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CARDIOVASCULAR IMPLICATIONS OF AFFECTIVE TEMPERAMENTS

Ph.D. thesis

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LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ARB	Angiotensin II receptor blocker
BDI	Beck Depression Inventory
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CACS	Coronary artery calcium score
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CHD	Coronary heart disease
CV	Cardiovascular
DBP	Diastolic blood pressure
ICA	Invasive coronary angiography
ICC	Intraclass correlation coefficient
LAD	Left anterior descending artery
LCX	Left circumflex artery
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMi	Left ventricular mass index
MRI	Magnetic resonance imaging
OR	Odds ratio
PTP	Pretest probability
RCA	Right coronary artery
SBP	Systolic blood pressure
SIS	Segment involvement score
SSS	Segment stenosis score
TEMPS-A	Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire

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1. INTRODUCTION

A virtual revolution in empirical studies in the field of temperaments took place in the previous decades and I had the privilege of taking an active part in this process at the dawn of my university studies. The notion that affective temperaments may carry significance in cardiovascular (CV) disease dates back to 2016 when Nemcsik et al. documented the positive correlation of hyperthymic scores and the serum level of brain-derived neurotrophic factor (BDNF), a documented vasculoprotective agent in chronic hypertensive patients (1). Subsequently, hyperthymic temperament was identified as an independent predictor of a reliable indicator of arterial stiffness, augmentation index (2). My student research years coincided with the time of this dynamic expansion of what we know about the cardiovascular implications of temperaments, and given that my research activity predominantly revolved around the psychosomatic aspects of cardiovascular diseases, my attention was drawn to this field. Relying on these promising initial results, we aspired to establish if affective temperaments carry CV implications on the level of end-organ damage, as well, in a series of investigations that lasted from 2016 to 2020.

1.1. THEORETICAL UNDERPINNINGS OF AFFECTIVE TEMPERAMENTS

While personality is the product of complex lifelong interactions among genetic, biological and environmental factors, affective temperament is considered the inherited biological core of personality traits (3). Akiskal introduced the theoretical framework of affective temperaments based on the combination of abstract temperamental models and clinical observations of affective disorder patients. His primary goal was to characterize subjects with regards to cognitive, social-behavioral and psychomotor traits and to delineate the relation of temperaments and the manifestation and course trajectories of affective illness (4). Affective temperaments comprise of five distinct dimensions: cyclothymic, hyperthymic, irritable, anxious and depressive. The 110 self-reported items of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) were formulated to quantify affective temperaments along these five subscales (5). These temperaments can be conceived as biological

predispositions toward certain patterns of emotions, cognitions and behaviors that characterize emotional reactivity to environmental stimuli (6, 7). Although a firm biological and genetic basis have been implied for temperaments, the relative temporal stability does not mean a complete lack of change or development, as temperament scores may exhibit mild changes over a 6-year period (8).

1.2. The impact of affective temperaments on psychopathology

Affective temperaments not only demonstrate a pathoplastic effect on the initiation, clinical course and core characteristics of major affective disorders but they are widely considered as the subclinical manifestations of these clinical conditions with heritable components (9). Akiskal conceptualized the idea that affective disturbances can manifest in a spectrum ranging from physiological emotional reactivity to affective disorders and this continuum between affective temperaments and mood disorders is now universally accepted (10). Affective temperament measures appear to be documented predictors of lifetime suicide risk and contribute more to predicting suicidal status than the presence of a major affective disorder (11, 12). Besides psychopathology, a growing body of evidence suggest the impact of affective temperaments on somatic diseases but limited attention has been paid to temperaments as potential risk factors of CV pathology (13, 14).

1.3. The health burden of cardiovascular diseases

CV disease remains the leading cause of morbidity and mortality in the majority of developed countries worldwide. It is estimated that 17.8 million death occurred globally due to CV disease in 2017 (15). In spite of substantial declines in CV disease mortality over the past four decades in Europe, it remains the most frequent cause of death on the continent, with coronary artery disease (CAD) accounting for 43 % of all CV deaths (16). Importantly, hypertension remains a major contributing factor to CV morbidity and mortality in patients with ischemic heart disease, recently emerging as the single leading risk factor for the overall global burden of the disease (17).

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1.4. THE CONCEPT OF VASCULAR AGING

Aging contributes to a large proportion of overall personal CV risk, however, individuals do not age at the same pace (18). This observation eventually led to the introduction of the concept of vascular age that describes the gradual deterioration of vascular structure and function, as opposed to chronological age that solely refers to the passage of time (19). The relation of arterial and chronological age provides means of establishing whether early vascular aging is present in an individual (20). Although conventional methods for the calculation of arterial age include carotid intima-media thickness and pulse wave velocity (21, 22), coronary artery calcium score (CACS) has recently emerged as a reliable method for the estimation of vascular age (23, 24). Based on this concept, the calculation relies on the estimation of an arterial age that is equivalent to the chronological age associated with the same coronary heart disease (CHD) as the observed CACS (25).

1.5. THE BURDEN OF CORONARY ARTERY DISEASE

Overall, the global prevalence of CAD was 154 million in 2016, a figure that represents 32.7 % of the global burden of CV disease and 2.2 of the overall global burden of disease (26). The precise assessment of individual CAD risk would, therefore, be of utmost importance to maximize the health benefits of prevention given that efficient preventive treatments are widely available (27).

Coronary computed tomography angiography (CCTA) has emerged as an accurate, non-invasive alternative to invasive coronary angiography (ICA) in patients with low to intermediate pretest probability for obstructive CAD (28). CCTA enables the detection of coronary atherosclerotic plaque morphology and composition, as well as allowing robust qualitative and quantitative assessment of atherosclerosis (29). The suitability of CCTA as a gatekeeper to select appropriate individuals for ICA and subsequent revascularization has been extensively documented and CCTA has recently received class I recommendation for the testing of patients with stable chest pain by the European guidelines (30–32). To date, a diameter stenosis of more than 70 % (or 50 % for the left

main coronary artery) has been considered as significant luminal narrowing and this threshold forms the basis for decision-making in clinical practice regarding the potential need for revascularization (33).

1.6. High blood pressure and its epidemiological significance

High blood pressure (BP) is still accountable for more CV deaths than any other modifiable CV risk factor (34). The documented prevalence of hypertension is 55 % in Europe, a figure that is by far the highest compared to other regions (35). Defined as an increase in left ventricular mass (LVM), left ventricular hypertrophy (LVH) has emerged as an independent predictor of CV morbidity and mortality in chronic hypertensive patients, particularly for stroke, heart failure, and atrial fibrillation (36–39). LVH is hypothesized to increase the risk of major adverse cardiac events and mortality through a series of unfavorable metabolic, functional, and cardiac structural changes (40–42). The currently available repertoire of non-invasive methods to quantify LVM include echocardiography, cardiac magnetic resonance imaging (MRI), and CTA (43). Although the widespread availability, moderate expense, and lack of radiation exposure have propagated the use of two-dimensional transthoracic echocardiography for LV measurements, it yields limited reproducibility (44, 45). CCTA is a robust, non-invasive modality that permits accurate simultaneous anatomical visualization of the coronaries and the myocardium (29, 32, 46). Previous studies have demonstrated high reproducibility for LV measurements by CCTA (47, 48).

In previous studies, affective temperaments have been associated with various aspects of CV and metabolic disorders (49–52). By delineating the impact of such psychological factors along with their genetic, biological, behavioral, cognitive and emotional correlates would not only elaborate our insight into the etiopathological background of such somatic conditions, but would also provide valuable means of risk screening, prevention, and interventions possibly impacting CV illness course and outcomes.

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2. OBJECTIVES

The currently used conventional multidetector and dedicated cardiac CT scanners at the Heart and Vascular Center of Semmelweis University allow the visualization of coronary anatomy and atherosclerosis as well as the accurate differentiation of endocardial and epicardial boundaries enabling precise measurement of left ventricular dimensions for patients undergoing clinically indicated CCTA.
The aims of our current studies were the followings:

2.1. ASSESSING THE LINK BETWEEN TEMPERAMENTS AND ACCELERATED VASCULAR AGING

We sought to estimate the arterial age of participants based on non-enhanced cardiac scans using CACS measures calculated by the Agatston's method and to assess the potential link between affective temperaments and accelerated vascular aging (53). Overall, 209 patients with stable angina underwent non-enhanced scans with a standardized acquisition protocol during an inclusion period that extended from March 2016 to March 2020.

2.2. ESTABLISHING ASSOCIATIONS BETWEEN TEMPERAMENT SCORES AND THE PRESENCE OF SEVERE CAD

Furthermore, we intended to assess the association of affective temperaments and the presence of significant coronary artery stenosis in low to intermediate CV risk patients with stable angina by analyzing the CCTA images performed at our institution (54). For this purpose, 225 patients were enrolled consecutively between March 2019 and March 2020.

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2.3. Evaluating the relationship of affective temperaments and left ventricular hypertrophy

The final aim of our studies was to evaluate the relationship of affective temperaments and LVH in chronic hypertensive patients, as assessed by CCTA (55). In this particular study, 296 hypertensive patients were enrolled consecutively between February 2020 and March 2021.

Based on previous studies, a positive correlation was hypothesized between cyclothymic and irritable temperament and CV pathology and a negative association between hyperthymic temperament and adverse CV conditions.

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3. RESULTS

3.1. AFFECTIVE TEMPERAMENTS AND ACCELERATED VASCULAR AGING

All investigations were approved by the Scientific and Research Ethics Committee of the Medical Research Council, the Hungarian Ministry of Health (ETT TUKEB 570/2014) and was carried out in accordance with the tenets of the Declaration of Helsinki.

Overall, we enrolled a total of 209 patients in the current cross-sectional sub-study consisting of subjects with stable anginal symptoms referred to clinically indicated CCTA. The mean age of our cohort was 60.3 years, approximately half of them (49.3 %) were female and had dyslipidemia (50.7 %). The median coronary artery calcium score (CACS), as calculated by the model of Agatston (56), was 8.2 in our cohort. The arterial age assigned to each patient was the age that has the same expected CHD risk as the observed CACS (57). A previously published model was applied for the calculations, using a mathematical equation for the conversion: arterial age = 39.1 + 7.25 * $\log_{10}$ (CACS + 1) (25). Eventually, by calculating the difference between vascular and chronological age, it can be established whether accelerated vascular aging is present on an individual level (Figure 1).

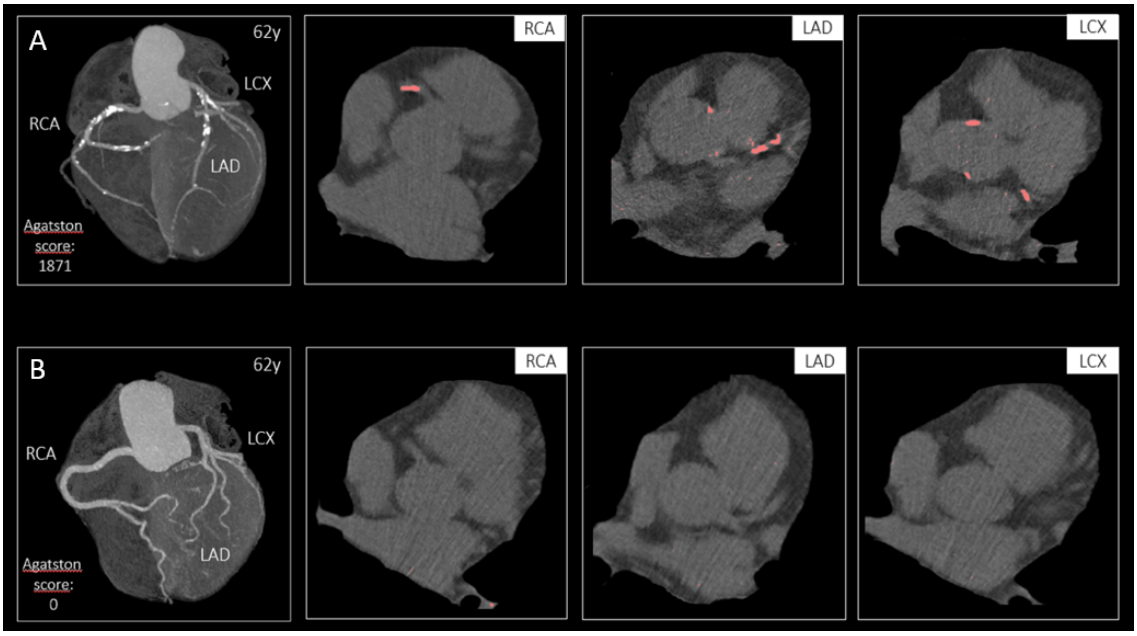

Figure 1. *Representative cross-sectional and volumetric images of two 62-year-old patients with markedly different extent of coronary calcification. (A) The calcium score*

of the first patient is 1871, which is the risk equivalent of 94 years of age, indicating accelerated vascular aging (94-62 = 32). (B) On the other hand, no macroscopic calcification was visible for the second patient (Agatston score: 0), thus demonstrating a case of lower 10-year CHD risk than expected (39-62 = -23).
Abbreviations: RCA, Right Coronary Artery; LAD, Left Anterior Descending Artery; LCX, Left Circumflex Artery.

In total, 100 patients presented with accelerated vascular aging on the basis of calcium score (vascular age > chronological age), while arterial age did not exceed chronological age in the remaining 109 subjects (vascular age ≤ chronological age). The prevalence of female sex was significantly higher in the healthy vascular ageing cohort, as compared to the accelerated vascular ageing group: 61.5 % vs. 36.0 %, respectively ($p < 0.001$). The proportion of patients with diabetes [23.0 % vs. 9.2 % ($p = 0.006$)] and dyslipidemia [62.0 % vs. 40.4 % ($p = 0.002$)] was significantly higher in patients with accelerated aging and subjects with accelerated vascular aging had significantly higher irritable temperament scores documented (4.2 ± 4.2 vs. 3.2 ± 3.3, $p = 0.03$).
Univariate linear regression analysis was used to assess the determinants of accelerated vascular aging in the whole cohort, and then in men and in women, separately. Traditional risk factors and psychometric parameters with $p < 0.10$ in the univariate model were entered into a multivariate linear model to assess independent association with accelerated vascular aging in the entire population and in both sexes, independently. Univariate regression model demonstrated that female sex was protective against vascular aging, while alcohol consumption, diabetes, dyslipidemia and irritable temperament correlated with advanced vascular aging. Female sex [$\beta = -10.82$ (95 % CI: -15.30 – -6.33), $p < 0.001$], diabetes [$\beta = 7.16$ (95 % CI: 1.20 – 13.12), $p = 0.02$] and dyslipidemia [$\beta = 8.28$ (95 % CI: 3.94 – 12.62), $p < 0.001$] maintained their significant independent association with accelerated aging in a multivariate setting. Table 1 provides the results of the multiple linear regression analyses in the whole cohort.

Table 1. Uni- and multivariate linear regression analysis of cardiovascular risk factors, affective temperaments, BDI-scores and the difference between vascular and chronological age.

	Univariate				Multivariate			
	β	95% CI, lower-upper		p	β	95% CI, lower-upper		p
Female sex	***-11.39***	***-15.67***	***-7.11***	***<0.001***	***-10.82***	***-15.30***	***-6.33***	***<0.001***
BMI (kg/m^2)	0.12	-0.30	0.54	0.58	-0.10	-0.52	0.31	0.63
Current smoker	3.33	-3.56	10.20	0.34	3.73	-2.57	10.03	0.24
Alcohol consumption	***5.06***	***0.56***	***9.56***	***0.03***	1.10	-3.33	5.52	0.63
Hypertension	1.58	-3.30	6.44	0.52	-1.90	-6.76	2.97	0.44
Diabetes	***7.56***	***1.41***	***13.71***	***0.02***	***7.16***	***1.20***	***13.12***	***0.02***
Dyslipidemia	***7.18***	***2.73***	***11.62***	***0.002***	***8.28***	***3.94***	***12.62***	***<0.001***
Depressive	0.18	-0.56	0.93	0.62				
Cyclothymic	0.48	-0.12	1.07	0.12				
Hyperthymic	0.19	-0.33	0.70	0.47				
Irritable	***0.07***	***0.05***	***1.39***	***0.04***	0.45	-0.19	1.08	0.17
Anxious	-0.07	-0.49	0.35	0.75				
BDI	0.18	-0.20	0.56	0.35				

Traditional risk factors and variables with $p < 0.10$ in univariate analysis were entered into the multivariate model.

BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BDI, Beck Depression Inventory.

Given that substantial sex differences have previously been proposed, potential associations were assessed separately in men and women, as well. No association was found regarding traditional risk factors for women, on the other hand, cyclothymic temperament independently predicted accelerated vascular aging in multivariate analysis

[β = 0.89 (95 % CI: 0.04 – 1.75), p = 0.04]. Detailed results of the multiple regression analyses in the female cohort is provided in Table 2.

Table 2. Results of the multiple linear regression analyses in female population.

	Univariate				Multivariate			
	β	95% CI, lower-upper		p	β	95% CI, lower-upper		p
BMI (kg/m^2)	-0.01	-0.55	0.53	0.96	-0.18	-0.76	0.41	0.55
Current smoker	4.88	-4.40	14.15	0.30	1.90	-7.52	11.33	0.69
Alcohol consumption	-0.94	-7.73	5.85	0.79	-1.98	-9.07	5.10	0.58
Hypertension	2.96	-3.91	9.84	0.40	0.18	-7.38	7.75	0.96
Diabetes	8.66	-0.23	17.56	0.06	7.95	-1.51	17.41	0.10
Dyslipidemia	3.65	-2.71	10.02	0.26	3.23	-3.43	9.89	0.34
Depressive	0.60	-0.46	1.67	0.26				
Cyclothymic	***0.94***	***0.12***	***1.76***	***0.03***	***0.89***	***0.04***	***1.75***	***0.04***
Hyperthymic	-0.20	-0.89	0.50	0.58				
Irritable	0.80	-0.22	1.82	0.12				
Anxious	0.27	-0.32	0.86	0.37				
BDI	0.23	-0.30	0.76	0.39				

Traditional risk factors and variables with p < 0.10 in univariate analysis were entered into the multivariate model.

BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure; BDI, Beck Depression Inventory.

While dyslipidemia proved to be an independent predictor of advanced vascular aging for men in multivariate regression analyses [β = 12.77 (95 % CI: 7.05 – 1.75), p < 0.001], no association could be noted, however, with affective temperaments and BDI scores, as presented in Table 3.

Table 3. Results of the multivariate linear regression analyses in male population.

	Univariate				Multivariate			
	β	95% CI, lower-upper		p	β	95% CI, lower-upper		p
BMI (kg/m^2)	0.04	-0.57	0.65	0.89	-0.10	-0.70	0.50	0.74
Current smoker	2.84	-6.34	12.03	0.54	4.63	-4.00	13.26	0.29
Alcohol consumption	3.93	-2,14	10.00	0.20	2.03	-3.72	7.78	0.48
Hypertension	0.76	-5.44	6.96	0.81	-3.78	-10.06	2.49	0.24
Diabetes	5.66	-2.03	13.35	0.15	5.16	-2.41	12.73	0.18
Dyslipidemia	***11.82***	***6.45***	***17.18***	***<0.001***	***12.77***	***7.05***	***18.48***	***<0.001***
Depressive	0.56	-0.40	1.52	0.25				
Cyclothymic	0.17	-0.60	0.93	0.67				
Hyperthymic	-0.03	-0.77	0.71	0.94				
Irritable	0.04	-0.80	0.88	0.93				
Anxious	0.04	-0.80	0.88	0.93				
BDI	0.38	-0.11	0.86	0.12				

Traditional risk factors and variables with p < 0.10 in univariate analysis were entered into the multivariate model.

BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure; BDI, Beck Depression Inventory.

3.2. Affective temperaments and the presence of significant coronary stenosis

In total, our sub-study population consisted of 225 patients undergoing clinically indicated CCTA at the Heart and Vascular Center of Semmelweis University. The age of our cohort was 58.5 years on average, approximately half of the cohort (46.7 %) were female and had dyslipidemia (52.0 %). Images were evaluated by experienced readers with 5-10 years of experience in cardiac CT. Severe CAD was defined as the presence of significant luminal diameter stenosis (≥ 70 % or ≥ 50 % in case of left main coronary artery) in ≥ 1 major coronary artery, as seen on Figure 2. Major coronary arteries included the left main, the left anterior descending, the left circumflex and the right coronary artery, as well as major side branches with a > 2 mm luminal diameter. In total, 41 patients presented with severe CAD (18.2 %). When comparing patients with and without significant stenosis, the mean age of patients with severe CAD was significantly higher: 63.0 ± 9.9 vs. 57.5 ± 12.4 years ($p = 0.03$). The proportion of women was significantly lower in those with severe CAD (36.6 %) vs. those without significant coronary artery stenosis (49.5 %) ($p < 0.001$). Among traditional risk factors, the prevalence of diabetes [29.3 % vs. 13.6 % ($p = 0.01$)] and dyslipidemia [78.0 % vs. 46.7 % ($p < 0.001$)] was significantly higher in the severe CAD group. However, no statistically significant association could be noted regarding psychometric parameters.

