 1990; 88:626–630. [PubMed: 2189306]
28. Davis PJ, Davis FB. Nongenomic actions of thyroid hormone. *Thyroid*. 1996; 6:497–504. [PubMed: 8936679]
29. Lantelme P, Khettab F, Custaud MA, et al. Spontaneous baroreflex sensitivity: toward an ideal index of cardiovascular risk in hypertension? *Journal of Hypertension*. 2002; 20:935–944. [PubMed: 12011655]
30. Sa Cunha R, Pannier B, Benetos A, et al. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. *Journal of Hypertension*. 1997; 15:1423–1430. [PubMed: 9431848]
31. Lantelme P, Mestre C, Lievre M, et al. Heart rate: an important confounder of pulse wave velocity assessment. *Hypertension*. 2002; 39:1083–1087. [PubMed: 12052846]
32. Ojamaa K, Klemperer JD, Klein I. Acute effects of thyroid hormone on vascular smooth muscle. *Thyroid*. 1996; 6:505–512. [PubMed: 8936680]
33. Valcavi R, Menozzi C, Roti E, et al. Sinus node function in hyperthyroid patients. *Journal of Clinical Endocrinology and Metabolism*. 1992; 75:239–242. [PubMed: 1619016]
34. Mancia G, Fagard R, Narkiewicz K, et al. ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Journal of Hypertension*. 2013; 31:1281–1357. [PubMed: 23817082]
35. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*. 2012; 22:1200–1235. [PubMed: 22954017]
36. Gammage MD, Parle JV, Holder RL, et al. Association between serum free thyroxine concentration and atrial fibrillation. *Archives of Internal Medicine*. 2007; 167:928–934. [PubMed: 17502534]

Table 1

Clinical characteristics of the cohort (n=5875).

Variable	Summary statistics*
Sex (M/F)	2579/3296
Age (years)	41.7 (29.0 -57.0)
BMI (Kg/m ²)	24.7 (21.8 - 28.1)
SBP (mmHg)	122 (112 - 136)
DBP (mmHg)	76 (70 - 83)
MBP (mmHg)	91 (84 - 101)
Heart rate (beats/min)	66 (59-74)
TSH (μUI/ml)	1.62 (1.04 - 2.33)
FT4 (pmol/L)	16.6 (15.1 – 18.1)
Total cholesterol (mg/dl)	206 (178 - 235)
LDL cholesterol (mg/dl)	124 (101 - 149)
HDL cholesterol (mg/dl)	62 (53 - 72)
Triglycerides (mg/dl)	71 (50 - 104)
PWV (m/s)	6.13 (5.20 - 7.56)
Smokers (n [%])	1196 (20.3%)
Hypertension (n [%])	1714 (29.2%)
Diabetes (n [%])	275 (4.68%)
Dyslipidaemia (n [%])	1146 (19.5%)
CV events (n [%])	96 (1.63%)

* Data are given as median (interquartile range); categorical data are expressed as absolute and relative frequencies.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; PWV, pulse wave velocity; CV, cardiovascular.

Table 2

Distribution of pulse wave velocity, TSH and FT₄ and test for trend across age categories.

	n	PWV (m/s)*	TSH (μUI/ml)*	FT4 (pmol/L)*
<30 (years)	1576	4.92 (4.46-5.41)	1.97 (1.43-2.67)	17.1 (15.7 - 18.7)
30-39 (years)	1172	5.68 (5.18-6.28)	1.71 (1.19-2.44)	16.7 (15.2 - 18.3)
40-49 (years)	1054	6.39 (5.71-7.19)	1.47 (0.96-2.20)	16.2 (14.8 - 17.8)
50-59 (years)	865	7.19 (6.40-8.43)	1.39 (0.88-2.04)	16.1 (14.5 - 17.6)
60-69 (years)	721	8.15 (7.18-9.63)	1.20 (0.79-1.86)	16.2 (14.5 - 17.8)
70 (years)	487	9.75 (8.49-11.8)	1.33 (0.83-2.01)	16.1 (14.5 - 17.9)
P _{trend}		<0.001	<0.001	<0.001

* Data are given as median (interquartile range).

n, absolute frequency, PWV, pulse wave velocity.

P_{trend} is the P-value for the test for trend across ordered groups.

Table 3

Multiple regression analysis of pulse wave velocity: best-fitting model.

PWV	Coeff	S.e.	t	P-value	St-coeff
Age	0.07	0.001	43.1	<0.001	0.52
BMI	0.06	0.005	10.9	<0.001	0.12
MBP	0.02	0.002	8.67	<0.001	0.12
Heart rate	0.02	0.002	9.65	<0.001	0.09
FT4	0.40	0.10	4.00	<0.001	0.04
Hypertension	0.40	0.07	6.00	<0.001	0.08
Diabetes	0.71	0.10	6.99	<0.001	0.06
Dyslipidaemia	0.13	0.05	2.46	0.014	0.02
Intercept	-2.68	0.26	-10.2	<0.001	-

PWV, pulse wave velocity; Coeff, beta coefficients; S.e., standard errors of the coefficients; t, t-test; St-coeff, standardized regression coefficients; BMI, body mass index; MBP, mean blood pressure.

Table 4

Pulse wave velocity across thyroid states.

Thyroid status	n	PWV(m/s) *	P-value [§]
Overt hyperthyroidism	25	6.4 (5.2-8.9)	<0.001
Subclinical hyperthyroidism	143	7.7 (5.9-9.0)	0.81
Euthyroidism	5385	6.1 (5.1-7.5)	reference
Subclinical hypothyroidism	287	6.0 (5.1-7.2)	0.81
Overt hypothyroidism	35	6.4 (5.7-8.1)	0.22

* Data are given as median (interquartile range).

[§] the P-value refers to the results of the multivariate analysis (*each group vs the reference*).

n, absolute frequency.