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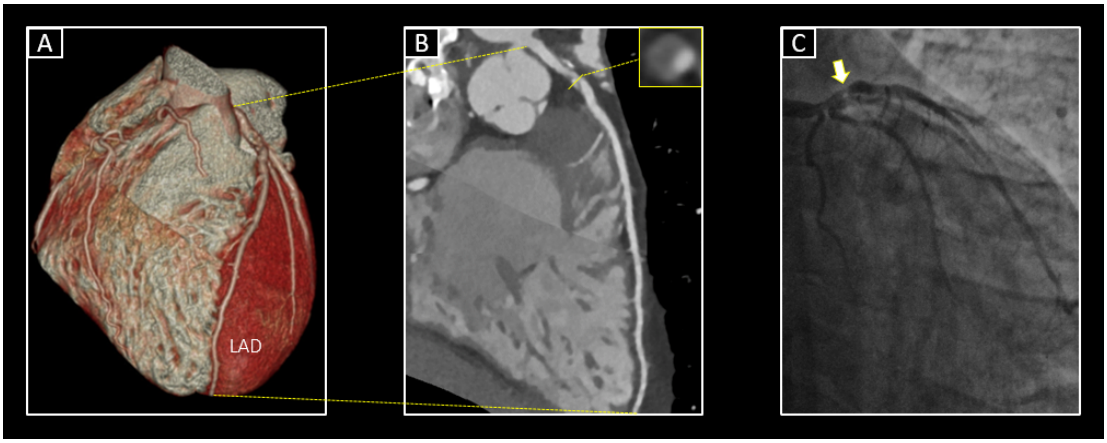

Figure 2. *(A) Representative 3D volumetric image of a 44-year-old male patient with marked cyclothymic traits (cyclothymic score: 12) presenting with typical angina. (B) Curved multiplanar reconstruction and cross-sectional image of the LAD shows a significant stenosis on the proximal segment. (C) Invasive coronary angiography confirmed the presence of severe stenosis and the subsequent need for percutaneous coronary intervention.*

Abbreviations: LAD, Left Anterior Descending Artery.

Logistic regression analysis was used to assess the determinants of severe CAD. Given that age and sex are documented and widely accepted predictors of CAD, our first model was primarily adjusted for these factors. Traditional risk factors and those psychometric parameters that had a $p < 0.10$ value in Model I were entered into further multivariate logistic models to assess independent association with severe CAD. Since a high degree of intercorrelation is existent between affective temperaments, affective temperaments were fit into the multiple regression analyses separately (Model II and Model III). In our logistic regression model, the traditional risk factor dyslipidemia and cyclothymic temperament were both associated with the presence of significant luminal stenosis. Multivariate analysis confirmed the independently predictive nature of both dyslipidemia [odds ratio (OR) = 4.73 CI: 1.95–11.49, $p < 0.001$] and cyclothymic affective temperament (OR = 1.12 CI: 1.02–1.23, $p = 0.02$), while hyperthymic temperament (OR = 0.91 CI: 0.83–0.96, $p = 0.04$) was associated with a significantly decreased odds of severe CAD. Table 4 details the results of the multivariate logistic regression analyses.

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Table 4. Uni- and multivariate logistic regression analysis of affective temperaments, cardiovascular risk factors and severe coronary artery disease, adjusted for age and sex.

	Model I.			Model II.		
	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p
BMI (kg/m^2)	1.01	0.95-1.08	0.75	0.99	0.91-1.07	0.75
Current smoker	1.62	0.59-4.47	0.35	2.03	0.67-6.11	0.21
Hypertension	0.89	0.38-2.06	0.79	0.59	0.21-1.64	0.31
Diabetes	1.95	0.85-4.47	0.10	1.50	0.57-3.95	0.41
Dyslipidemia	***3.81***	***1.69-8.58***	***0.001***	***5.36***	***2.16-13.28***	***<0.001***
PTP	***1.08***	***1.00-1.16***	***0.045***	***1.10***	***1.01-1.19***	***0.03***
Depressive	1.08	0.96-1.22	0.18			
Cyclothymic	***1.10***	***1.01-1.20***	***0.03***	***1.12***	***1.02-1.23***	***0.02***
Hyperthymic	0.92	0.85-1.00	0.053			
Irritable	1.06	0.96-1.18	0.26			
Anxious	1.03	0.97-1.11	0.32			
BDI	1.03	0.97-1.09	0.31			

	Model III.		
	OR	95% CI, lower-upper	p
BMI (kg/m^2)	0.96	0.92-1.08	0.91
Current smoker	2.19	0.72-6.60	0.17

Hypertension	0.59	0.21-1.66	0.32
Diabetes	1.57	0.61-4.06	0.35
Dyslipidemia	***4.73***	***1.95-11.49***	***<0.001***
PTP	***1.09***	***1.00-1.18***	***0.04***
Depressive			
Cyclothymic			
Hyperthymic	***0.91***	***0.83-0.96***	***0.04***
Irritable			
Anxious			
BDI			

Model I: traditional risk factors and psychometric parameters, primarily adjusted for age and gender; Model II and Model III: multivariate analyses including traditional risk factors and each temperament score with $p < 0.10$ in Model I.
BMI, Body mass index; PTP, pretest probability; BDI, Beck Depression Inventory.

3.3. Affective temperaments and the presence of left ventricular hypertrophy

Among a series of 382 consecutive patients who underwent CCTA in the inclusion period, we excluded 1) 27 patients because of prior AMI/PCI, 2) 19 patients due to severe comorbidity, 3) 2 patients because of inadequate CTA image quality, and 4) 38 patients due to the presence of severe coronary artery stenosis. Overall, 296 patients met the inclusion criteria of the current study. LV measurements were performed by an experienced reader with 4 years of experience in CCTA, while a second CV radiologist (with 6 years of experience in CCTA) subsequently re-evaluated 10 datasets to measure reproducibility. Myocardial mass was quantified in a semi-automated fashion (Simpson method) and LVM was indexed by the body surface area to acquire LVMi (Figure 3). Previously documented CTA-derived reference values were used to define LVH (men: ≥

67.2 g/m^2, women: ≥ 54.7 g/m^2). Given that CCTA displays a tendency to overestimate LVM compared to echocardiography (58), we applied cut-off values that were specifically determined for CTA-derived measurements (59). The prevalence of LVH in the enrolled 296 patients (44.9 % female; mean age 59.4 ± 10.6 years) was 35.7 % (76/296). The mean age of patients proved to be significantly lower in the LVH group: 55.9 ± 10.8 vs. 60.9 ± 10.3 years, ($p = 0.01$). Regarding patient anthropometrics, both body mass index (BMI) [30.3 ± 4.4 vs. 28.8 ± 3.9 kg/m^2, ($p = 0.005$)] and body surface area (BSA) [2.2 ± 0.3 vs. 1.9 ± 0.2 m^2, ($p < 0.001$)] were significantly higher in the LVH group. As expected, a substantial difference in LVMi could be observed between the LVH and healthy group: 70.3 (62.5 - 76.8) vs. 53.4 (46.1 - 61.3) g/m^2, ($p < 0.001$). Regarding psychometric parameters, no measures were statistically different between the two groups. Overall, more than 67 % of the hypertensive patients received a beta blocker regularly, while approximately half of them were on ACE-inhibitor. The proportion of patients regularly taking angiotensin receptor blockers was higher in patients with LVH: 70 (30.8 %) vs. 35 (46.1 %), $p = 0.04$.

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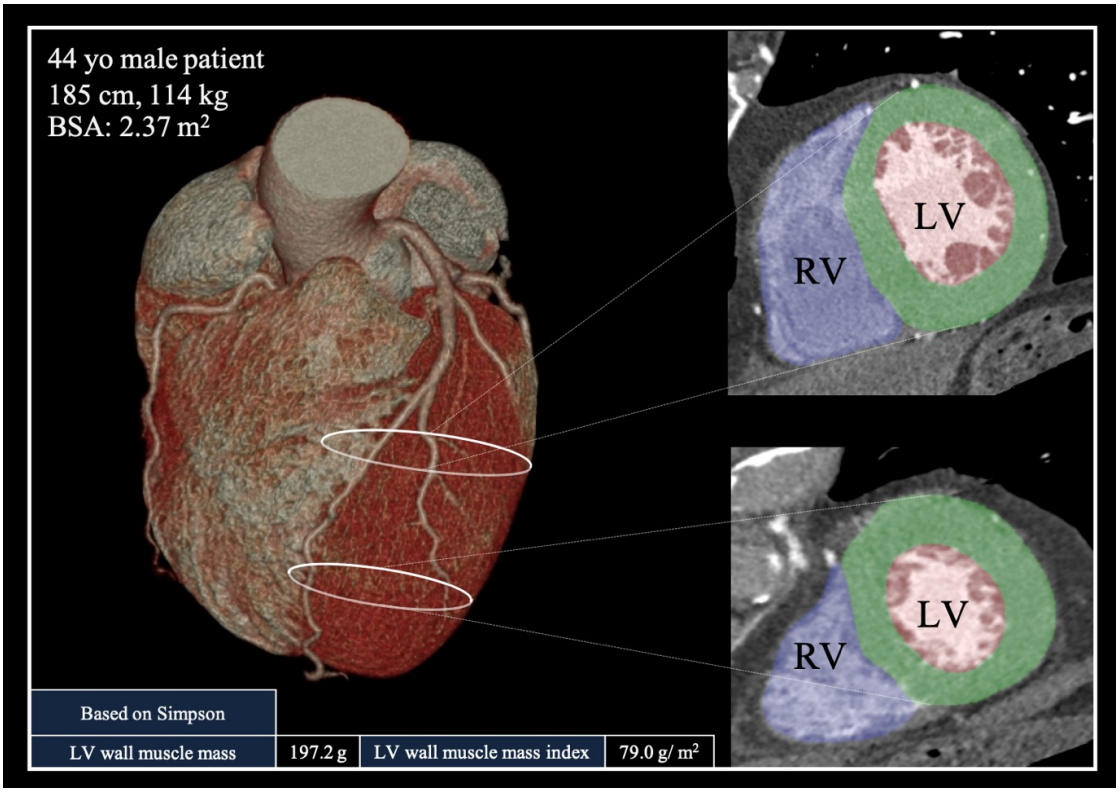

Figure 3. *Representative image of LV hypertrophy in a 44-year-old male patient with hypertension, as assessed by CCTA. Myocardial segmentation on short axis series was performed in a semiautomatic fashion. LV mass was measured in end-diastole by tracing the ventricular cavity and myocardium.*

Abbreviations: LV, left ventricle; RV, right ventricle; CCTA, coronary computed tomography angiography.

It has been proposed that CCTA could perform LV measurements with excellent inter-reader correlation (60) and our results confirmed this previous proposal. Inter-observer variability of LVM measurements was currently characterized by intraclass correlation coefficient (ICC), which demonstrated excellent reproducibility (ICC: 0.91) based on the re-evaluation of 10 CTA datasets.

Uni- and multivariate logistic regression analyses were used to determine predictors of elevated LVM. Assessment of patient baseline data demonstrated that BMI increased the odds of hypertrophy (OR = 1.07 CI: 1.02–1.13, p = 0.01), while age was inversely associated with the presence of LVH (OR = 0.97 CI: 0.94–0.99, p = 0.01). Antihypertensive agents and variables with $p < 0.10$ in univariate analysis were entered into the multivariate model.

While BMI remained independently predictive in a multivariate setting (OR = 1.04 CI: 1.01–1.10, p = 0.04), none of the regularly prescribed antihypertensive agents correlated significantly with the presence of LVH. Moreover, cyclothymic affective temperament was a further independent predictor of LVH in the multivariate analysis (OR = 1.06 CI: 1.00–1.12, p = 0.04). Overall, a 1-point higher cyclothymic affective temperament score resulted in a 6 % increase in the odds of LVH. Table 5 summarizes the results of the multiple regression analyses.

Table 5. Uni- and multivariate logistic regression analysis of the association of cardiovascular risk factors, affective temperaments, and left ventricular hypertrophy.

	Univariate			Multivariate		
	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p
Age (years)	***0.97***	***0.94 – 0.99***	***0.01***	1.00	0.95 – 1.01	0.11
Female sex	0.61	0.36 – 1.03	0.07	0.77	0.41 – 1.35	0.38
BMI (kg/m^2)	***1.07***	***1.02 – 1.13***	***0.01***	***1.04***	***1.01 – 1.10***	***0.04***
Duration of hypertension, (years)	1.00	0.98 – 1.03	0.86			
Number of antihypertensive agents, n (%)	1.23	0.92 – 1.63	0.16			
ACE/ARB	2.50	0.73 – 8.63	0.15	2.12	0.60 – 7.50	0.24
Beta blocker	1.03	0.48 – 2.18	0.63	1.01	0.46 – 2.18	0.99
Calcium channel blocker	0.83	0.39 – 1.75	0.83	0.76	0.35 – 1.65	0.50
Diuretic	1.81	0.89 – 3.69	0.10	1.62	0.77 – 3.39	0.20

Alpha-adrenergic receptor blocker	2.08	0.80 – 5.36	0.13	1.77	0.67 – 4.68	0.25
Current smoker	0.67	0.29 – 1.52	0.33			
Diabetes	1.50	0.76 – 2.96	0.24			
Dyslipidemia	0.83	0.49 – 1.40	0.48			
SSS	0.99	0.93 – 1.05	0.68			
SIS	0.97	0.89 – 1.07	0.59			
Depressive	0.97	0.89 – 1.06	0.54			
Cyclothymic	1.06	0.99 – 1.12	0.09	***1.06***	***1.00 – 1.12***	***0.04***
Hyperthymic	1.06	1.00 – 1.13	0.07	1.04	0.98 – 1.15	0.12
Irritable	1.04	0.96 – 1.13	0.33			
Anxious	0.96	0.91 – 1.01	0.10			

Antihypertensive agents and variables with $p < 0.10$ in univariate analysis were entered into the multivariate model.

BMI, Body mass index; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; SSS, Segment stenosis score; SIS, Segment involvement score.

4. DISCUSSION

In our cross-sectional studies investigating the association of affective temperaments and cardiovascular diseases, three major findings have been underlined. A significant association was demonstrated between cyclothymic temperament and accelerated vascular aging in women with low- to intermediate CV risk. Furthermore, aside from traditional CV risk factors, cyclothymic and hyperthymic temperaments predicted the presence of severe CAD in patients referred for CCTA, while cyclothymic temperament also proved to be an independent predictor of LVH in chronic hypertensive patients. Our results further expand the already available evidence regarding the involvement of subclinical, trait-related characteristics in somatic diseases and CV illnesses, in particular.

4.1. THE ROLE OF CORONARY CT ANGIOGRAPHY

Due to its outstanding negative predictive value, CCTA has emerged as a compelling alternative to ICA (61). Importantly, CCTA may rule out obstructive CAD in a non-invasive setting with a low risk of adverse events (28). Besides the ability to accurately visualize coronary lumen and wall, CCTA also allows precise LVM measurements (62). Traditionally, cardiac MRI has been considered the gold-standard for the quantification of LV volume and mass (63). Despite prevailing concerns regarding the requirement of both contrast and radiation (64), previous studies have suggested that CCTA has the potential of performing LV measurements with excellent inter-reader reproducibility (60), a finding that we were also able to demonstrate in our study.

4.2. PSYCHIATRIC ASPECTS OF CARDIOVASCULAR DISEASE

Although conventional modifiable and non-modifiable risk factors of CV disease have extensively been studied to date and incorporated into CV risk estimator models, it has generally been recognized in the past decades that the initiation, course and clinical outcome of CV diseases is substantially affected by psychosocial factors, as well. Personality traits and mental state influence the development and course of cardiovascular disease in complex ways. Cynical hostility is associated with elevated circulating levels

of inflammatory markers, such as tumor necrosis factor-alpha, interleukin-6 and C-reactive protein (65). This is a possible mechanism through which certain personality traits may exert their negative CV risk-enhancing effects. Adjusted for traditional cardiovascular risk factors, hostility, anger and anxiety - traits that frequently co-occur on an individual level - were found to be significant predictors of coronary heart disease (66). Similar associations were described in a Middle-Eastern study, which described the relationship of type-A personality and CAD and the incidence of acute myocardial infarction. Individuals with pronounced type-A traits were also more likely to suffer from diabetes and hypertension compared to the control group (67). On the other hand, it is widely accepted that manifest affective disorders also impact the development and effect of CV diseases. Mild depressive symptoms are documented to increase CV risk even without diagnosed major affective disorder, while patients with diagnosed depression face a two-fold increase regarding CV mortality (68, 69). In patients with documented acute myocardial infarction, a 1.4-fold relative risk increase for adverse cardiac events was observed in those with diagnosed anxiety disorder (70). Furthermore, depression and anxiety disorders are associated with a significantly increased odds of CAD and cardiac mortality (71, 72). Our results provide further evidence on the deleterious role of psychometric parameters on CV pathology, also shedding light on the detrimental role of affective temperaments.

4.3. THE THEORETICAL GROUNDS OF AFFECTIVE TEMPERAMENTS

The initially constructed models of affective temperaments were composed based on the healthy personality. The insight to the development, manifestations and clinical impact of affective temperaments, on the other hand, was provided by longitudinal data acquired from affective disorder patients and their healthy first-degree relatives (73). The five subscales of temperaments have traditionally been referred to as cyclothymic, hyperthymic, irritable, anxious and depressive. In brief, cyclothymic temperament is characterized by frequent alternations between mood polarities and instability of self-esteem and energy. Hyperthymic temperament incorporates optimistic, upbeat and overenergetic traits. Irritable temperament is best described by vehement behavior and a predisposition to being litigious in response to encountered stimuli. Anxious temperament

is characterized by a tendency to brooding and hypersensitivity to separation, while depressive temperament includes frequent worrying, low levels of energy and pessimistic attributes (4, 5, 74).

4.4. Temperaments and predispositions to affective disorders

The link between affective temperaments and psychopathology has extensively been documented in literature. Previous investigations implied a common genetic background for hyperthymic temperament and the pathogenesis of bipolar I disorder and as compared to healthy controls, patients with documented suicidal attempts demonstrated significantly higher hyperthymic scores (75). Cyclothymic temperament, in particular, is considered to be the precursor of bipolar disorders and is well-documented to be the most marked affective temperament trait in type II bipolar patients (76, 77). Cyclothymic traits are regarded to lie on a polygenic continuum between excessive temperament and bipolar disorder (78). Cyclothymic temperament contributes to suicidal behavior of patients independent of current major depressive episode (79). Moreover, the manifestation of unipolar depression shares common traits with individuals who express more pronounced depressive temperament scores (80).

4.5. Psychosomatic implications of affective temperaments

Apart from its well-documented role in psychopathology, however, the deleterious role of affective temperaments extends far beyond the field of psychiatry, as cumulating evidence suggests their pathoplastic impact on a broad array of somatic diseases. Temperaments have been measured in a wide array of different populations, emphasizing their importance in the therapeutic adherence of diabetic individuals, the development of gestational hypertension and some aggravating factors of psoriasis also seem to be associated with particular temperamental traits (81–83). Furthermore, some important implications have been proposed on the impact of temperaments on inflammatory bowel disease, polycystic ovary syndrome, allergic rhinitis and myofascial pain syndrome, as well (84–87).

On the other hand, several previous investigations have addressed the potential role of affective temperament on cardiovascular pathology. Cyclothymic, irritable and hyperthymic temperaments, in particular, have emerged as valuable tools in establishing the risk components of developing particular CV diseases. We have recently discovered the association between cyclothymic temperament and the earlier manifestation of hypertension and in hypertensive patients, the marked expression of cyclothymic temperament correlated with the history of coronary events (88, 89). According to our results, it seems plausible that cyclothymic temperament may carry significance in the context of coronary atherosclerosis and hypertensive end-organ damage, as well. Regarding irritable temperament, we have previously reported the significant correlation between irritable temperament and nighttime peripheral and central systolic blood pressure values (90). Although these factors may contribute to the pathogenesis of atherosclerosis and other manifestations of end-organ damage, irritable temperament demonstrated no significant associations in multivariate analyses, suggesting that its impact may be mediated through conventional CV risk factors. The evaluation of hyperthymic temperament has also demonstrated promising results in the context of CV pathology, as its score measured by TEMPS-A demonstrated a positive association with a reliable indicator of arterial stiffness (augmentation index) and we have also previously provided data about its inverse relation with the presence of coronary atherosclerosis (13, 91). The protective role of hyperthymic temperament on CV pathology is further underlined by our current findings. The evidence provided in the current studies expand our insight on the pathoplastic role of affective temperaments on cardiovascular pathology, while also emphasizing sex-related differences. Sex differences in the context of cardiovascular pathology and personality traits have already been established in literature. Elucidation of the underlying pathophysiology in the context of affective temperaments requires further investigation, including analysis of other factors such as menopausal status or the regular administration of hormonal contraception.

4.6. Potential underlying mediators behind the impact of temperaments

It can be hypothesized that the detrimental effect of cyclothymic temperament on cardiovascular pathology is expressed through various mediating factors, however, these

constellations have not been delineated entirely. It has been proposed previously that cyclothymic temperament may be associated with more unfavorable phenotypes of hypertension as cyclothymic scores were elevated in patients with resistant hypertension but it may also be presumed that the frequent endo-reactive shifts of patients with pronounced cyclothymic traits influence the BP and blood sugar values substantially, potentially rendering office measurements unreliable (14). It has further been documented that cyclothymic temperament precipitates poorer medication adherence in patients with type II diabetes and it is highly conceivable that similar tendencies exist for other chronically treated CV diseases, as well, such as for hypertension and dyslipidemia (92). Another potential explanation for our findings is the association of cyclothymic temperament with modifiable cardiovascular risk factors. The prevalence of obesity, smoking and alcohol dependence are all higher in patients with marked cyclothymic scores (50, 93, 94). Moreover, cyclothymic and irritable temperaments correlate substantially and share numerous common traits (95). Anger and hostility are considered main characteristics of irritable affective temperament (96). In individuals with marked hostility, increased catecholamine and cortisol secretion have been measured in response to anger-inducing stimuli, with elevated levels of cortisol also observed during daily activities (97). In young healthy adults, the high frequency component of the diurnal physiological variability of heart rate, which is regulated by the parasympathetic system, showed an inverse relationship with hostility (98). These findings suggest an overactivity of the sympathetic system in hostility, which may also lead to adverse effects, but the relationship of cyclothymic temperament in this regard is not clear yet.

As for hyperthymic temperament, it has been established before that patients with marked hyperthymic traits engage in sports and leisure activities more frequently, which might explain its protective role in CV diseases, as these factors are not incorporated into currently applied pretest probability models, however, the mediating factors need to be explored in future investigations (99). In addition to the association with risk factors, the direct impact of hyperthymic temperament on pathophysiological processes may also explain our findings. In chronic hypertensive patients, serum levels of neuroprotective BDNF were found to be elevated in subjects with marked hyperthymic traits, an association that was not prevalent in patients without treated hypertension (1). All things

considered, it cannot be safely excluded that temperaments express their impact through more direct, not yet discovered biomolecular pathways.

The assessment of affective temperaments is a low-cost, easy-to-apply method and it seems plausible that reporting temperament scores on patient medical records could assist primary care physicians by drawing attention to patients with potentially inadequate therapeutic compliance and by facilitating the timely identification of consequent end-organ damage. Patients with more pronounced cyclothymic traits may require more frequently scheduled follow-ups and their treatment may necessitate stricter target values set for BP, cholesterol and Hemoglobin A1C levels. The TEMPS-A evaluation can also function as a gatekeeper for seeking professional mental health support, as referral of patients with severe manifestation of cyclothymic traits to a specialist could significantly increase their chance of improving self-care attitude provided there is an underlying affective disorder. In spite of their apparent role in increasing the precision of risk estimation by personality-based screening, future efforts should be made to identify the biological, behavioral and cognitive-emotional mediating factors of affective temperaments.

4.7. LIMITATIONS

We acknowledge that there are limitations pertaining to the current studies. The cross-sectional design precludes causal inference. Considering the self-reporting nature of the autoquestionnaire, a complete exclusion of misinterpretations or mistakes by patients is impossible even after the exclusion of individuals with dementia. Furthermore, generalizability of our results is limited by the fact that only low to intermediate risk patients with stable angina were enrolled. Since race-specific differences are well-documented in the pattern of affective temperaments, the fact that all of the enrolled patients were Caucasian is a shortcoming. Finally, it has to be noted that the lack of information about compliance of patients and their laboratory parameters is an important limitation.

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5. CONCLUSIONS

Our findings demonstrated that aside from conventional CV risk factors, affective temperaments independently predict a number of cardiovascular diseases. Temperaments yield implications in both accelerated vascular aging and the presence of severe CAD, as well as having a significant association with the presence of LVH in chronic hypertensive patients. Our results provide further evidence on the detrimental role of psychometric parameters on CV disease and establish novel potential risk factors for CV pathologies. Provided that prospective investigations confirm their utility in clinical practice, affective temperaments might add incremental value to the CV risk stratification of patients and emerge as novel tools that aid the identification of patients with elevated CV risk as potential targets for earlier and more aggressive primary intervention. The delineation of the pathophysiological background of the current findings remains a topic of focus and identifying the factors potentially mediating the effect of affective temperaments in CV pathology requires further prospective studies.

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6. SUMMARY

Despite the fact that psychometric parameters may add incremental value to cardiovascular (CV) risk stratification of patients, aspects of personality and temperament have not been incorporated to contemporary risk models. Affective temperaments are considered to constitute the heritable component of personality. The relationship of temperaments and affective disorders has been widely documented, as Akiskal has conceptualized a spectrum of affective conditions, ranging from temperaments to manifest mood disorders, however, their impact on somatic diseases has also been implied before. The objective of our investigations was to assess the relationship of temperaments and various CV disorders, assessed by coronary CT angiography (CCTA).

In addition to previously documented associations, we have provided novel evidence to the deleterious role of affective temperaments in CV pathology. Cyclothymic temperament, in particular, may yield emphasized importance in the relation of CV disease, as the detrimental role of cyclothymic temperament was documented on accelerated vascular aging, the presence of severe coronary artery disease and left ventricular hypertrophy in our cohort. We also found that hyperthymic affective temperament may have implications in the presence of severe CAD, which extends our knowledge on the protective role of hyperthymic temperament on psychosomatic conditions. It seems plausible that these trait-related characteristics independently predict the presence of several adverse CV conditions and their assessment may aid the identification patient with elevated CV risk.

In conclusion, affective temperaments – cyclothymic, in particular – may emerge as novel risk factors for a number of CV diseases. Besides the role of affective temperaments as a gatekeeper for the referral of patients to mental health professionals, these psychosomatic relations should not be ignored. Whether these documented associations are due to endo-reactive dissonances, inadequate therapeutic adherence or other lifestyle-associated discrepancies remain a topic of discussion and future prospective studies should focus on the biological, behavioral and cognitive-emotional background of these associations to achieve a more efficient personality-based screening of patients.

7. REFERENCES

1. Nemcsik J, László A, Lénárt L, Eörsi D, Torzsa P, Korösi B, Cseprekál O, Tislér A, Tabák Á, Gonda X, Rihmer Z, Hodrea J, Nemcsik-Bencze Z, Fekete A. (2016) Hyperthymic affective temperament and hypertension are independent determinants of serum brain-derived neurotrophic factor level. Ann Gen Psychiatry, 15. doi:10.1186/s12991-016-0104-4

2. László A, Tabák Á, Korösi B, Eörsi D, Torzsa P, Cseprekál O, Tislér A, Reusz G, Nemcsik-Bencze Z, Gonda X, Rihmer Z, Nemcsik J. (2016) Association of affective temperaments with blood pressure and arterial stiffness in hypertensive patients: A cross-sectional study. BMC Cardiovasc Disord, 16: 1–10.

3. Rihmer Z, Akiskal KK, Rihmer A, Akiskal HS. (2010) Current research on affective temperaments. Curr Opin Psychiatry, 23: 12–18.

4. Akiskal KK, Akiskal HS. (2005) The theoretical underpinnings of affective temperaments: Implications for evolutionary foundations of bipolar disorder and human nature. J Affect Disord, 85: 231–239.

5. Akiskal HS, Akiskal KK, Haykal RF, Manning JS, Connor PD. (2005) TEMPS-A: Progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. J Affect Disord, 85: 3–16.

6. Vázquez GH, Tondo L, Mazzarini L, Gonda X. (2012) Affective temperaments in general population : A review and combined analysis from national studies. J Affect Disord, 139: 18–22.

7. Előry A, Gonda X, Torzsa P, Kalabay L, Rihmer Z. (2011) Affective temperaments: from neurobiological roots to clinical application. Orv Hetil, 152: 1879–1886.

8. Kawamura Y, Akiyama T, Shimada T, Minato T, Umekage T, Noda Y, Ukawa K, Hashidume C, Sakai Y, Otowa T, Sasaki T, Akiskal HS. (2010) Six-Year Stability of Affective Temperaments as Measured by TEMPS-A. Psychopathology, 43: 240–247.

9. H. Vazquez G, Gonda X. (2013) Affective Temperaments and Mood Disorders: A Review of Current Knowledge. Curr Psychiatry Rev, 9: 21–32.

10. Perugi G, Toni C, Maremmani I, Tusini G, Ramacciotti S, Madia A, Fornaro M, Akiskal HS. (2012) The influence of affective temperaments and psychopathological traits on the definition of bipolar disorder subtypes: A study on Bipolar i Italian National sample. J Affect Disord, 136. doi:10.1016/j.jad.2009.12.027

11. Baldessarini RJ, Innamorati M, Erbuto D, Serafini G, Fiorillo A, Amore M, Girardi P, Pompili M. (2017) Differential associations of affective temperaments and diagnosis of major affective disorders with suicidal behavior. J Affect Disord, 210: 19–21.

12. Pompili M, Rihmer Z, Akiskal H, Amore M, Gonda X, Innamorati M, Lester D, Perugi G, Serafini G, Telesforo L, Tatarelli R, Girardi P. (2012) Temperaments mediate suicide risk and psychopathology among patients with bipolar disorders. Compr Psychiatry, 53: 280–285.

13. Laszlo A, Tabak A, Korosi B, Eorsi D, Torzsa P, Cseprekal O, Tisler A, Reusz G, Nemcsik-Bencze Z, Gonda X, Rihmer Z, Nemcsik J. (2016) Association of affective temperaments with blood pressure and arterial stiffness in hypertensive patients: a cross-sectional study. BMC Cardiovasc Disord, 16: 158.

14. Kőrösi B, Gyöngyösi H, Batta D, László A, Kovács I, Tislér A, Cseprekál O, Nemcsik-Bencze Z, Gonda X, Rihmer Z, Nemcsik J. (2020) Evaluation of affective temperaments and arterial stiffness in different hypertension phenotypes. Hypertens Res,. doi:10.1038/s41440-020-0513-2

15. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. (2018)Lancet (London, England), 392: 1736–1788.

16. Townsend N, Kazakiewicz D, Lucy Wright F, Timmis A, Huculeci R, Torbica A, Gale CP, Achenbach S, Weidinger F, Vardas P. (2022) Epidemiology of cardiovascular disease in Europe. Nat Rev Cardiol, 19: 133–143.

17. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Jarlais DCD, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FGR, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang Y, Khatibzadeh S, Khoo J, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Hanafiah KM, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CDH, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJC, Steenland K, Stöckl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Dingenen RV, Donkelaar AV, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJL, Ezzati M, AlMazroa MA, Memish ZA. (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters

in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet, 380: 2224–2260.

18. Paneni F, Diaz Cañestro C, Libby P, Lüscher TF, Camici GG. (2017) The Aging Cardiovascular System: Understanding It at the Cellular and Clinical Levels. J Am Coll Cardiol, 69: 1952–1967.

19. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andrés V. (2020) Biological Versus Chronological Aging: JACC Focus Seminar. J Am Coll Cardiol, 75: 919–930.

20. Nilsson P. (2008) Early vascular aging (EVA): consequences and prevention. Vasc Health Risk Manag, Volume 4: 547–552.

21. Stein JH, Fraizer MC, Aeschlimann SE, Nelson-Worel J, McBride PE, Douglas PS. (2004) Vascular age: Integrating carotid intima-media thickness measurements with global coronary risk assessment. Clin Cardiol, 27: 388–392.

22. Mattace-Raso FUS, Van Der Cammen TJM, Hofman A, Van Popele NM, Bos ML, Schalekamp MADH, Asmar R, Reneman RS, Hoeks APG, Breteler MMB, Witteman JCM. (2006) Arterial stiffness and risk of coronary heart disease and stroke: The Rotterdam Study. Circulation, 113: 657–663.

23. Schisterman EF, Whitcomb BW. (2004) Coronary age as a risk factor in the modified Framingham risk score. BMC Med Imaging, 4. doi:10.1186/1471-2342-4-1

24. Nasir K, Vasamreddy C, Blumenthal RS, Rumberger JA. (2006) Comprehensive coronary risk determination in primary prevention: An imaging and clinical based definition combining computed tomographic coronary artery calcium score and national cholesterol education program risk score. Int J Cardiol, 110: 129–136.

25. McClelland RL, Nasir K, Budoff M, Blumenthal RS, Kronmal RA. (2009) Arterial Age as a Function of Coronary Artery Calcium (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol, 103: 59–63.

26. Bauersachs R, Zeymer U, Brière J-B, Marre C, Bowrin K, Huelsebeck M. (2019)

Burden of Coronary Artery Disease and Peripheral Artery Disease: A Literature Review. Cardiovasc Ther, 2019: 8295054.

27. Lagerweij GR, De Wit GA, Moons KGM, Van Der Schouw YT, Monique Verschuren WM, Dorresteijn JAN, Koffijberg H. (2018) A new selection method to increase the health benefits of CVD prevention strategies. Eur J Prev Cardiol, 25: 642–650.

28. Maurovich-Horvat P, Bosserdt M, Kofoed KF, Rieckmann N, Benedek T, Donnelly P, Rodriguez-Palomares J, Erglis A, Štěchovský C, Šakalyte G, Čemerlić Adić N, Gutberlet M, Dodd JD, Diez I, Davis G, Zimmermann E, Kępka C, Vidakovic R, Francone M, Ilnicka-Suckiel M, Plank F, Knuuti J, Faria R, Schröder S, Berry C, Saba L, Ruzsics B, Kubiak C, Gutierrez-Ibarluzea I, Hansen KS, Müller-Nordhorn J, Merkely B, Knudsen AD, Benedek I, Orr C, Valente FX, Zvaigzne L, Suchánek V, Zajančkauskiene L, Adić F, Woinke M, Hensey M, Lecumberri I, Thwaite E, Laule M, Kruk M, Neskovic AN, Mancone M, Kuśmierz D, Feuchtner G, Pietilä M, Ribeiro VG, Drosch T, Delles C, Matta G, Fisher M, Szilveszter B, Larsen L, Ratiu M, Kelly S, Blanco BGD, Rubio A, Drobni ZD, Jurlander B, Rodean I, Regan S, Calabria HC, Boussoussou M, Engstrøm T, Hodas R, Napp AE, Haase R, Feger S, Serna-Higuita LM, Neumann K, Dreger H, Rief M, Wieske V, Estrella M, Martus P, Dewey M. (2022) CT or Invasive Coronary Angiography in Stable Chest Pain. N Engl J Med, 386: 1591–1602.

29. Celeng C, Takx RAP, Ferencik M, Maurovich-Horvat P. (2016) Non-invasive and invasive imaging of vulnerable coronary plaque. Trends Cardiovasc Med, 26: 538–547.

30. Chinnaiyan KM, Raff GL, Goraya T, Ananthasubramaniam K, Gallagher MJ, Abidov A, Boura JA, Share D, Peyser PA. (2012) Coronary computed tomography angiography after stress testing: Results from a multicenter, statewide registry, acic (advanced cardiovascular imaging consortium). J Am Coll Cardiol, 59: 688–695.

31. Marwick TH, Cho I, Ó Hartaigh B, Min JK. (2015) Finding the gatekeeper to the cardiac catheterization laboratory: Coronary CT angiography or stress testing? J Am Coll Cardiol, 65: 2747–2756.

32. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ. (2020) 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J, 41: 407–477.

33. Budoff, M.J., Shinbane JS. Cardiac CT Imaging, 2nd ed. Springer, London, 2010: 241–242.

34. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, Ezzati M. (2009) The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med, 6: e1000058.

35. Reuter H, Jordan J. (2019) Status of hypertension in Europe. Curr Opin Cardiol, 4: 342-349.

36. de Simone G, Gottdiener JS, Chinali M, Maurer MS. (2008) Left ventricular mass predicts heart failure not related to previous myocardial infarction: the Cardiovascular Health Study. Eur Heart J, 29: 741–747.

37. Heckbert SR, Post W, Pearson GDN, Arnett DK, Gomes AS, Jerosch-Herold M, Hundley WG, Lima JA, Bluemke DA. (2006) Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. J Am Coll Cardiol, 48: 2285–2292.

38. Milani R V, Lavie CJ, Mehra MR, Ventura HO, Kurtz JD, Messerli FH. (2006) Left ventricular geometry and survival in patients with normal left ventricular ejection fraction. Am J Cardiol, 97: 959–963.

39. Lavie CJ, Milani R V, Ventura HO, Messerli FH. (2006) Left ventricular geometry and mortality in patients >70 years of age with normal ejection fraction. Am J Cardiol, 98: 1396–1399.

40. Muiesan ML, Salvetti M, Paini A, Monteduro C, Galbassini G, Bonzi B, Poisa P, Belotti E, Agabiti Rosei C, Rizzoni D, Castellano M, Agabiti Rosei E. (2007) Inappropriate left ventricular mass changes during treatment adversely affects cardiovascular prognosis in hypertensive patients. Hypertens (Dallas, Tex 1979), 49: 1077–1083.

41. Turakhia MP, Schiller NB, Whooley MA. (2008) Prognostic significance of increased left ventricular mass index to mortality and sudden death in patients with stable coronary heart disease (from the Heart and Soul Study). Am J Cardiol, 102: 1131–1135.

42. Kishi S, Magalhaes TA, George RT, Dewey M, Laham RJ, Niinuma H, Friedman LA, Cox C, Tanami Y, Schuijf JD, Vavere AL, Kitagawa K, Chen MY, Nomura CH, Brinker JA, Rybicki FJ, Di Carli MF, Arbab-Zadeh A, Lima JAC. (2015) Relationship of left ventricular mass to coronary atherosclerosis and myocardial ischaemia: the CORE320 multicenter study. Eur Hear journal Cardiovasc Imaging, 16: 166–176.

43. Alkema M, Spitzer E, Soliman OII, Loewe C. (2016) Multimodality Imaging for Left Ventricular Hypertrophy Severity Grading: A Methodological Review. J Cardiovasc Ultrasound, 24: 257–267.

44. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, Gottdiener J, Haluska B, Ofili E, Segers P, Senior R, Tapp RJ, Zamorano JL. (2015) Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE)†. Eur Hear journal Cardiovasc Imaging, 16: 577–605.

45. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt J-U. (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr Off

Publ Am Soc Echocardiogr, 28: 1-39.e14.

46. Maurovich-Horvat P, Ferencik M, Voros S, Merkely B, Hoffmann U. (2014) Comprehensive plaque assessment by coronary CT angiography. Nat Rev Cardiol, 11: 390–402.

47. Mao SS, Li D, Rosenthal DG, Cerilles M, Zeb I, Wu H, Flores F, Gao Y, Budoff MJ. (2013) Dual-standard reference values of left ventricular volumetric parameters by multidetector CT angiography. J Cardiovasc Comput Tomogr, 7: 234–240.

48. Juneau D, Erthal F, Clarkin O, Alzahrani A, Alenazy A, Hossain A, Inacio JR, Dwivedi G, Dick AJ, Rybicki FJ, Chow BJW. (2017) Mid-diastolic left ventricular volume and mass: Normal values for coronary computed tomography angiography. J Cardiovasc Comput Tomogr, 11: 135–140.

49. László A, Babos L, Kis-Igari Z, Pálfy A, Torzsa P, Eory A, Kalabay L, Gonda X, Rihmer Z, Cseprekál O, Tislér A, Hodrea J, Lénárt L, Fekete A, Nemcsik J. (2015) Identification of hypertensive patients with dominant affective temperaments might improve the psychopathological and cardiovascular risk stratification: A pilot, case-control study. Ann Gen Psychiatry, 14: 1–8.

50. Amann B, Mergl R, Torrent C, Perugi G, Padberg F, El-Gjamal N, Laakmann G. (2009) Abnormal temperament in patients with morbid obesity seeking surgical treatment. J Affect Disord, 118: 155–160.

51. Eory A, Gonda X, Lang Z, Torzsa P, Kalman J, Kalabay L, Rihmer Z. (2014) Personality and cardiovascular risk: Association between hypertension and affective temperaments-A cross-sectional observational study in primary care settings. Eur J Gen Pract, 20: 247–252.

52. Gois C, Barbosa A, Ferro A, Santos AL, Sousa F, Akiskal H, Akiskal K, Figueira ML. (2011) The role of affective temperaments in metabolic control in patients with type 2 diabetes. J Affect Disord, 134: 52–58.

53. Vecsey-Nagy M, Szilveszter B, Kolossváry M, Boussoussou M, Vattay B, Gonda

X, Rihmer Z, Merkely B, Maurovich-Horvat P, Nemcsik J. (2021) The association between accelerated vascular aging and cyclothymic affective temperament in women. J Psychosom Res, 145: 110423.

54. Vecsey-Nagy M, Szilveszter B, Kolossváry M, Boussoussou M, Vattay B, Gonda X, Rihmer Z, Merkely B, Maurovich-Horvat P, Nemcsik J. (2021) Association between affective temperaments and severe coronary artery disease. J Affect Disord, 295: 914–919.

55. Vecsey-Nagy M, Szilveszter B, Kolossváry M, Boussoussou M, Vattay B, Gonda X, Rihmer Z, Merkely B, Maurovich-Horvat P, Nemcsik J. (2022) Cyclothymic affective temperament is independently associated with left ventricular hypertrophy in chronic hypertensive patients. J Psychosom Res, 160: 110988.

56. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. (1990) Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol, 15: 827–832.

57. Terentes-Printzios D, Vlachopoulos C, Xaplanteris P, Ioakeimidis N, Aznaouridis K, Baou K, Kardara D, Georgiopoulos G, Georgakopoulos C, Tousoulis D. (2017) Cardiovascular Risk Factors Accelerate Progression of Vascular Aging in the General Population: Results from the CRAVE Study (Cardiovascular Risk Factors Affecting Vascular Age). Hypertension, 70: 1057–1064.

58. Lee JW, Nam KJ, Kim JY, Jeong YJ, Lee G, Park SM, Lim SJ, Choo KS. (2020) Simultaneous Assessment of Left Ventricular Function and Coronary Artery Anatomy by Third-generation Dual-source Computed Tomography Using a Low Radiation Dose. J Cardiovasc imaging, 28: 21–32.

59. Mao SS, Li D, Rosenthal DG, Cerilles M, Zeb I, Wu H, Flores F, Gao Y, Budoff MJ. (2013) Dual-standard reference values of left ventricular volumetric parameters by multidetector CT angiography. J Cardiovasc Comput Tomogr, 7: 234–240.

60. Madaj PM, Pagali SR, Hamirani YS, Raina S, Nair S, Zeb I, Mao S, Budoff MJ. (2010) Coronary artery calcium and plaque association with left ventricular mass,

assessed by multi-row detector computed tomography. Coron Artery Dis, 21: 428–434.

61. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK. (2008) Diagnostic Performance of 64-Multidetector Row Coronary Computed Tomographic Angiography for Evaluation of Coronary Artery Stenosis in Individuals Without Known Coronary Artery Disease. Results From the Prospective Multicenter ACCURACY (Assessment by Coro. J Am Coll Cardiol, 52: 1724–1732.

62. Fuchs A, Mejdahl MR, Kühl JT, Stisen ZR, Nilsson EJP, Køber L V, Nordestgaard BG, Kofoed KF. (2016) Normal values of left ventricular mass and cardiac chamber volumes assessed by 320-detector computed tomography angiography in the Copenhagen General Population Study. Eur Hear journal Cardiovasc Imaging, 17: 1009–1017.

63. Nasir K, Katz R, Mao S, Takasu J, Bomma C, Lima JAC, Bluemke DA, Kronmal R, Carr JJ, Budoff MJ. (2008) Comparison of left ventricular size by computed tomography with magnetic resonance imaging measures of left ventricle mass and volumes: the multi-ethnic study of atherosclerosis. J Cardiovasc Comput Tomogr, 2: 141–148.

64. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, Pearson G, Sinha S, Arai A, Lima JAC, Bluemke DA. (2006) Cardiovascular function in multi-ethnic study of atherosclerosis: normal values by age, sex, and ethnicity. AJR Am J Roentgenol, 186: S357-65.

65. Boisclair Demarble J, Moskowitz DS, Tardif JC, D'Antono B. (2014) The relation between hostility and concurrent levels of inflammation is sex, age, and measure dependent. J Psychosom Res, 76: 384–393.

66. Boyle SH, Michalek JE, Suarez EC. (2006) Covariation of psychological attributes and incident coronary heart disease in U.S. Air Force veterans of the Vietnam war. Psychosom Med, 68: 844–850.

67. Jamil G, Haque A, Namawar A, Jamil M. (2013) „Personality traits and heart

disease in the Middle East“. Is there a link? Am J Cardiovasc Dis, 3: 163–9.

68. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W. (2001) Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry, 58: 221–7.

69. Rafanelli C, Sirri L, Grandi S, Fava GA. (2013) Is depression the wrong treatment target for improving outcome in coronary artery disease? Psychother Psychosom, 82: 285–291.

70. Roest AM, Martens EJ, Denollet J, De Jonge P. (2010) Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: A meta-analysis. Psychosom Med, 72: 563–569.

71. Lespérance F, Frasure-Smith N, Talajic M, Bourassa MG. (2002) Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation, 105: 1049–1053.

72. Janszky I, Ahnve S, Lundberg I, Hemmingsson T. (2010) Early-Onset Depression, Anxiety, and Risk of Subsequent Coronary Heart Disease. 37-Year Follow-Up of 49,321 Young Swedish Men. J Am Coll Cardiol, 56: 31–37.

73. Kesebir S, Vahip S, Akdeniz F, Yüncü Z, Alkan M, Akiskal H. (2005) Affective temperaments as measured by TEMPS-A in patients with bipolar I disorder and their first-degree relatives: a controlled study. J Affect Disord, 85: 127–133.

74. Rovai L, Maremmani AGI, Rugani F, Bacciardi S, Pacini M, Dell'osso L, Akiskal HS, Maremmani I. (2013) Do Akiskal & Mallya's affective temperaments belong to the domain of pathology or to that of normality? Eur Rev Med Pharmacol Sci, 17: 2065–2079.

75. Röttig D, Röttig S, Brieger P, Marneros A. (2007) Temperament and personality in bipolar I patients with and without mixed episodes. J Affect Disord, 104: 97–102.

76. Akiskal HS, Hantouche EG, Allilaire JF. (2003) Bipolar II with and without cyclothymic temperament: „dark“ and „sunny“ expressions of soft bipolarity. J

Affect Disord, 73: 49–57.

77. Ardani AR, Hosseini FF, Asadpour Z, Hashemian AM, Dadpour B, Nahidi M. (2017) Affective temperaments, as measured by TEMPS-A, among self-poisoning nonlethal suicide attempters. Psychiatry Res, 247: 125–129.

78. Akiskal HS, Djenderedjian AH, Rosenthal RH, Khani MK. (1977) Cyclothymic disorder: Validating criteria for inclusion in the bipolar affective group. Am J Psychiatry, 134: 1227–1233.

79. Hantouche EG, Akiskal HS, Lancrenon S, Allilaire JF, Sechter D, Azorin JM, Bourgeois M, Fraud JP, Châtenet-Duchêne L. (1998) Systematic clinical methodology for validating bipolar-II disorder: Data in mid-stream from a french national multi-site study (EPIDEP). J Affect Disord, 50: 163–173.

80. Akiskal HS, Akiskal K, Allilaire JF, Azorin JM, Bourgeois ML, Sechter D, Fraud JP, Chatenêt-Duchêne L, Lancrenon S, Perugi G, Hantouche EG. (2005) Validating affective temperaments in their subaffective and socially positive attributes: Psychometric, clinical and familial data from a French national study. J Affect Disord, 85: 29–36.

81. Shamsi A, Khodaifar F, Arzaghi SM, Sarvghadi F, Ghazi A. (2014) Is there any relationship between medication compliance and affective temperaments in patients with type 2 diabetes? J Diabetes Metab Disord, 13: 96.

82. Rezaei Ardani A, Tara F, Naghizadeh Kashani S, Hatami SB, Emadzadeh M, Nahidi M. (2020) Is gestational hypertension associated with affective temperaments? Hypertens pregnancy, 39: 159–164.

83. Kiliç a., Güleç MY, Gül Ü, Güleç H. (2008) Temperament and character profile of patients with psoriasis. J Eur Acad Dermatology Venereol, 22: 537–542.

84. Bieliński M, Lesiewska N, Bielińska J, Liebert A, Mieczkowski A, Sopońska-Brzoszczyk P, Brzoszczyk B, Kłopocka M, Borkowska A. (2018) Affective temperament in inflammatory bowel diseases: Another brick in the wall of differentiation. PLoS One, 13: e0205606.

85. Ozcan Dag Z, Alpua M, Isik Y, Buturak SV, Tulmac OB, Turkel Y. (2017) The evaluation of temperament and quality of life in patients with polycystic ovary syndrome. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol, 33: 250–253.

86. Tas HI, Caglar O. (2019) The role of anxious temperament in patients with allergic rhinitis. Saudi Med J, 40: 45–51.

87. Badil Güloğlu S, Tunç S. (2022) The assessment of affective temperament and life quality in myofascial pain syndrome patients. Int J Psychiatry Clin Pract, 26: 79–84.

88. Körösi B, Vecsey-Nagy M, Kolossváry M, Nemcsik-Bencze Z, Szilveszter B, László A, Batta D, Gonda X, Merkely B, Rihmer Z, Maurovich-Horvat P, Eörsi D, Torzsa P, Nemcsik J. (2019) Association between Cyclothymic Affective Temperament and Age of Onset of Hypertension. Int J Hypertens, 2019: 1–6.

89. Eory A, Rozsa S, Torzsa P, Kalabay L, Gonda X, Rihmer Z. (2014) Affective temperaments contribute to cardiac complications in hypertension independently of depression. Psychother Psychosom, 83: 187–189.

90. Kőrösi B, Batta D, Gonda X, Rihmer Z, Nemcsik-Bencze Z, László A, Vecsey-Nagy M, Nemcsik J. (2019) Association between Irritable Affective Temperament and Nighttime Peripheral and Central Systolic Blood Pressure in Hypertension. Artery Res, 25: 41.

91. Nemcsik J, Vecsey-Nagy M, Szilveszter B, Kolossváry M, Karády J, László A, Kőrösi B, Nemcsik-Bencze Z, Gonda X, Merkely B, Rihmer Z, Maurovich-Horvat P. (2017) Inverse association between hyperthymic affective temperament and coronary atherosclerosis: A coronary computed tomography angiography study. J Psychosom Res, 103: 108–112.

92. Yamamoto T, Sakurai K, Watanabe M, Sakuma I, Kanahara N, Shiina A, Hasegawa T, Watanabe H, Iyo M, Ishibashi R. (2021) Cyclothymic Temperament is Associated with Poor Medication Adherence and Disordered Eating in Type 2 Diabetes Patients: A Case-Control Study. Diabetes Ther Res Treat Educ diabetes Relat Disord, 12: 2611–2624.

93. Bisol LW, Soldado F, Albuquerque C, Lorenzi TM, Lara DR. (2010) Emotional and affective temperaments and cigarette smoking in a large sample. J Affect Disord, 127: 89–95.

94. Rovai L, Maremmani AGI, Bacciardi S, Gazzarrini D, Pallucchini A, Spera V, Perugi G, Maremmani I. (2017) Opposed effects of hyperthymic and cyclothymic temperament in substance use disorder (heroin- or alcohol-dependent patients). J Affect Disord, 218: 339–345.

95. Walsh MA, Brown LH, Barrantes-Vidal N, Kwapil TR. (2013) The expression of affective temperaments in daily life. J Affect Disord, 145: 179–186.

96. Suarez EC, Kuhn CM, Schanberg SM, Williams RB, Zimmermann EA. (1998) Neuroendocrine, cardiovascular, and emotional responses of hostile men: The role of interpersonal challenge. Psychosom Med, 60: 78–88.

97. Pope MK, Smith TW. (1991) Cortisol excretion in high and low cynically hostile men. In: Psychosomatic Medicine. Bd 53 S. 386–392

98. Sloan RP, Bagiella E, Shapiro PA, Kuhl JP, Chernikhova D, Berg J, Myers MM. (2001) Hostility, gender, and cardiac autonomic control. Psychosom Med, 63: 434–440.

99. Krumm-Merabet C, Meyer TD. (2005) Leisure activities, alcohol, and nicotine consumption in people with a hypomanic/hyperthymic temperament. Pers Individ Dif, 38: 701–712.

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8. BIBILIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

8.1. PUBLICATIONS RELATED TO THE PRESENT THESIS

1. **Vecsey-Nagy M**, Szilveszter B, Kolossváry M, Boussoussou M, Vattay B, Gonda X, Rihmer Z, Merkely B, Maurovich-Horvat P, Nemcsik J. (2021) The association between accelerated vascular aging and cyclothymic affective temperament in women. J Psychosom Res, 145: 110423. **(IF: 4.62)**

2. **Vecsey-Nagy M**, Szilveszter B, Kolossváry M, Boussoussou M, Vattay B, Gonda X, Rihmer Z, Merkely B, Maurovich-Horvat P, Nemcsik J. (2021) Association between affective temperaments and severe coronary artery disease. J Affect Disord, 295: 914–919. **(IF: 6.53)**

3. **Vecsey-Nagy M**, Szilveszter B, Kolossváry M, Boussoussou M, Vattay B, Gonda X, Rihmer Z, Merkely B, Maurovich-Horvat P, Nemcsik J. (2022) Cyclothymic affective temperament is independently associated with left ventricular hypertrophy in chronic hypertensive patients. J Psychosom Res, 160: 110988. **(IF: 4.62)**

8.2. PUBLICATIONS NOT RELATED TO THE PRESENT THESIS

1. Szilveszter B, Kolossváry M, Karády J, Jermendy ÁL, Károlyi M, Panajotu A, Bagyura Z, **Vecsey-Nagy M**, Cury RC, Leipsic JA, Merkely B, Maurovich-Horvat P. (2017) Structured reporting platform improves CAD-RADS assessment. J Cardiovasc Comput Tomogr, 11: 449–454. **(IF: 3.10)**

2. **Vecsey-Nagy M**, Jermendy Á, Szabó G, Benke K, Szabolcs Z, Merkely B, Maurovich-Horvat P. (2017) Bilateral Coronary Ostial Stenosis after Bentall Procedure in a Patient with Marfan Syndrome. J Cardiovasc Emergencies, 3: 193–196.

3. Nemcsik J, **Vecsey-Nagy M**, Szilveszter B, Kolossváry M, Karády J, László A, Kőrösi B, Nemcsik-Bencze Z, Gonda X, Merkely B, Rihmer Z, Maurovich-Horvat P. (2017) Inverse association between hyperthymic affective temperament and coronary atherosclerosis: A coronary computed tomography angiography study. J Psychosom Res, 103: 108–112. **(IF: 2.95)**

4. Maurovich-Horvat P, **Vecsey-Nagy M**, Simon J, Szilveszter B, Karády J, Jermendy Á, Merkely B. (2018) Role of Multidetector Computed Tomography in Transcatheter Aortic Valve Implantation – from Pre-procedural Planning to Detection of Post-procedural Complications. J Cardiovasc Emergencies, 4: 178–186.

5. Körösi B, **Vecsey-Nagy M**, Kolossváry M, Nemcsik-Bencze Z, Szilveszter B, László A, Batta D, Gonda X, Merkely B, Rihmer Z, Maurovich-Horvat P, Eörsi D, Torzsa P, Nemcsik J. (2019) Association between Cyclothymic Affective Temperament and Age of Onset of Hypertension. Int J Hypertens, 2019: 1–6. **(IF: 1.13)**

6. Kőrösi B, Batta D, Gonda X, Rihmer Z, Nemcsik-Bencze Z, László A, **Vecsey-Nagy M**, Nemcsik J. (2019) Association between Irritable Affective Temperament and Nighttime Peripheral and Central Systolic Blood Pressure in Hypertension. Artery Res, 25: 41. **(IF: 0.52)**

7. Kolossváry M, Jávorszky N, Karády J, **Vecsey-Nagy M**, Dávid TZ, Simon J, Szilveszter B, Merkely B, Maurovich-Horvat P. (2021) Effect of vessel wall segmentation on volumetric and radiomic parameters of coronary plaques with adverse characteristics. J Cardiovasc Comput Tomogr, 15: 137–145. **(IF: 3.81)**

8. Vattay B, Boussoussou M, Borzsák S, **Vecsey-Nagy M**, Simon J, Kolossváry M, Merkely B, Szilveszter B. (2021) Myocardial perfusion imaging using computed tomography: Current status, clinical value and prognostic implications. Imaging, 13: 49–60.

9. Boussoussou M, Vattay B, Szilveszter B, Kolossváry M, Simon J, **Vecsey-Nagy M**, Merkely B, Maurovich-Horvat P. (2021) Functional assessment of coronary plaques using CT based hemodynamic simulations: Current status, technical principles and clinical value. Imaging, 13: 37–48.

10. **Vecsey-Nagy M**, Szeberin Z, Csobay-Novák C. (2021) Unusual hybrid repair of a thoracoabdominal and mesenteric aneurysm with aberrant right hepatic artery. J Vasc Surg Cases, Innov Tech, 7: 458–461.

11. Szilveszter B, Vattay B, Bossoussou M, **Vecsey-Nagy M**, Simon J, Merkely B, Maurovich-Horvat P, Kolossváry M. (2021) CAD-RADS may underestimate coronary plaque progression as detected by serial CT angiography. Eur Hear J - Cardiovasc Imaging, 00: 1-10. **(IF: 9.13)**

12. **Vecsey-Nagy M**, Jermendy ÁL, Suhai FI, Panajotu A, Csőre J, Borzsák S, Fontanini DM, Kolossváry M, Vattay B, Boussoussou M, Csobay-Novák C, Merkely B, Maurovich-Horvat P, Szilveszter B. (2021) Model-based adaptive filter for a dedicated cardiovascular CT scanner: Assessment of image noise, sharpness and quality. Eur J Radiol, 145: 110032. **(IF: 4.53)**

13. Vattay B, Nagy AI, Apor A, Kolossváry M, Manouras A, **Vecsey-Nagy M**, Molnár L, Boussoussou M, Bartykowszki A, Jermendy ÁL, Kováts T, Zsarnóczay E, Maurovich-Horvat P, Merkely B, Szilveszter B. (2022) The Predictive Value of Left Atrial Strain Following Transcatheter Aortic Valve Implantation on Anatomical and Functional Reverse Remodeling in a Multi-Modality Study. Front Cardiovasc Med, 9: 841658. **(IF: 5.85)**

14. Csőre J, Suhai FI, Gyánó M, Pataki ÁA, Juhász G, **Vecsey-Nagy M**, Pál D, Fontanini DM, Bérczi Á, Csobay-Novák C. (2022) Quiescent-Interval Single-Shot Magnetic Resonance Angiography May Outperform Carbon-Dioxide Digital

Subtraction Angiography in Chronic Lower Extremity Peripheral Arterial Disease. J Clin Med, 11: 4485. **(IF: 4.96)**

15. Boussoussou M, Szilveszter B, Vattay B, Kolossváry M, **Vecsey-Nagy M**, Salló Z, Orbán G, Péter P, Katalin P, Vivien NK, István O, Maurovich-Horvat P, Merkely B, Gellér L, Szegedi N. (2022) The effect of left atrial wall thickness and pulmonary vein sizes on the acute procedural success of atrial fibrillation ablation. Int J Cardiovasc Imaging, 38: 1601–1611. **(IF: 2.32)**

16. Szegedi N, **Vecsey-Nagy M**, Simon J, Szilveszter B, Herczeg S, Kolossváry M, Idelbi H, Osztheimer I, Klaudia Nagy V, Tahin T, Széplaki G, Delgado V, Bax JJ, Maurovich-Horvat P, Merkely B, Gellér L. (2022) Orientation of the right superior pulmonary vein affects outcome after pulmonary vein isolation. Eur Hear J - Cardiovasc Imaging, 23: 515–523. **(IF: 9.13)**

17. **Vecsey-Nagy M**, Szilveszter B, Kolossváry M, Boussoussou M, Vattay B, Merkely B, Maurovich-Horvat P, Radovits T, Nemcsik J. (2022) Correlation between Coronary Artery Calcium- and Different Cardiovascular Risk Score-Based Methods for the Estimation of Vascular Age in Caucasian Patients. J Clin Med, 11: 1111. **(IF: 4.96)**

18. Borzsák S, Szentiványi A, Süvegh A, Fontanini DM, **Vecsey-Nagy M**, Banga P, Szeberin Z, Sótonyi P, Csobay-Novák C. (2022) Complex Aortic Interventions Can Be Safely Introduced to the Clinical Practice by Physicians Skilled in Basic Endovascular Techniques. Life, 12: 902. **(IF: 3.25)**

19. **Vecsey-Nagy M**, Jermendy ÁL, Kolossváry M, Vattay B, Boussoussou M, Suhai FI, Panajotu A, Csőre J, Borzsák S, Fontanini DM, Csobay-Novák C, Merkely B, Maurovich-Horvat P, Szilveszter B. (2022) Heart Rate-Dependent Degree of Motion Artifacts in Coronary CT Angiography Acquired by a Novel Purpose-Built Cardiac CT Scanner. J Clin Med, 11: 4336. **(IF: 4.96)**

20. Borzsák S, Süvegh A, Szentiványi A, Fontanini DM, **Vecsey-Nagy M**, Banga P, Sótonyi P, Szeberin Z, Csobay-Novák C. (2022) Midterm Results of Iliac Branch Devices in a Newly Established Aortic Center. Life, 12: 1154. **(IF: 3.25)**

Articles in Hungarian

1. Csobay-Novák C, Entz L, Banga P, Pólos M, Szabolcs Z, Csikós G, Fontanini DM, **Vecsey-Nagy M**, Szeberin Z. (2021) Fenestrated endovascular repair of a thoracoabdominal aortic aneurysm in chronic dissection. Orv Hetil, 162: 1260–1264. **(IF: 0.71)**

2. Fontanini DM, Borzsák S, **Vecsey-Nagy M**, Jokkel Z, Szeberin Z, Szentiványi A, Süvegh A, Sótonyi P, Csobay-Novák C. (2022) Endoanchoring may be effective in the endovascular aortic repair of juxtarenal aneurysms. Orv Hetil, 163: 631–636. **(IF: 0.71)**

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The association between accelerated vascular aging and cyclothymic affective temperament in women

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ABSTRACT

Objective: Affective temperaments (depressive, anxious, irritable, hyperthymic, cyclothymic) are regarded as the biologically stable core of personality. Accumulating data suggest their relationship with cardiovascular diseases. However, there are currently limited data on the association of affective temperaments and accelerated vascular aging. The aim of our study was to evaluate the relationship between affective temperaments and vascular age, as assessed by coronary artery calcium scoring (CACS).
Methods: In our cross-sectional study, 209 consecutive patients referred to coronary computed tomography angiography (CCTA) due to suspected coronary artery disease (CAD) were included. All patients completed the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A) and the Beck Depression Inventory (BDI). Vascular age was estimated using CACS and its difference from chronological age for each patient was calculated. Linear regression analysis was used to identify predictors of accelerated vascular aging in the entire cohort and in male and female sub-populations.
Results: Besides traditional risk factors, cyclothymic temperament score proved to be an independent predictor of accelerated vascular aging in women ($\beta = 0.89$ [95%CI: 0.04–1.75]), while this association was absent in men.
Conclusions: Our results suggest that cyclothymic affective temperament is associated with accelerated vascular aging in women. Assessment of affective temperaments may potentiate more precise cardiovascular risk stratification of patients.

1. Introduction

Vascular aging is the gradual deterioration of vascular structure and function, with time [1]. As opposed to chronological age that solely refers to the passage of time, the concept of vascular age characterizes the structural and functional decline [2]. The assessment of arterial age and its relation to chronological age allows clinicians to determine if early vascular aging is present at an individual level [3]. Several algorithms have been proposed for the calculation of arterial age, including carotid intima-media thickness and pulse wave velocity [4,5]. In addition, it has been suggested that the assessment of vascular age on the basis of coronary artery calcium score (CACS) is a reliable method [6,7]. The concept is to determine the age that is associated with the same coronary heart disease (CHD) risk as the observed CACS, hence defining the arterial age of each participant [8]. In these circumstances, arterial age and health becomes even more important because arterial pulsation and relaxation are most relevant for a sufficiently working glymphatic system of the brain, and thereby for aging in general [9–12].

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Temperaments are considered to be the inherited, biologically stable core of personality. While most temperamental models describe personality and emotional reactivity in general, the model of affective temperaments, specifically, was developed based on affective disorder patients and their healthy first-degree relatives to describe affective temperamental dimensions. These temperaments are regarded as subclinical, trait-related characteristics and can be conceptualized as subclinical manifestations of major affective states, especially in their more pronounced presentations [13]. The model of affective temperaments encompasses five distinct temperament types: depressive, irritable, anxious, hyperthymic and cyclothymic [14]. These temperaments can be characterized through five temperament scales, as assessed by the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A), containing 110 items [15]. Cyclothymic temperament is characterized by rapid fluctuations in mood and emotional instability. Irritable temperament includes a predisposition to being litigious and aggressive to encountering difficulties in interpersonal relationships. Hyperthymic temperament is best described by upbeat, overenergetic and overconfident traits and a warm and extroverted attitude. Depressive temperament incorporates self-denying, pessimistic and passive attributes, while anxious temperament is frequently brooding, hypersensitive to separation and has exaggerated worries [14–17]. While they are documented predictors of psychopathology and growing evidence suggest a continuum between affective temperaments and mood disorders [18], recently, the association of affective temperaments (or their pathologic manifestations, such as bipolar disorders) and cardiovascular risk factors and diseases has also been documented [19]. Cyclothymic temperament showed a significant correlation with coronary events in hypertensive patients [20], while hyperthymic temperament proved to be an independent predictor of CAD [21].

The aim of our study was to calculate vascular age based on coronary artery calcium score and to assess the relationship between affective temperaments and vascular age. We hypothesized a positive association with cyclothymic and irritable temperaments and an inverse relationship with increased vascular age in case of hyperthymic temperament. Given that substantial sex differences have previously been documented, we sought to study these potential associations in the whole cohort and in men and women.

2. Methods

2.1. Study population

In our cross-sectional single center study, 209 consecutive Caucasian patients with stable chest pain referred to clinically indicated CCTA were enrolled between March 2015 and March 2020. Regarding our study cohort, 182 patients of our population had been co-enrolled in our previous study that sought to investigate the relationship between CAD and affective temperaments [21]. Patients above 18 years who gave approval to data retrieval and analysis met the inclusion criteria. Patients with previous coronary intervention, coronary bypass operation or with non-diagnostic image quality were excluded from the current study. Those with ongoing psychiatric disorders or with dementia potentially interfering with the completion of questionnaires were also excluded from our study. Prior to the examination, patients completed their demographic, anthropometric and medical history, as well as the psychometric questionnaires.

Prior to participation, all patients gave written informed consent. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, the Hungarian Ministry of Health (ETT TUKEB 570/2014) and was carried out in accordance with the tenets of the Declaration of Helsinki.

2.2. Assessment of coronary artery calcium and calculation of vascular age

All patients underwent coronary artery scans using a 256-slice CT scanner (Philips Brilliance iCT, Best, The Netherlands) with the following parameters: 270 msec rotation time, 128 × 0.625 mm collimation, tube voltage 120 kVp and tube current 30 mAs. Images were acquired during a single breath-hold, using prospective ECG-triggering. Blood pressure and heart rate were measured once on the left arm in sitting position, one hour prior to the CT examination. Quantification of calcium score was carried out by the physicians performing the CT scan in a semiautomatic manner, according to the area and density method, as proposed by Agatston [22]. Calcified regions were identified by a dedicated software, defined as voxels above the density of 130 Hounsfield units (HU) and each reader manually selected calcification pertaining to coronary arteries. The area of calcified plaques in mm^2 was calculated by the software on each CT slice. The measured area was then automatically multiplied by 1, 2, 3, or 4 depending on the highest visualized density inside of the plaque to acquire the CACS for that slice. Agatston score for all CT slices were eventually summed up to acquire the total CACS for each patient. The method has been reported to yield excellent interreader correlation, with observed coefficients above 0.98 [23,24].

Regarding the calculation of arterial age, we applied a method that has previously been described by McLelland et al. [8]. Arterial age of an individual can be expressed as the risk equivalent of CACS if we consider arterial age as the age at which the estimated CHD risk corresponds to that of the observed CACS. The conversion can be executed through a mathematical equation: arterial age = 39.1 + 7.25log(CACS+1). Thereafter, the difference of vascular and chronological age was calculated. A positive difference implies that a subject's 10-year CHD risk is higher than what would be expected given the documented chronological age (vascular age > chronological age, accelerated vascular aging). A negative difference indicates that a participant's 10-year CHD risk is less than that applying his or her chronological age (vascular age < chronological age, healthy vascular aging). Fig. 1 demonstrates two examples for accelerated and healthy vascular aging.

2.3. Evaluation of affective temperaments and depression

The Hungarian validated and standardized version of Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) was used to assess affective temperaments on depressive, cyclothymic, hyperthymic, irritable, and anxious subscales, requiring "yes" (score 1) or "no" (score 0) answers [15]. TEMPS-A contains 110 items (109 in the version for males) that can be answered by yes or no indicating whether the described characteristic is present or not.

TEMPS-A has been extensively studied, translated into more than 25 languages and validated in several languages. Similarities and differences were also found in national samples, which suggests that the distribution of affective temperaments has both universal and culture-specific characteristics [25].

The Beck Depression Inventory (BDI) is a 21-question multiple-choice, self-report questionnaire, one of the widely used instruments for measuring the severity of depression. Participants are asked to make ratings on a four point scale, where a higher score correlates with more severe depression [26].

2.4. Statistical analysis

Descriptive data are expressed as mean ± standard deviation or median with interquartile ranges or percentages as appropriate. Normality of continuous parameters was tested with the Kolmogorov-Smirnov test. Differences between descriptive characteristics and hemodynamic parameters, as well as TEMPS-A and BDI scores were compared between accelerated vascular aging and healthy vascular

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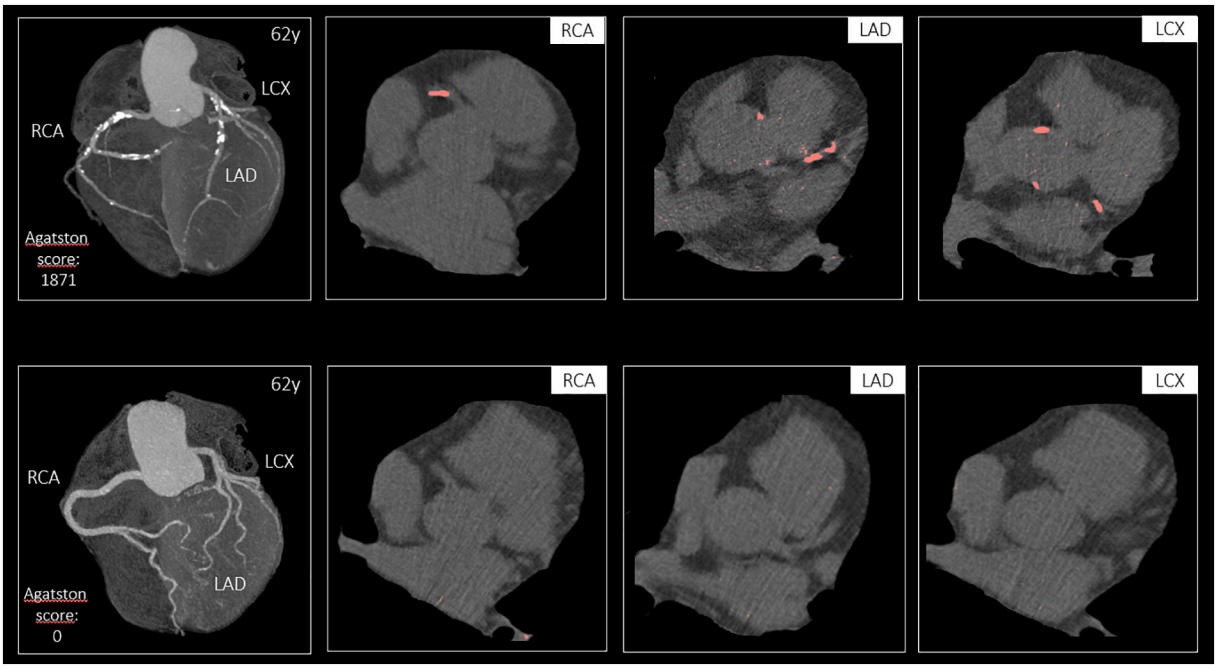

Fig. 1. Representative 3D volumetric and axial non-enhanced CT images of a patient with extensive coronary artery calcification and one with a calcium score of 0, both at the age of 62. The CHD risk equivalent of an Agatston score of 1871 is 94 years of arterial age, thus the upper row demonstrates a case of accelerated vascular aging (94–62 = 32), while the patient in the lower row has a smaller 10-year CHD risk than what would be expected from her chronological age (39–62 = −23). RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; LCX: Left Circumflex Artery.

aging groups using unpaired Student's *t*-tests or Mann–Whitney rank-sum test for data failing tests of normality. Univariate linear regression analysis was used to assess the determinants of accelerated vascular aging in the whole cohort, and then in men and in women, separately. Traditional risk factors and those psychometric parameters that were significant in univariate linear regression were entered into a multivariate linear model to assess independent association with accelerated vascular aging in the entire population and in both sexes, independently. A two-sided $p < 0.05$ was considered to be significant in all analyses. SPSS (Armonk, NY, USA version 25.0) was used for all calculations.

3. Results

A total of 209 patients were enrolled in our study. The mean age of our cohort was 60.3 years, approximately half of them (49.3%) were female and had dyslipidemia (50.7%). Demographic parameters, clinical data and scores in the different scales of affective temperaments are summarized in Table 1.

Based on the Agatston score-derived arterial age, accelerated vascular aging was observed in 100 patients (vascular age > chronological age), while in 109 cases, biological age was equal to or less than chronological age (vascular age ≤ chronological age). Significantly more women were observed in the healthy vascular aging group, as compared to the accelerated vascular aging group: 61.5% vs 36.0%, respectively ($p < 0.001$). Regarding the accelerated vascular aging group, the prevalence of diabetes mellitus [23.0% vs 9.2% ($p = 0.006$)] and dyslipidemia [62.0% vs 40.4% ($p = 0.002$)] were significantly higher than in the healthy vascular aging population. Participants with accelerated vascular aging scored substantially higher irritable temperament score (4.2 ± 4.2 vs 3.2 ± 3.3, $p = 0.03$).

In univariate analysis, female sex proved to be a protective factor, while alcohol consumption, diabetes mellitus, dyslipidemia and irritable temperament were associated with accelerated vascular aging in the entire cohort. Female sex (β = −10.82 [95%CI: −15.30 to −6.33], $p < 0.001$), diabetes mellitus (β = 7.16 [95%CI: 1.20–13.12], $p = 0.02$) and dyslipidemia (β = 8.28 [95%CI: 3.94–12.62], $p < 0.001$) remained to be

Table 1
Demographic parameters, cardiovascular risk factors, TEMPS-A and BDI scores in patients with and without accelerated vascular aging.

	Total	Vasc. age > Chron. age	Vasc. age ≤ Chron. age	*p*-value
	(*N* = 209)	(*N* = 100)	(*N* = 109)	
Demographics				
Age (years)	60.3 ± 19.5	60.6 ± 18.3	55.0 ± 19.9	0.70
Female sex, *n* (%)	***103 (49.3)***	***36 (36.0)***	***67 (61.5)***	***<0.001***
BMI (kg/m^2)	27.7 ± 6.5	27.9 ± 6.6	27.5 ± 5.8	0.73
Office SBP (mmHg)	145.7 ± 20.7	147.4 ± 21.4	144.0 ± 19.9	0.28
Office DBP (mmHg)	89.7 ± 12.2	89.0 ± 12.6	90.3 ± 11.9	0.47
Agatston score	***8.2 (0.0–121.0)***	***130.5 (28.8–512.8)***	***0.0 (0.0–4.0)***	***<0.001***
Cardiovascular risk factors				
Current smoker, *n* (%)	26 (12.4)	13 (13.0)	13 (11.9)	0.81
Alcohol consumption	101 (48.3)	55 (55.0)	46 (42.2)	0.15
Hypertension, *n* (%)	142 (67.2)	73 (73.0)	69 (63.3)	0.13
Diabetes mellitus, *n* (%)	***33 (15.8)***	***23 (23.0)***	***10 (9.2)***	***0.006***
Dyslipidemia, *n* (%)	***106 (50.7)***	***62 (62.0)***	***44 (40.4)***	***0.002***
Affective temperaments				
Depressive	6.0 ± 4.0	6.0 ± 4.0	6.0 ± 4.0	0.86
Cyclothymic	3.0 ± 5.0	3.0 ± 6.0	3.0 ± 5.0	0.54
Hyperthymic	13.0 ± 6.0	13.0 ± 5.0	13.0 ± 6.5	0.56
Irritable	***4.0 ± 4.0***	***4.2 ± 4.2***	***3.2 ± 3.3***	***0.03***
Anxious	5.0 ± 8.0	5.0 ± 7.8	5.0 ± 7.5	0.57
Beck depression inventory	5.0 ± 7.0	5.0 ± 8.0	5.0 ± 6.0	0.73

Bold italic indicates statistical significance ($p < 0.05$). Vasc. age: vascular age, Chron. age: chronological age, BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, BDI: Beck Depression Inventory.

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independent predictors of more advanced arterial aging in multivariate analysis. Table 2 details the assessment of the entire patient population in multiple linear regression analyses.

Regarding female participants, no association was found in case of traditional risk factors, cyclothymic affective temperament, however, proved to be independently predictive for accelerated vascular aging in multivariate analysis (β = 0.89 [95%CI: 0.04–1.75], $p = 0.04$). Table 3 demonstrates the results of the uni-, and multivariate analyses in the female cohort.

Further assessing the male population separately in Table 4, dyslipidemia was associated with accelerated vascular aging in univariate analysis and remained to be an independent predictor in multivariate analysis, as well (β = 12.77 [95%CI: 7.05–1.75], p = 0.04). No association was found, however, with affective temperaments and BDI scores.

4. Discussion

To the best of our knowledge, our study was the first to evaluate the relationship between affective temperaments and accelerated vascular aging, as assessed by CCTA. In women, we demonstrated a significant association between cyclothymic temperament and increased vascular age, relative to the observed chronological age. This relationship was absent in men.

Although the concept of vascular age as a surrogate marker of CV risk is a relatively novel idea, it has been incorporated in CV risk tables as a result of the Framingham study since 2008, as it adds incremental value to well-documented traditional risk factors [27]. Furthermore, it is a substantially more comprehensible way to report individual risk to patients [28]. Vascular aging is the structural and functional deterioration of arterial wall that ultimately leads to end organ damage of the heart, kidney and brain [29]. Traditionally and nowadays, affective temperaments and mood disorders are effectively treated by lithium [30,31]. On the other hand, lithium was recently found to support and protect arterial function via pathways involving vascular calcium homeostasis and myosin light chain phosphorylation, thus being protective for vascular events such stroke [9,10,32,33]. Besides the beneficial effect of lithium, the impact of Mediterranean diet and regular aerobic exercise on vascular aging have been established [34,35] and moderate alcohol consumption may also favorably affect the process of arterial aging [36]. Smoking and inflammation, on the other hand, are documented propagators of accelerated vascular aging [37,38]. Furthermore, extensive evidence is available regarding the deleterious effect of dyslipidemia and diabetes mellitus on vascular aging, findings that we also reproduced in our study [39,40].

The impact of psychopathological factors on cardiovascular pathology is also becoming increasingly obvious. A two-fold increase in relative risk was documented regarding cardiovascular mortality in people with diagnosed depression [41]. Also, depression and anxiety disorders significantly increase the risk of CAD and cardiac mortality [42,43]. The role of psychopathological factors as indicators of accelerated vascular aging, however, is not well established. Previously, the association of different psychosocial traits with coronary artery calcium deposition and its progression could not be confirmed [44].

The association between affective temperaments and psychopathology is well-documented. Cyclothymic affective temperament, specifically, was shown to be the most pronounced affective temperament type in patients with bipolar II disorder [45], and is considered to be the precursor of bipolar disorder often presenting with atypical features [46]. Furthermore, suicide attempters scored significantly higher cyclothymic scores, compared to healthy controls [47]. Besides its well-described role in psychopathology, cyclothymic temperament seems to have importance in relation of cardiovascular pathology, as well, especially regarding hypertension. An association was demonstrated with cyclothymic temperament and chronic hypertension and in hypertensive patients, brachial systolic blood pressure was also associated with the expression of cyclothymic temperament [48,49]. Additionally, our recent study discovered the association of cyclothymic temperament both with white-coat and resistant hypertension [50]. Furthermore, dominant cyclothymic temperament was associated with acute coronary events in hypertensive patients [20]. Our research expands the evidence on the role of cyclothymic temperament on CV pathology but also emphasizes the presence of sex-related differences. Sex differences in the context of cardiovascular pathology and personality traits have already been established in literature. The association of trait anger and carotid arterial stiffening was only present in men [51], furthermore, the ability of affective temperaments to predict systolic blood pressure and pulse wave velocity displays substantial differences depending on sex [48]. Recently, we also demonstrated that in women the expression of cyclothymic temperament is associated with the age of the development of hypertension, but this association was missing in men [52]. However, available data concerning the potential underlying pathophysiological mechanisms are scarce in literature.

Irritable temperament is best described by skeptical and critical traits and is frequently associated with impulsiveness and obtrusiveness and common characteristics include anger and hostility [53]. Patients with more pronounced hostility scores react to external stimuli with more intense catecholamine and cortisol secretion [54], moreover, they exhibit increased levels of cortisol during their daytime activity [55]. Regarding healthy individuals, there is an inverse relationship between hostility scores and high frequency components of heart rate variability power spectrum [56]. We recently demonstrated in hypertensive patients that nighttime peripheral and central systolic blood pressure are

Table 2
Uni- and multivariate linear regression analysis of cardiovascular risk factors, affective temperaments, BDI-scores and the difference between vascular and chronological age.

Multivariate	Univariate				Multivarite			
	β	95% CI, lower-upper		*p*	β	95% CI, lower-upper		*p*
Female sex	***−11.39***	***−15.67***	***−7.11***	***<0.001***	***−10.82***	***−15.30***	***−6.33***	***<0.001***
BMI (kg/m^2)	0.12	−0.30	0.54	0.58	−0.10	−0.52	0.31	0.63
Current smoker	3.33	−3.56	10.20	0.34	3.73	−2.57	10.03	0.24
Alcohol consumption	***5.06***	***0.56***	***9.56***	***0.03***	1.10	−3.33	5.52	0.63
Hypertension	1.58	−3.30	6.44	0.52	−1.90	−6.76	2.97	0.44
Diabetes mellitus	***7.56***	***1.41***	***13.71***	***0.02***	***7.16***	***1.20***	***13.12***	***0.02***
Dyslipidemia	***7.18***	***2.73***	***11.62***	***0.002***	***8.28***	***3.94***	***12.62***	***<0.001***
Depressive	0.18	−0.56	0.93	0.62				
Cyclothymic	0.48	−0.12	1.07	0.12				
Hyperthymic	0.19	−0.33	0.70	0.47				
Irritable	***0.07***	***0.05***	***1.39***	***0.04***	0.45	−0.19	1.08	0.17
Anxious	−0.07	−0.49	0.35	0.75				
Beck depression inventory	0.18	−0.20	0.56	0.35				

Bold italic indicates statistical significance (p < 0.05). BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, BDI: Beck Depression Inventory.

Table 3
Results of the multiple linear regression analyses in female population.

	Univariate				Multivariate			
	β	95% CI, lower-upper		*p*	β	95% CI, lower-upper		*p*
BMI (kg/m^2)	−0.01	−0.55	0.53	0.96	−0.18	−0.76	0.41	0.55
Current smoker	4.88	−4.40	14.15	0.30	1.90	−7.52	11.33	0.69
Alcohol consumption	−0.94	−7.73	5.85	0.79	−1.98	−9.07	5.10	0.58
Hypertension	2.96	−3.91	9.84	0.40	0.18	−7.38	7.75	0.96
Diabetes mellitus	8.66	−0.23	17.56	0.06	7.95	−1.51	17.41	0.10
Dyslipidemia	3.65	−2.71	10.02	0.26	3.23	−3.43	9.89	0.34
Depressive	0.60	−0.46	1.67	0.26				
Cyclothymic	***0.94***	***0.12***	***1.76***	***0.03***	***0.89***	***0.04***	***1.75***	***0.04***
Hyperthymic	−0.20	−0.89	0.50	0.58				
Irritable	0.80	−0.22	1.82	0.12				
Anxious	0.27	−0.32	0.86	0.37				
Beck depression inventory	0.23	−0.30	0.76	0.39				

Bold italic indicates statistical significance ($p < 0.05$). BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table 4
Results of the multiple linear regression analyses in male population.

	Univariate				Multivariate			
	β	95% CI, lower-upper		*p*	β	95% CI, lower-upper		*p*
BMI (kg/m^2)	0.04	−0.57	0.65	0.89	−0.10	−0.70	0.50	0.74
Current smoker	2.84	−6.34	12.03	0.54	4.63	−4.00	13.26	0.29
Alcohol consumption	3.93	−2,14	10.00	0.20	2.03	−3.72	7.78	0.48
Hypertension	0.76	−5.44	6.96	0.81	−3.78	−10.06	2.49	0.24
Diabetes mellitus	5.66	−2.03	13.35	0.15	5.16	−2.41	12.73	0.18
Dyslipidemia	***11.82***	***6.45***	***17.18***	***<0.001***	***12.77***	***7.05***	***18.48***	***<0.001***
Depressive	0.56	−0.40	1.52	0.25				
Cyclothymic	0.17	−0.60	0.93	0.67				
Hyperthymic	−0.03	−0.77	0.71	0.94				
Irritable	0.04	−0.80	0.88	0.93				
Anxious	0.04	−0.80	0.88	0.93				
Beck depression inventory	0.38	−0.11	0.86	0.12				

Bold italic indicates statistical significance ($p < 0.05$). BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure.

associated with irritable affective temperament [57]. These factors could potentially contribute to earlier vascular aging. In our study, despite higher irritable score of subjects with accelerated vascular aging compared to subjects with healthy vascular aging and the significant association with accelerated vascular aging in univariate analysis, irritable temperament did not prove to be an independent predictor in a multivariate setting, suggesting that its association with accelerated vascular aging is mediated by traditional CV risk factors.

Recently, lower hyperthymic affective temperament scores exhibited a significant relationship with augmentation index, a reliable indicator of arterial stiffness and previously, we demonstrated an inverse association between hyperthymic temperament and coronary atherosclerosis [21,50]. Although it was reasonable to hypothesize an inverse relationship between hyperthymic scores and accelerated vascular aging, our research did not provide evidence to this concept.

The present study has limitations that should be considered. Although our methodology used standardized autoquestionnaires and excluded patients with dementia, a complete exclusion of misinterpretations or mistakes by patients is nevertheless impossible. We enrolled solely patients that were referred to CCTA, which limits the generalizability of our results. Furthermore, the cross-sectional design of the study precludes causal inferences. Given that race-specific differences are well-documented in the pattern of affective temperaments, the fact that all of the enrolled patients were Caucasian is a shortcoming. Additionally, evaluation of blood pressure was not executed according to current guidelines, as it was measured only once. Therefore, we decided not to include our blood pressure data into the regression analysis. Further limitations are the lack of the information about the concomitant medications and laboratory parameters. Finally, as we found the cyclothymic temperament score as an independent predictor of accelerated vascular aging only in women, our single-center study may be underpowered. Hence further studies, potentially with a multicenter design are needed.

In conclusion, aside from traditional CV risk factors, our results demonstrated that in women referred to clinically indicated CCTA, cyclothymic affective temperament is significantly associated with accelerated vascular aging. Our results confirm the adverse effect of cyclothymic temperament not only on psychopathology, but also on cardiovascular pathology. With further studies supporting our hypothesis, the evaluation of affective temperaments, especially cyclothymic temperament may potentially help to identify subgroups of patients with elevated CV risk as a target for preventive intervention.

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Declaration of Competing Interest

None declared.

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References

[1] R.E. Climie, et al., Macrovasculature and microvasculature at the crossroads between type 2 diabetes mellitus and hypertension, Hypertension 73 (6) (2019) 1138–1149.
[2] M.R. Hamczyk, R.M. Nevado, A. Barettino, V. Fuster, V. Andrés, Biological versus chronological aging: JACC focus seminar, J. Am. Coll. Cardiol. 75 (8) (2020) 919–930.
[3] M.A. Gomez-Marcos, et al., Association between different risk factors and vascular accelerated ageing (EVA study): study protocol for a cross-sectional, descriptive observational study, BMJ Open 6 (6) (2016) 1–10.
[4] J.H. Stein, M.C. Fraizer, S.E. Aeschlimann, J. Nelson-Worel, P.E. McBride, P. S. Douglas, Vascular age: integrating carotid intima-media thickness measurements with global coronary risk assessment, Clin. Cardiol. 27 (7) (2004) 388–392.
[5] F.U.S. Mattace-Raso, et al., Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study, Circulation 113 (5) (2006) 657–663.
[6] E.F. Schisterman, B.W. Whitcomb, Coronary age as a risk factor in the modified Framingham risk score, BMC Med. Imaging 4 (2004) 1.
[7] K. Nasir, C. Vasamreddy, R.S. Blumenthal, J.A. Rumberger, Comprehensive coronary risk determination in primary prevention: an imaging and clinical based definition combining computed tomographic coronary artery calcium score and national cholesterol education program risk score, Int. J. Cardiol. 110 (2) (2006) 129–136.
[8] R.L. McClelland, K. Nasir, M. Budoff, R.S. Blumenthal, R.A. Kronmal, Arterial age as a function of coronary artery calcium (from the multi-ethnic study of atherosclerosis [MESA]), Am. J. Cardiol. 103 (1) (2009) 59–63.
[9] B. Bosche, et al., A differential impact of lithium on endothelium-dependent but not on endothelium-independent vessel relaxation, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 67 (2016) 98–106.
[10] B. Bosche, et al., Low-dose lithium stabilizes human endothelial barrier by decreasing MLC phosphorylation and universally augments cholinergic vasorelaxation capacity in a direct manner, Front. Physiol. 7 (2016) 1–12, no. DEC.
[11] B. Bosche, P. Mergenthaler, T.R. Doeppner, J. Hescheler, M. Molcanyi, Complex clearance mechanisms after intraventricular hemorrhage and rt-PA treatment—A review on clinical trials, Transl. Stroke Res. 11 (3) (2020) 337–344.
[12] M. Nedergaard, S.A. Goldman, Glymphatic failure as a final common pathway to dementia, Science 56 (2020) 50–56, no. October.
[13] Z. Rihmer, K.K. Akiskal, A. Rihmer, H.S. Akiskal, Current research on affective temperaments, Curr. Opin. Psychiatry 23 (1) (2010) 12–18.
[14] K.K. Akiskal, H.S. Akiskal, The theoretical underpinnings of affective temperaments: implications for evolutionary foundations of bipolar disorder and human nature, J. Affect. Disord. 85 (1–2) (2005) 231–239.
[15] H.S. Akiskal, K.K. Akiskal, R.F. Haykal, J.S. Manning, P.D. Connor, TEMPS-A: Progress towards validation of a self-rated clinical version of the temperament evaluation of the Memphis, Pisa, Paris, and San Diego autoquestionnaire, J. Affect. Disord. 85 (1–2) (2005) 3–16.
[16] L. Rovai, et al., Do Akiskal & Mallya's affective temperaments belong to the domain of pathology or to that of normality? Eur. Rev. Med. Pharmacol. Sci. 17 (15) (2013) 2065–2079.
[17] G.H. Vázquez, X. Gonda, R. Zaratiegui, L.S. Lorenzo, K. Akiskal, H.S. Akiskal, Hyperthymic temperament may protect against suicidal ideation, J. Affect. Disord. 127 (1–3) (2010) 38–42.
[18] G. Perugi, et al., The influence of affective temperaments and psychopathological traits on the definition of bipolar disorder subtypes: A study on Bipolar i Italian National sample, J. Affect. Disord. 136 (2012) 1–2.
[19] V.S. Marshe, et al., C-reactive protein and cardiovascular risk in bipolar disorder patients: a systematic review, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 79 (2017) 442–451.
[20] A. Eory, S. Rozsa, P. Torzsa, L. Kalabay, X. Gonda, Z. Rihmer, Affective temperaments contribute to cardiac complications in hypertension independently of depression, Psychother. Psychosom. 83 (3) (2014) 187–189.
[21] J. Nemcsik, et al., Inverse association between hyperthymic affective temperament and coronary atherosclerosis: A coronary computed tomography angiography study, J. Psychosom. Res. 103 (2017) 108–112.
[22] A.S. Agatston, W.R. Janowitz, F.J. Hildner, N.R. Zusmer, M. Viamonte, R. Detrano, Quantification of coronary artery calcium using ultrafast computed tomography, J. Am. Coll. Cardiol. 15 (4) (1990) 827–832.
[23] J.P. Shields, C.H.J. Mielke, P. Watson, Inter-rater reliability of electron beam computed tomography to detect coronary artery calcification, Am. J. Card. Imaging 10 (2) (Apr. 1996) 91–96.
[24] J.P. Shields, C.H.J. Mielke, T.H. Rockwood, R.A. Short, F.K. Viren, Reliability of electron beam computed tomography to detect coronary artery calcification, Am. J. Card. Imaging 9 (2) (Apr. 1995) 62–66.
[25] G.H. Vázquez, L. Tondo, L. Mazzarini, X. Gonda, Affective temperaments in general population: a review and combined analysis from national studies, J. Affect. Disord. 139 (1) (2012) 18–22.
[26] A.T. Beck, C.H. Ward, M. Mendelson, J. Mock, J. Erbaugh, Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. Archives of general psychiatry, 4, 561-571, J. R. Coll. Gen. Pract. 18 (88) (1969) 267–271.
[27] R.B. D'Agostino, et al., General cardiovascular risk profile for use in primary care: the Framingham heart study, Circulation 117 (6) (2008) 743–753.
[28] J.I. Cuende, N. Cuende, J. Calaveras-Lagartos, How to calculate vascular age with the SCORE project scales: a new method of cardiovascular risk evaluation, Eur. Heart J. 31 (19) (2010) 2351–2358.
[29] Z. Ungvari, G. Kaley, R. De Cabo, W.E. Sonntag, A. Csiszar, Mechanisms of vascular aging: new perspectives, J. Geronotl. A Biol. Sci. Med. Sci. 65 (10) (2010) 1028–1041.
[30] S. Rej, et al., Lithium dosing and serum concentrations across the age Spectrum: from early adulthood to the tenth decade of life, Drugs Aging 31 (12) (2014) 911–916.
[31] J.K. Rybakowski, Lithium treatment in the era of personalized medicine, Drug Dev. Res. (2020) 1–7, no. March.
[32] M. Haupt, et al., Lithium enhances post-stroke blood-brain barrier integrity, activates the MAPK/ERK1/2 pathway and alters immune cell migration in mice, Neuropharmacology 181 (2020), 108357.
[33] B. Bosche, M. Schäfer, R. Graf, F.V. Härtel, U. Schäfer, T. Noll, Lithium prevents early cytosolic calcium increase and secondary injurious calcium overload in glycolytically inhibited endothelial cells, Biochem. Biophys. Res. Commun. 434 (2) (2013) 268–272.
[34] M.C. Patino-Alonso, et al., Factors associated with adherence to the mediterranean diet in the adult population, J. Acad. Nutr. Diet. 114 (4) (2014) 583–589.
[35] M.A. Gomez-Marcos, et al., Relationship between physical activity and plasma fibrinogen concentrations in adults without chronic diseases, PLoS One 9 (2) (2014) 1–7.
[36] L. Karimi, F.U.S. Mattace-Raso, J. Van Rosmalen, F. Van Rooij, A. Hofman, O. H. Franco, Effects of combined healthy lifestyle factors on functional vascular aging: the Rotterdam Study, J. Hypertens. 34 (5) (2016) 853–859.
[37] A. Csiszar, A. Podlutsky, M.S. Wolin, G. Losonczy, P. Pacher, Z. Ungvari, Oxidative stress and accelerated vascular aging: implications for cigarette smoking, Front. Biosci. 14 (8) (2009) 3128–3144.
[38] J.Y. Kim, O.Y. Kim, J.K. Paik, D.Y. Kwon, H.J. Kim, J.H. Lee, Association of age-related changes in circulating intermediary lipid metabolites, inflammatory and oxidative stress markers, and arterial stiffness in middle-aged men, Age (Omaha) 35 (4) (2013) 1507–1519.
[39] D. Terentes-Printzios, et al., Cardiovascular risk factors accelerate progression of vascular aging in the general population: results from the CRAVE study (cardiovascular risk factors affecting vascular age), Hypertension 70 (5) (2017) 1057–1064.
[40] P.M. Nilsson, Early vascular aging in hypertension, Front. Cardiovasc. Med. 7 (2020) 1–5, no. February.
[41] B.W. Penninx, et al., Depression and cardiac mortality: results from a community-based longitudinal study, Arch. Gen. Psychiatry 58 (3) (2001) 221–227.
[42] F. Lespérance, N. Frasure-Smith, M. Talajic, M.G. Bourassa, Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction, Circulation 105 (9) (2002) 1049–1053.
[43] I. Janszky, S. Ahnve, I. Lundberg, T. Hemmingsson, Early-onset depression, anxiety, and risk of subsequent coronary heart disease. 37-year follow-up of 49,321 young Swedish men, J. Am. Coll. Cardiol. 56 (1) (2010) 31–37.
[44] A.G. Abdulla, P. Buzkova, R. Nakanishi, M.J. Budoff, Association of psychosocial traits with coronary artery calcium development and progression: The Multi-Ethnic Study of Atherosclerosis, J. Cardiovasc. Comput. Tomogr. (2020) 1–9, no. September 2019.
[45] H.S. Akiskal, E.G. Hantouche, J.F. Allilaire, Bipolar II with and without cyclothymic temperament: 'dark' and 'sunny' expressions of soft bipolarity, J. Affect. Disord. 73 (1–2) (2003) 49–57.
[46] H.S. Akiskal, Validating 'hard' and 'soft' phenotypes within the bipolar spectrum: continuity or discontinuity? J. Affect. Disord. 73 (1–2) (2003) 1–5.
[47] A.R. Ardani, F.F. Hosseini, Z. Asadpour, A.M. Hashemian, B. Dadpour, M. Nahidi, Affective temperaments, as measured by TEMPS-A, among self-poisoning nonlethal suicide attempters, Psychiatry Res. 247 (1–2) (2017) 125–129.
[48] A. László, et al., Association of affective temperaments with blood pressure and arterial stiffness in hypertensive patients: a cross-sectional study, BMC Cardiovasc. Disord. 16 (1) (2016) 1–10.
[49] A. Eory, et al., Personality and cardiovascular risk: association between hypertension and affective temperaments-a cross-sectional observational study in primary care settings, Eur. J. Gen. Pract. 20 (4) (2014) 247–252.
[50] B. Kőrösi, et al., Evaluation of affective temperaments and arterial stiffness in different hypertension phenotypes, Hypertens. Res. 16 (2016) 158.
[51] J.E. Williams, R. Din-Dzietham, M. Szklo, Trait anger and arterial stiffness: results from the atherosclerosis risk in communities (ARIC) study, Prev. Cardiol. 9 (2006) 14–20.
[52] B. Kőrösi, et al., Association between cyclothymic affective temperament and age of onset of hypertension, Int. J. Hypertens. (2019), 9248247, https://doi.org/10.1155/2019/9248247.
[53] H.S. Akiskal, et al., TEMPS-I: delineating the most discriminant traits of the cyclothymic, depressive, hyperthymic and irritable temperaments in a nonpatient population, J. Affect. Disord. 51 (1) (1998) 7–19.
[54] E.C. Suarez, C.M. Kuhn, S.M. Schanberg, R.B. Williams, E.A. Zimmermann, Neuroendocrine, cardiovascular, and emotional responses of hostile men: the role of interpersonal challenge, Psychosom. Med. 60 (1) (1998) 78–88.
[55] M.K. Pope, T.W. Smith, Cortisol excretion in high and low cynically hostile men, Psychosom. Med. 53 (4) (1991) 386–392.
[56] R.P. Sloan, et al., Hostility, gender, and cardiac autonomic control, Psychosom. Med. 63 (3) (2001) 434–440.
[57] B. Kőrösi, et al., Association between irritable affective temperament and nighttime peripheral and central systolic blood pressure in hypertension, Artery Res. 25 (1–2) (2019) 41–47.

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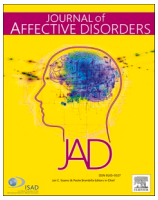

Research paper

Association between affective temperaments and severe coronary artery disease

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ABSTRACT

Background: Affective temperaments are regarded as subclinical manifestations of major mood disorders and cumulating evidence suggest their role in cardiovascular (CV) pathology. We wished to analyze associations between affective temperaments and severe coronary artery disease (CAD), as assessed by coronary computed tomography angiography (CCTA).

Methods: 225 consecutive patients referred to CCTA due to suspected CAD were included. Medical history and demographic parameters were recorded and all patients completed the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A). The severity and extent of CAD was evaluated by CCTA. Logistic regression analysis was used to identify predictors of severe CAD (≥70% luminal stenosis in ≥1 major coronary artery).

Results: According to multivariate logistic regression analysis, elevated hyperthymic affective temperament scores significantly decreased the odds of severe CAD (OR=0.92 CI: 0.84–1.00, $p = 0.04$), while independent positive associations were observed in case of dyslipidemia (OR=4.23 CI: 1.81–9.88, $p = 0.001$) and cyclothymic affective temperament scores (OR=1.12 CI: 1.02–1.23, $p = 0.02$). Furthermore, receiver operating curve (ROC) analysis was used to define ideal cutoff values. Hyperthymic temperament scores >11 (OR=0.41 CI: 0.19–0.90, $p = 0.03$), cyclothymic scores >7 (OR=3.23 CI: 1.35–7.76, $p = 0.01$) and irritable scores >6 (OR=2.79 CI: 1.17–6.69, $p = 0.02$) were also independently associated with severe CAD.

Limitations: Our study was limited by the cross-sectional design and the self-report nature of the questionnaires.

Conclusions: Evaluation of affective temperaments might help to identify patients with elevated risk for severe CAD and subsequent need for coronary intervention.

1. Introduction

Temperaments represent the inherited core of personality and are considered to be the biologically stable part of emotional reactivity (Akiskal and Akiskal, 2005c). Affective temperaments (depressive, irritable, anxious, hyperthymic, cyclothymic) are trait-related characteristics and commonly the antecedents and subclinical expressions of minor and major mood disorders, especially in their more pronounced

Abbreviations: AUC, Area Under the Curve; BDI, Beck Depression Inventory; CV, Cardiovascular; CAD, Coronary artery disease; CCTA, Coronary CT angiography; ICA, Invasive coronary angiography; LA, Left atrium; MPS, Myocardial perfusion scintigraphy; OR, Odds ratio; ROC, Receiver operating characteristic; SPECT, Single-photon emission CT; TEMPS-A, Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire.

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manifestations (Rihmer et al., 2010). The model of affective temperaments was developed in affective disorder patients and in their healthy first-degree relatives and it was designed to characterize subjects in the aspects of emotional reactivity, as well as related cognitive, psychomotor, circadian and social-behavioral traits (Akiskal et al., 1998). Affective temperaments can be quantified along five temperamental dimension scales using the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A), consisting of 110 self-reported items (Akiskal et al., 2005b). The continuum between affective temperaments and mood disorders is well-documented and extensive evidence is available regarding the pathoplastic role of these temperaments in psychopathology (Perugi et al., 2012; Pompili et al., 2012). Affective temperament measures appear to be independent predictors of lifetime suicide attempt and contribute more to predicting suicidal status than the presence of a major affective disorder (Baldessarini et al., 2017). Furthermore, recent investigations have suggested the impact of affective temperaments on CV pathology, as well (László et al., 2016; Kőrösi et al., 2020).

Cardiovascular (CV) diseases remain to be the leading cause of morbidity and mortality in the majority of developed countries worldwide, generating a substantial burden on health care and economy (Wilkins et al., 2017). Overall, the prevalence of coronary artery disease (CAD) is 6.7% in US adults ≥ 20 years of age and by 2030, it is projected to increase by 16.6% (Virani et al., 2020). Since effective preventive treatments are widely available, it is of outmost importance to accurately assess individual CAD risk, in order to maximize the health benefits of prevention (Lagerweij et al., 2018). Coronary computed tomography angiography (CCTA) has emerged as a reliable, non-invasive method for the diagnosis of CAD and allows for robust qualitative and quantitative assessment of atherosclerotic plaques (Celeng et al., 2016). Extensive evidence supports the role of CCTA as a gatekeeper that accurately selects individuals for invasive coronary angiography (ICA) (Chinnaiyan et al., 2012; Marwick et al., 2015). Significant luminal stenosis is assumed when the diameter reduction of the coronary lumen appears to be more than 70% and this threshold is widely required as an angiographic criterion for the need for revascularization (Budoff and Shinbane, 2010).

We have previously documented the inverse association of hyperthymic temperament and the presence of CAD, however, the role of affective temperaments in relation to severe CAD has not been shown yet (Nemcsik et al., 2017). The current study aimed to evaluate the associations between affective temperaments and the presence of significant coronary artery stenosis, as assessed by CCTA. Based on our previous findings (Eory et al., 2014; László et al., 2016; Nemcsik et al., 2017), we hypothesized a positive association in case of cyclothymic and an inverse association in case of hyperthymic temperament.

2. Methods

2.1. Study population

Overall, 225 consecutive Caucasian patients with stable anginal symptoms referred to clinically indicated CCTA were enrolled in a cross-sectional design. Inclusion criteria included patients older than 18 years, who gave approval to data retrieval and analysis. Patients with known CAD, previous coronary intervention, coronary bypass operation or with non-diagnostic image quality were excluded from the current study. Further exclusion criteria included ongoing psychiatric disorders (administration of antipsychotic agents or ongoing major depressive episode) and dementia potentially interfering with the completion of questionnaires. Demographic, anthropometric and medical data of all patients were recorded, and participants were asked to complete the psychometric autoquestionnaire before the examination. Patients were documented to have dyslipidemia if statins were regularly prescribed. Definition of hypertension relied on the regular administration of antihypertensive medications. The modified Diamond-Forrester model was used to define pretest probability (PTP) of obstructive CAD (Al'Aref et al., 2020).

All patients agreed to data retrieval and analysis and provided written informed consent prior to the examination. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, the Hungarian Ministry of Health (ETT TUKEB 570/2014) and was carried out in accordance with the tenets of the Declaration of Helsinki.

2.2. Coronary computed tomography angiography

CCTA examinations were performed using a 256-slice CT scanner (Philips Brilliance iCT, Best, The Netherlands) with prospective ECG-triggered axial acquisition mode. Tube voltage of 100–120 kVp and tube current of 200–300 mAs was implemented, according to individual anthropometrics. Image acquisition was performed with 270 msec rotation time and 128 × 0.625 mm collimation. Blood pressure and heart rate were measured once on the left arm in sitting position, one hour prior to the CT examination. A maximum of 100 mg metoprolol was given orally and up to 20 mg intravenously for heart rate control, if the patient's heart rate exceeded 65 beats/min. All patients received sublingual nitroglycerin (0.8 mg) to induce proper vasodilation during CCTA. Iomeprol contrast material (Iomeron 400, Bracco Ltd, Milan, Italy) through antecubital venous access was used with 85–95 ml contrast agent at a flow rate of 4.5–5.5 ml/*sec* using a four-phasic protocol (Karády et al., 2017). In order to obtain proper scan timing, bolus tracking in the left atrium (LA) was used. CTA datasets were reconstructed using iterative reconstruction algorithms with 0.8 mm slice thickness and 0.4 mm increment (iDose5 and IMR, Philips Healthcare, Cleveland, OH, USA).

2.3. Assessment of coronary artery disease

Evaluation of the images was performed by experienced readers (with 5–10 years of experience in cardiac CT). All images were processed using an advanced analysis platform (Philips IntelliSpace Portal, Philips Healthcare, Best, The Netherlands). The extent, severity and distribution of CAD was reported. All readers assessed coronary lesions according to Society of Cardiovascular Computed Tomography (SCCT) guidelines using an 18-segment coronary tree model (Abbara et al., 2016). We defined severe CAD as the presence of significant luminal diameter stenosis (≥70% or ≥50% in case of LM) in ≥1 major coronary artery (LM, LAD, Cx, RCA, major side branches: >2 mm luminal diameter). Representative images of a patient with severe CAD are presented on Fig. 1.

2.4. Evaluation of affective temperaments and depression

The Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) is an 110-item self-report instrument, developed to assess affective temperaments in depressive, cyclothymic, hyperthymic, irritable, and anxious subscales, requiring "yes" (score 1) or "no" (score 0) answers (Akiskal et al., 2005b).

The Beck Depression Inventory (BDI) is a 21-question multiple-choice, self-report questionnaire, a widely used instrument that was used to evaluate severity of depression (Beck et al., 1961).

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are expressed as numbers and percentages. Differences between descriptive characteristics, as well as TEMPS-A and BDI scores were compared between groups using unpaired Student's *t*-test for continuous variables and chi-square test for categorical values. Logistic regression analysis was used to assess the determinants of severe CAD. The predictive power of affective temperaments was

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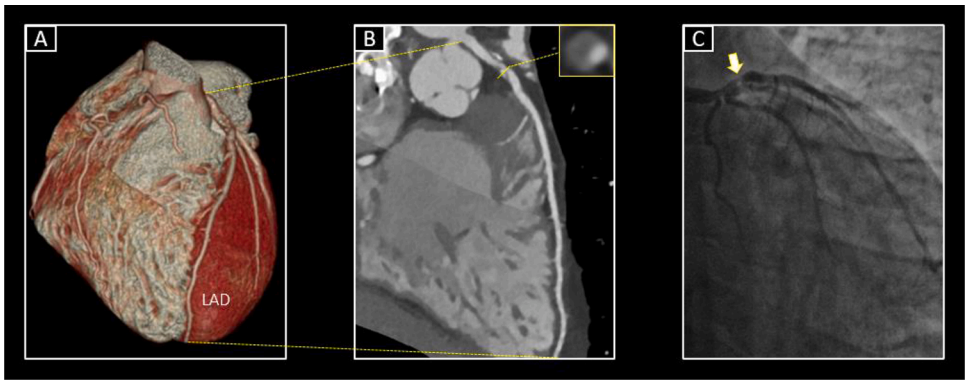

Fig. 1. (A) Representative 3D volumetric image of a 44-year-old male patient with significant coronary artery stenosis and a cyclothymic temperament score of 12. (B) Curved multiplanar reformatted image of the left anterior descending artery (LAD) and cross-sectional image of a partially calcified plaque causing severe stenosis. (C) Subsequently performed coronary angiogram. Arrow points to the severe stenosis, corresponding with the location seen on CT.
LAD: Left Anterior Descending Artery.

initially investigated as continuous variables. Given that age and sex are documented and widely accepted predictors of CAD, our first model was primarily adjusted for these factors. Traditional risk factors and those psychometric parameters that had a $p<0.10$ value in Model I were entered into further multivariate logistic models to assess independent association with severe CAD. Since a high degree of intercorrelation is existent between affective temperaments, affective temperaments were fit into the multiple regression analyses separately (Model II and Model III). Receiver operating curve (ROC) analysis was performed thereafter, and optimal cutoff values were defined based on Youden index (sensitivity + specificity minus 1) for affective temperament scores in each five subscales. Model I was primarily adjusted for age and gender, as well, while cutoff values for each temperament score that proved to have a $p<0.10$ were consecutively entered into Model II, Model III and Model IV, along with traditional risk factors. A two-sided $p < 0.05$ was considered to be significant in all analyses. SPSS (Armonk, NY, USA version 25.0) was used for all calculations.

3. Results

In total, our study population consisted of 225 patients. The mean age of our cohort was 58.5 ± 12.14 years, approximately half of them (106/225; 46.7%) were female and had dyslipidemia (118/225; 52.0%). Severe CAD was observed in 41 cases (18.2%). The mean age of patients with severe CAD was significantly higher, as compared to the other group: 63.0 ± 9.9 vs 57.5 ± 12.4 years ($p = 0.03$). The proportion of women was significantly lower in those with severe CAD: 36.6% of those with severe CAD vs 49.5% of those without significant coronary artery stenosis ($p<0.001$). Regarding traditional risk factors in the severe CAD cohort, the prevalence of diabetes mellitus [29.3% vs 13.6% ($p = 0.01$)] and dyslipidemia [78.0% vs 46.7% ($p<0.001$)] proved to be significantly higher. No statistically significant difference could be observed regarding psychometric parameters. Demographic parameters, clinical data and scores in the different scales of affective temperaments are summarized in Table 1.

In order to determine the predictors of significant coronary stenosis, uni- and multivariate logistic regression analyses were applied. Of all the baseline characteristics, dyslipidemia and cyclothymic temperament were associated with severe CAD in the regression model corrected for age and sex (Model I). Dyslipidemia (OR = 4.85 CI: 1.99–11.81, $p = 0.001$) and cyclothymic affective temperament (OR = 1.12 CI: 1.02–1.23, $p = 0.02$) remained to be independent predictors of severe CAD in multivariate analysis, while hyperthymic temperament (OR = 0.92 CI: 0.84–1.00, $p = 0.04$) significantly decreased the odds of significant luminal stenosis (Model II and III). Table 2 details the results of the multiple logistic regression analyses.

Based on multiple ROC analyses, depressive scores >6 [sensitivity: 48.8%; specificity: 60.9%; AUC (Area Under the Curve): 0.53], cyclothymic scores >7 (sensitivity: 31.7%; specificity: 83.2%; AUC: 0.56), hyperthymic scores >11 (sensitivity: 56.1%; specificity: 60.3%; AUC: 0.58), irritable scores >6 (sensitivity: 39.0%; specificity: 77.2%; AUC: 0.54), and anxious scores >5 (sensitivity: 29.3%; specificity: 85.3%; AUC: 0.53) yielded the highest Youden index and were thus defined as optimal cutoff values. Model I was primarily adjusted for gender and sex. According to further logistic regression analyses, cyclothymic scores >6 [odds ratio (OR) = 3.23 CI: 1.35–7.76, $p = 0.01$], hyperthymic temperament scores >11 (OR = 0.41 CI: 0.19–0.90, $p = 0.03$), and irritable scores >6 (OR = 2.79 CI: 1.17–6.69, $p = 0.02$) independently

Table 1
Demographic parameters, cardiovascular risk factors, TEMPS-A and BDI scores in patients with and without severe coronary artery stenosis.

		Severe stenosis		
	Total	(+)	(–)	p-value
Number	225	41	184	–
Demographics				
Age (years)	***58.5±12.1***	***63.0±9.9***	***57.5±12.4***	***0.03***
Female sex, n (%)	**106 (46.7)**	**15 (36.6)**	**91 (49.5)**	***<0.001***
BMI (kg/m^2)	28.7±5.4	29.3±5.7	28.6±5.3	0.75
Cardiovascular risk factors				
Current smoker, n (%)	24 (10.6)	3 (7.3)	21 (11.4)	0.44
Hypertension, n (%)	156 (69.3)	31 (75.6)	125 (67.9)	0.34
Antihypertensive medication, n (%)				
ACE-inhibitor	53 (23.3)	11 (26.8)	42 (22.8)	0.60
ARB	58 (25.6)	13 (31.7)	45 (24.5)	0.35
Calcium channel blocker	43 (18.9)	5 (12.2)	38 (20.7)	0.21
Beta blocker	98 (43.2)	20 (48.8)	78 (42.4)	0.47
Diuretic	78 (34.4)	14 (34.1)	64 (34.8)	0.92
Alpha-adrenergic receptor blocker	19 (8.4)	3 (7.3)	16 (8.7)	0.77
Centrally acting agents	9 (4.0)	3 (7.3)	6 (3.3)	0.23
Number of antihypertensive agents				0.88
1	32 (14.1)	8 (19.5)	24 (13.0)	
2	43 (18.9)	8 (19.5)	35 (19.0)	
3	37 (16.3)	8 (19.5)	29 (15.8)	
4	23 (10.1)	4 (9.8)	19 (10.3)	
5	5 (2.2)	1 (2.4)	4 (2.2)	
6	2 (0.9)	0 (0.0)	2 (1.1)	
Diabetes mellitus, n (%)	***37 (16.3)***	***12 (29.3)***	***25 (13.6)***	***0.01***
Dyslipidemia, n (%)	***118 (52.0)***	***32 (78.0)***	***86 (46.7)***	***<0.001***
PTP,%				
Updated Diamond-Forrester	***6.8±5.8***	***10.3±7.6***	***6.1±5.0***	***<0.001***
Affective temperaments				
Depressive	6.4±3.0	6.7±3.4	6.3±3.0	0.41
Cyclothymic	4.2 ±3.8	5.2±4.7	4.0±3.6	0.33
Hyperthymic	12.0±4.4	11.0±4.4	12.2±4.4	0.44
Irritable	4.5±3.3	4.8±3.6	4.4±3.3	0.14
Anxious	6.4±5.4	6.7±6.7	6.4±5.1	0.40
Beck Depression Inventory	6.5±6.0	7.3±7.1	6.3±5.7	0.46

BMI, Body mass index; PTP, pretest probability.
Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are expressed as numbers and percentages.

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Table 2
Uni- and multivariate logistic regression analysis of affective temperaments, cardiovascular risk factors and severe coronary artery disease, primarily adjusted for age and sex.

	Model I.			Model II.			Model III.		
	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p
BMI (kg/m^2)	1.01	0.95–1.08	0.75	0.99	0.91–1.07	0.75	0.96	0.92–1.08	0.91
Current smoker	1.62	0.59–4.47	0.35	2.03	0.67–6.11	0.21	2.19	0.72–6.60	0.17
Hypertension	0.89	0.38–2.06	0.79	0.59	0.21–1.64	0.31	0.59	0.21–1.66	0.32
Diabetes mellitus	1.95	0.85–4.47	0.10	1.50	0.57–3.95	0.41	1.57	0.61–4.06	0.35
Dyslipidemia	***3.81***	***1.69–8.58***	***0.001***	***5.36***	***2.16–13.28***	***<0.001***	***4.73***	***1.95–11.49***	***<0.001***
PTP	***1.08***	***1.00–1.16***	***0.045***	***1.10***	***1.01–1.19***	***0.03***	***1.09***	***1.00–1.18***	***0.04***
Depressive	1.08	0.96–1.22	0.18						
Cyclothymic	***1.10***	***1.01–1.20***	***0.03***	***1.12***	***1.02–1.23***	***0.02***			
Hyperthymic	0.92	0.85–1.00	0.053				***0.91***	***0.83–0.96***	***0.04***
Irritable	1.06	0.96–1.18	0.26						
Anxious	1.03	0.97–1.11	0.32						
Beck Depression Inventory	1.03	0.97–1.09	0.31						

BMI, Body mass index; PTP, pretest probability.
Model I: traditional risk factors and psychometric parameters, primarily adjusted for age and gender; Model II and Model III: multivariate analyses including traditional risk factors and each temperament score with $p<0.10$ in Model I.

predict severe CAD (Model II, III and IV). Based on the results, a hyperthymic score >11 decreases the odds for severe CAD by 59%, whereas cyclothymic score >7 and irritable score >6 cause a 3.23- and a 2.79-fold increase in the odds of significant luminal stenosis, respectively. Table 3 summarizes the results of the final multivariate logistic regression analysis.

4. Discussion

Our study revealed that aside from traditional risk factors and pretest probability, cyclothymic and hyperthymic affective temperaments are independent predictors of the presence of significant coronary artery stenosis. While higher cyclothymic temperament score increases the odds of severe CAD, an inverse association could be observed in case of hyperthymic scores. Furthermore, a hyperthymic affective temperament score >11 proved to be independently protective of severe CAD, while scores of cyclothymic temperament >7 and irritable >6 had a direct relationship with the presence of significant luminal stenosis in our cohort of 225 patients.

Standard modifiable and non-modifiable risk factors of coronary atherosclerosis that include age, male gender, smoking, dyslipidemia, hypertension and diabetes have extensively been studied to date. However, growing evidence demonstrates the impact of psychosocial factors on coronary heart disease as well (Piepoli et al., 2016). A two-fold increase in relative risk was revealed regarding CV mortality in people with diagnosed depression but mild depressive symptoms elevate CV risk without diagnosed major depressive disorder, as well (Penninx et al., 2001; Rafanelli et al., 2013). Additionally, hostility and anger traits are associated with an increased risk for CV events in both healthy and CAD populations (Chida and Steptoe, 2009). Our results further expand evidence on the detrimental role of dyslipidemia on CAD, while also establishing the potential effect of different affective temperaments. In contrast to literature, however, no association was found in our cohort with the severity of depression, which can be the consequence of the low average depression score of the study population.

Substantial evidence supports the association between affective temperaments and psychopathology. Previous studies have implicated a genetic association between hyperthymic affective temperament and the pathogenesis of bipolar I disorder (Röttig et al., 2007). Cyclothymic affective temperament was shown to be the most pronounced affective temperament type in patients with bipolar II disorder (Akiskal et al., 2003), and is considered to be the precursor of bipolar disorder often presenting with atypical features (Akiskal, 2003). Furthermore, cumulating evidence supports the association of depressive temperament and unipolar depression (Akiskal et al., 2005a).

Apart from their importance in psychopathology, extensive evidence is available regarding the relationship of affective temperaments and CV pathology, especially in case of cyclothymic, irritable and hyperthymic temperaments.

Cyclothymic traits appear to lie on a polygenic continuum between

Table 3
Results of the multiple regression analyses applying different cut-off values for affective temperaments, primarily adjusted for age and gender.

	Model I.			Model II.			Model III.			Model IV.		
	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p
Current smoker	1.62	0.59–4.47	0.35	2.04	0.68–6.17	0.21	2.02	0.67–6.09	0.21	2.31	0.78–6.90	0.13
BMI (kg/m^2)	1.01	0.95–1.08	0.75	0.99	0.92–1.08	0.99	0.96	0.92–1.08	0.90	0.98	0.91–1.07	0.68
Hypertension	0.89	0.38–2.06	0.79	0.58	0.21–1.65	0.58	0.60	0.22–1.69	0.34	0.59	0.21–1.66	0.32
Diabetes mellitus	1.95	0.85–4.47	0.10	1.49	0.57–3.91	0.42	1.62	0.62–4.20	0.32	1.51	0.58–3.98	0.40
Dyslipidemia	***3.81***	***1.69–8.58***	***<0.001***	***5.37***	***2.15–13.39***	***<0.001***	***4.73***	***1.95–11.48***	***<0.001***	***5.43***	***2.19–13.49***	***<0.001***
PTP	***1.08***	***1.00–1.16***	***0.045***	***1.10***	***1.01–1.20***	***0.02***	***1.09***	***1.00–1.18***	***0.04***	1.08	0.10–1.18	0.06
Depressive>6	1.78	0.87–3.64	0.12									
Cyclothymic>7	***2.80***	***1.24–6.32***	***0.01***	***3.59***	***1.46–8.85***	***0.005***						
Hyperthymic>11	0.50	0.24–1.05	0.07				***0.43***	***0.19–0.99***	***0.048***			
Irritable>6	***2.27***	***1.05–4.93***	***0.04***							***2.89***	***1.21–6.87***	***0.02***
Anxious>5	1.42	0.64–3.13	0.39									
Beck Depression Inventory>9	1.63	0.74–3.60	0.22									

BMI, Body mass index; PTP, pretest probability.
Model I: traditional risk factors and ROC analysis derived optimal cutoff values for psychometric scores, primarily adjusted for age and gender; Model II, Model III and Model IV: multivariate analyses including traditional risk factors and each temperament with an association of $p<0.10$ in Model I.

excessive temperament and bipolar disorder (Akiskal et al., 1977). Cyclothymic affective temperament is characterized by erratic instability in mood and the hallmark of the temperament is the chronic, biphasic dysregulation of vigilance, self-esteem, and circadian rhythm (Akiskal et al., 2005c). Our previous studies have demonstrated the effect of cyclothymic temperament on the age of onset of hypertension, while this temperament also correlated with the history of coronary events in hypertensive patients (Eory et al., 2014; Kőrösi et al., 2019). Additionally, our recent findings revealed the relationship of cyclothymic temperament both with white-coat and resistant hypertension (Kőrösi et al., 2020). Our findings further expand the evidence on the impact of cyclothymic affective temperament on CV pathology.

Irritable temperament has been characterized by a tendency to overreact to aversive stimuli with negative affect and is best described by impulsiveness, anger and hostility (Suarez et al., 1998). An inverse relationship between hostility scores and high frequency components of heart rate variability power spectrum were observed previously (Sloan et al., 2001). Furthermore, we recently demonstrated in hypertensive patients that nighttime peripheral and central systolic blood pressure are associated with irritable affective temperament (Kőrösi et al., 2019). Our results highlight that while these factors are documented predictors of CAD, irritable affective temperament may also be associated with severe CAD, especially in its more pronounced form.

Hyperthymic affective temperament mirrors state-like positive affects as it is a trait characterized by exuberant, upbeat, overenergetic and overconfident lifelong traits and stimulus-seeking attributes (Akiskal, 1992). This temperament is regarded as a protective factor against suicide and major depressive disorder (Vázquez et al., 2010). Regarding CV pathology, higher hyperthymic temperament score is associated with better pulse wave reflection (augmentation index) in chronic hypertensive patients (Laszlo et al., 2016). We also demonstrated an inverse association between hyperthymic temperament and coronary atherosclerosis (Nemcsik et al., 2017). Our present research provides further evidence to the protective role of hyperthymic temperament on CV pathology.

Its exquisite negative predictive value has established CCTA as a highly effective noninvasive alternative to invasive coronary angiography to rule out obstructive CAD (Budoff et al., 2008). Currently, a luminal stenosis of $\geq$70% is widely regarded as the threshold for the indication of intervention in clinical practice (Budoff and Shinbane, 2010).

The present study was limited by its cross-sectional design, which precluded causal inference. However, since affective temperaments are regarded as the stable core of personality, developing in childhood, and remain relatively stable through life, it is safe to assume that prevailing coronary artery disease does not contribute to changes in affective temperaments. Nevertheless, prospective studies should be targeted at confirming this hypothesis in the future. Although our methodology used standardized autoquestionnaires and excluded patients with dementia, a complete exclusion of misinterpretations or mistakes by patients is nevertheless impossible. Moreover, generalizability of our results is limited by the fact that we enrolled solely patients that were referred to CCTA. Given that race-specific differences are well-documented in the pattern of affective temperaments, the fact that all of the enrolled patients were Caucasian is a shortcoming. Additionally, blood pressure was not evaluated according to current guidelines, as it was measured only once. Therefore, we decided not to include our blood pressure data into the regression analysis. Given that controlled and uncontrolled hypertensive patients were not distinguished in our patient population, uncontrolled hypertension could not be built into the multivariate analysis. It is plausible to assume that such a variable yields stronger predictive value than hypertension in general and could potentially decrease the demonstrated effect of affective temperaments.

In conclusion, our results revealed that in patients referred to clinically indicated CCTA, affective temperaments are independent predictors of severe CAD after the adjustment for traditional CV risk factors and pretest probability. Our study suggests that evaluation of affective temperaments may have an incremental value in cardiovascular risk stratification of patients and with further evidence supporting our findings, their assessment could potentially be exploited for CV prevention purposes. Evaluation of affective temperaments is an easy-to-apply, low cost method that may establish further potential means of identifying patients with elevated risk for severe CAD as potential targets for earlier and more aggressive primary prevention.

Author statement

Contributors

MV, BS, MK, XG, ZR, BM, PM, and JN contributed to the design of the work. MB and BV contributed to the acquisition, analysis, and interpretation of data for the work. MV drafted the manuscript. BS, MK, MB, BV, XG, ZR, BM, PM, and JN critically revised the manuscript. All listed authors have approved the final article.

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Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary materials

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References

Abbara, S., Blanke, P., Maroules, C.D., Cheezum, M., Choi, A.D., Han, B.K., Marwan, M., Naoum, C., Norgaard, B.L., Rubinshtein, R., Schoenhagen, P., Villines, T., Leipsic, J., 2016. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of Cardiovascular Computed Tomography Guidelines Committee: endorsed by the North American Society for Cardiovascular Imaging (NASCI). J. Cardiovasc. Comput. Tomogr. 10, 435–449. https://doi.org/10.1016/j.jcct.2016.10.002.

Akiskal, H.S., 2003. Validating "hard" and "soft" phenotypes within the bipolar spectrum: continuity or discontinuity? J. Affect. Disord. 73, 1–5. https://doi.org/10.1016/S0165-0327(02)00390-7.

Akiskal, H.S., 1992. Delineating irritable and hyperthymic variants of the cyclothymic temperament. J. Pers. Disord. 6, 326–342.

Akiskal, H.S., Akiskal, K., Allilaire, J.F., Azorin, J.M., Bourgeois, M.L., Sechter, D., Fraud, J.P., Chatenêt-Duchêne, L., Lancrenon, S., Perugi, G., Hantouche, E.G., 2005a. Validating affective temperaments in their subaffective and socially positive attributes: psychometric, clinical and familial data from a French national study. J. Affect. Disord. 85, 29–36. https://doi.org/10.1016/j.jad.2003.12.009.

Akiskal, H.S., Akiskal, K.K., Haykal, R.F., Manning, J.S., Connor, P.D., 2005b. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. J. Affect. Disord. 85, 3–16. https://doi.org/10.1016/j.jad.2004.12.001.

Akiskal, H.S., Djenderedjian, A.H., Rosenthal, R.H., Khani, M.K., 1977. Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. Am. J. Psychiatry 134, 1227–1233. https://doi.org/10.1176/ajp.134.11.1227.

Akiskal, H.S., Hantouche, E.G., Allilaire, J.F., 2003. Bipolar II with and without cyclothymic temperament: "dark" and "sunny" expressions of soft bipolarity. J. Affect. Disord. 73, 49–57. https://doi.org/10.1016/S0165-0327(02)00320-8.

Akiskal, H.S., Mendlowicz, M.V., Jean-Louis, G., Rapaport, M.H., Kelsoe, J.R., Gillin, J.C., Smith, T.L., 2005c. TEMPS-A: validation of a short version of a self-rated instrument designed to measure variations in temperament. J. Affect. Disord. 85, 45–52. https://doi.org/10.1016/j.jad.2003.10.012.

Akiskal, H.S., Placidi, G.F., Maremmani, I., Signoretta, S., Liguori, A., Gervasi, R., Mallya, G., Puzantian, V.R., 1998. TEMPS-I: delineating the most discriminant traits of the cyclothymic, depressive, hyperthymic and irritable temperaments in a nonpatient population. J. Affect. Disord. 51, 7–19. https://doi.org/10.1016/S0165-0327(98)00152-9.

Al'Aref, S.J., Maliakal, G., Singh, G., van Rosendael, A.R., Ma, X., Xu, Z., Alawamlh, O.A. H., Lee, B., Pandey, M., Achenbach, S., Al-Mallah, M.H., Andreini, D., Bax, J.J., Berman, D.S., Budoff, M.J., Cademartiri, F., Callister, T.Q., Chang, H.-.J., Chinnaiyan, K., Chow, B.J.W., Cury, R.C., DeLago, A., Feuchtner, G., Hadamitzky, M., Hausleiter, J., Kaufmann, P.A., Kim, Y.-.J., Leipsic, J.A., Maffei, E., Marques, H., Gonçalves, P.de A., Pontone, G., Raff, G.L., Rubinshtein, R., Villines, T. C., Gransar, H., Lu, Y., Jones, E.C., Peña, J.M., Lin, F.Y., Min, J.K., Shaw, L.J., 2020. Machine learning of clinical variables and coronary artery calcium scoring for the prediction of obstructive coronary artery disease on coronary computed tomography angiography: analysis from the CONFIRM registry. Eur. Heart J. 41, 359–367. https://doi.org/10.1093/eurheartj/ehz565.

Baldessarini, R.J., Innamorati, M., Erbuto, D., Serafini, G., Fiorillo, A., Amore, M., Girardi, P., Pompili, M., 2017. Differential associations of affective temperaments and diagnosis of major affective disorders with suicidal behavior. J. Affect. Disord. 210, 19–21. https://doi.org/10.1016/j.jad.2016.12.003.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., Beck, 1.9.6.9., A., T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J, 1961. An inventory for measuring depres- sion. Arch. Gen. Psychiatry 4, 561–571. J. R. Coll. Gen. Pract. 18, 267–71.

Budoff, M.J., Shinbane, J.S., 2010. Cardiac CT Imaging 241–242.

Budoff, M.J., Dowe, D., Jollis, J.G., Gitter, M., Sutherland, J., Halamert, E., Scherer, M., Bellinger, R., Martin, A., Benton, R., Delago, A., Min, J.K., 2008. Diagnostic Performance of 64-Multidetector Row Coronary Computed Tomographic Angiography for Evaluation of Coronary Artery Stenosis in Individuals Without Known Coronary Artery Disease. Results From the Prospective Multicenter ACCURACY (Assessment by Coro. J. Am. Coll. Cardiol. 52, 1724–1732. https://doi.org/10.1016/j.jacc.2008.07.031.

Celeng, C., Takx, R.A.P., Ferencik, M., Maurovich-Horvat, P., 2016. Non-invasive and invasive imaging of vulnerable coronary plaque. Trends Cardiovasc. Med. 26, 538–547. https://doi.org/10.1016/j.tcm.2016.03.005.

Chida, Y., Steptoe, A., 2009. The Association of Anger and Hostility With Future Coronary Heart Disease. A Meta-Analytic Review of Prospective Evidence. J. Am. Coll. Cardiol. 53, 936–946. https://doi.org/10.1016/j.jacc.2008.11.044.

Chinnaiyan, K.M., Raff, G.L., Goraya, T., Ananthasubramaniam, K., Gallagher, M.J., Abidov, A., Boura, J.A., Share, D., Peyser, P.A., 2012. Coronary computed tomography angiography after stress testing: results from a multicenter, statewide registry, acic (advanced cardiovascular imaging consortium). J. Am. Coll. Cardiol. 59, 688–695. https://doi.org/10.1016/j.jacc.2011.10.886.

Eory, A., Rozsa, S., Torzsa, P., Kalabay, L., Gonda, X., Rihmer, Z., 2014. Affective temperaments contribute to cardiac complications in hypertension independently of depression. Psychother. Psychosom. 83, 187–189. https://doi.org/10.1159/000357364.

Karády, J., Panajotu, A., Kolossváry, M., Szilveszter, B., Jermendy, Á.L., Bartykowszki, A., Károlyi, M., Celeng, C., Merkely, B., Maurovich-horvat, P., 2017. The effect of four-phasic versus three-phasic contrast media injection protocols on extravasation rate in coronary CT angiography: a randomized controlled trial. Eur. Radiol. 27, 4538–4543. https://doi.org/10.1007/s00330-017-4866-0.

Kőrösi, B., Vecsey-Nagy, M., Kolossváry, M., Nemcsik-Bencze, Z., Szilveszter, B., László, A., Batta, D., Gonda, X., Merkely, B., Rihmer, Z., Maurovich-Horvat, P., Eörsi, D., Torzsa, P., Nemcsik, J., 2019. Association between Cyclothymic Affective Temperament and Age of Onset of Hypertension. Int. J. Hypertens.

Kőrösi, B., Gyöngyösi, H., Batta, D., László, A., Kovács, I., Tislér, A., Cseprekál, O., Nemcsik-Bencze, Z., Gonda, X., Rihmer, Z., Nemcsik, J., 2020. Evaluation of affective temperaments and arterial stiffness in different hypertension phenotypes. Hypertens. Res. https://doi.org/10.1038/s41440-020-0513-2.

Lagerweij, G.R., De Wit, G.A., Moons, K.G.M., Van Der Schouw, Y.T., Monique Verschuren, W.M., Dorresteijn, J.A.N., Koffijberg, H., 2018. A new selection method to increase the health benefits of CVD prevention strategies. Eur. J. Prev. Cardiol. 25, 642–650. https://doi.org/10.1177/2047487317752948.

Laszlo, A., Tabak, A., Korosi, B., Eorsi, D., Torzsa, P., Cseprekal, O., Tisler, A., Reusz, G., Nemcsik-Bencze, Z., Gonda, X., Rihmer, Z., Nemcsik, J., 2016. Association of affective temperaments with blood pressure and arterial stiffness in hypertensive patients: a cross-sectional study. BMC Cardiovasc. Disord. 16, 158. https://doi.org/10.1186/s12872-016-0337-9.

Marwick, T.H., Cho, I., Ó Hartaigh, B., Min, J.K., 2015. Finding the gatekeeper to the cardiac catheterization laboratory: coronary CT angiography or stress testing? J. Am. Coll. Cardiol. 65, 2747–2756. https://doi.org/10.1016/j.jacc.2015.04.060.

Nemcsik, J., Vecsey-Nagy, M., Szilveszter, B., Kolossváry, M., Karády, J., László, A., Kőrösi, B., Nemcsik-Bencze, Z., Gonda, X., Merkely, B., Rihmer, Z., Maurovich-Horvat, P., 2017. Inverse association between hyperthymic affective temperament and coronary atherosclerosis: a coronary computed tomography angiography study. J. Psychosom. Res. 103 https://doi.org/10.1016/j.jpsychores.2017.10.013.

Penninx, B.W., Beekman, A.T., Honig, A., Deeg, D.J., Schoevers, R.A., van Eijk, J.T., van Tilburg, W., 2001. Depression and cardiac mortality: results from a community-based longitudinal study. Arch. Gen. Psychiatry 58, 221–227. https://doi.org/10.1001/archpsyc.58.3.221.

Perugi, G., Toni, C., Maremmani, I., Tusini, G., Ramacciotti, S., Madia, A., Fornaro, M., Akiskal, H.S., 2012. The influence of affective temperaments and psychopathological traits on the definition of bipolar disorder subtypes: a study on Bipolar i Italian National sample. J. Affect. Disord. 136 https://doi.org/10.1016/j.jad.2009.12.027.

Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., Catapano, A.L., Cooney, M. T., Corrà, U., Cosyns, B., Deaton, C., Graham, I., Hall, M.S., Hobbs, F.D.R., Løchen, M.L., Löllgen, H., Marques-Vidal, P., Perk, J., Prescott, E., Redon, J., Richter, D.J., Sattar, N., Smulders, Y., Tiberi, M., Van Der Worp, H.B., Van Dis, I., Verschuren, W.M.M., Binno, S., De Backer, G., Roffi, M., Aboyans, V., Bachl, N., Carerj, S., Cho, L., Cox, J., De Sutter, J., Egidi, G., Fisher, M., Fitzsimons, D., Franco, O.H., Guenoun, M., Jennings, C., Jug, B., Kirchhof, P., Kotseva, K., Lip, G.Y. H., Mach, F., Mancia, G., Bermudo, F.M., Mezzani, A., Niessner, A., Ponikowski, P., Rauch, B., Stauder, A., Turc, G., Wiklund, O., Windecker, S., Zamorano, J.L., Achenbach, S., Badimon, L., Barón-Esquivias, G., Baumgartner, H., Bax, J.J., Dean, V., Erol, Ç., Gaemperli, O., Kolh, P., Lancellotti, P., Nihoyannopoulos, P., Torbicki, A., Carneiro, A.V., Metzler, B., Najafov, R., Stelmashok, V., De Maeyer, C., Dilić, M., Gruev, I., Miličić, D., Vaverkova, H., Gustafsson, I., Attia, I., Duishvili, D., Ferrières, J., Kostova, N., Klimiashvili, Z., Hambrecht, R., Tsioufis, K., Szabados, E., Andersen, K., Vaughan, C., Zafrir, B., Novo, S., Davletov, K., Jashari, F., Kerimkulova, A., Mintale, I., Saade, G., Petrulioniene, Z., Delagardelle, C., Magri, C. J., Rudi, V., Oukerraj, L., Çölkesen, B.E., Schirmer, H., Dos Reis, R.P., Gherasim, D., Nedogoda, S., Zavatta, M., Giga, V., Filipova, S., Padial, L.R., Kiessling, A., Mahdhaoui, A., Ural, D., Nesukay, E., Gale, C., 2016. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur. Heart J. 37, 2315–2381. https://doi.org/10.1093/eurheartj/ehw106.

Pompili, M., Rihmer, Z., Akiskal, H., Amore, M., Gonda, X., Innamorati, M., Lester, D., Perugi, G., Serafini, G., Telesforo, L., Tatarelli, R., Girardi, P., 2012. Temperaments mediate suicide risk and psychopathology among patients with bipolar disorders. Compr. Psychiatry 53, 280–285. https://doi.org/10.1016/j.comppsych.2011.04.004.

Rafanelli, C., Sirri, L., Grandi, S., Fava, G.A., 2013. Is depression the wrong treatment target for improving outcome in coronary artery disease? Psychother. Psychosom. 82, 285–291. https://doi.org/10.1159/000351586.

Rihmer, Z., Akiskal, K.K., Rihmer, A., Akiskal, H.S., 2010. Current research on affective temperaments. Curr. Opin. Psychiatry. https://doi.org/10.1097/YCO.0b013e32833299d4.

Röttig, D., Röttig, S., Brieger, P., Marneros, A., 2007. Temperament and personality in bipolar I patients with and without mixed episodes. J. Affect. Disord. 104, 97–102. https://doi.org/10.1016/j.jad.2007.02.019.

Sloan, R.P., Bagiella, E., Shapiro, P.A., Kuhl, J.P., Chernikhova, D., Berg, J., Myers, M.M., 2001. Hostility, gender, and cardiac autonomic control. Psychosom. Med. 63, 434–440. https://doi.org/10.1097/00006842-200105000-00012.

Suarez, E.C., Kuhn, C.M., Schanberg, S.M., Williams, R.B., Zimmermann, E.A., 1998. Neuroendocrine, cardiovascular, and emotional responses of hostile men: the role of interpersonal challenge. Psychosom. Med. 60, 78–88. https://doi.org/10.1097/00006842-199801000-00017.

Vázquez, G.H., Gonda, X., Zaratiegui, R., Lorenzo, L.S., Akiskal, K., Akiskal, H.S., 2010. Hyperthymic temperament may protect against suicidal ideation. J. Affect. Disord. 127, 38–42. https://doi.org/10.1016/j.jad.2010.04.015.

Virani, S.S., Alonso, A., Benjamin, E.J., Bittencourt, M.S., Callaway, C.W., Carson, A.P., Chamberlain, A.M., Chang, A.R., Cheng, S., Delling, F.N., Djousse, L., Elkind, M.S.V., Ferguson, J.F., Fornage, M., Khan, S.S., Kissela, B.M., Knutson, K.L., Kwan, T.W., Lackland, D.T., Lewis, T.T., Lichtman, J.H., Longenecker, C.T., Loop, M.S., Lutsey, P. L., Martin, S.S., Matsushita, K., Moran, A.E., Mussolino, M.E., Perak, A.M., Rosamond, W.D., Roth, G.A., Sampson, U.K.A., Satou, G.M., Schroeder, E.B., Shah, S. H., Shay, C.M., Spartano, N.L., Stokes, A., Tirschwell, D.L., VanWagner, L.B., Tsao, C. W., Wong, S.S., Heard, D.G., 2020. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. https://doi.org/10.1161/CIR.0000000000000757.

Wilkins, E., Wilson, L., Wickramasinghe, K., Bhatnagar, P., Leal, J., Luengo-Fernandez, R., Burns, R., Rayner, M., Townsend, N., 2017. European Cardiovascular Disease Statistics 2017 edition. Eur. Hear. Network, Brussels 192 https://doi.org/978-2-9537898-1-2.

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Cyclothymic affective temperament is independently associated with left ventricular hypertrophy in chronic hypertensive patients

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ABSTRACT

Objective: Affective temperaments (depressive, anxious, irritable, hyperthymic, and cyclothymic) are regarded as the stable core of personality and when present in their dominant form, are considered subclinical manifestations and high-risk states for various affective disorders. Furthermore, cumulating evidence supports their relationship with cardiovascular diseases. Our aim was to assess the association between affective temperaments and left ventricular hypertrophy (LVH) in chronic hypertensive patients.

Methods: In the present cross-sectional study, 296 patients referred to coronary computed tomography angiography (CCTA) due to suspected coronary artery disease were analyzed. All patients completed the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A). Left ventricular mass was quantified by CCTA and indexed to the body surface area (LVMi). Logistic regression analysis was used to identify predictors of LVH (men: $\geq$67.2 g/m^2 and women: $\geq$54.7 g/m^2).

Results: Among our patient cohort (mean age: 59.4 $\pm$ 10.6, 44.9% female), the median LVM and LVMi were 115.5 [88.4–140.7] g and 58.4 [47.4–64.2] g/m^2, respectively. Elevated BMI (OR = 1.04 CI: 1.01–1.10, $p = 0.04$) and cyclothymic affective temperament scores (OR = 1.06 CI: 1.00–1.12, p = 0.04) significantly increased the odds of LVH in multivariate logistic regression analysis.

Conclusion: Assessment of affective temperaments may allow for the identification of chronic hypertensive patients with elevated risk for LVH as a potential target for earlier primary intervention.

1. Introduction

Akiskal developed the modern theoretical conceptualization of affective temperaments based on theoretical temperamental models combined with clinical studies of affective disorder patients and their first degree relatives to understand how temperaments, the strongly inherited biological core of the personality are related to the manifestation and course trajectories of affective illness [1]. According to Akiskal's theory of affective temperaments, affective disturbances may potentially manifest in a spectrum from physiological emotional reactivity to affective disorders. Affective temperaments comprise five distinct dimensions (depressive, irritable, anxious, hyperthymic, cyclothymic) that are considered the temporally stable part of emotional reactivity in adulthood [2,3], however, until adolescence and in older age they can demonstrate instability to some extent [4]. Affective temperaments determine reaction to environmental stimuli and their model was designed to characterize subjects in the aspects of cognitive, psychomotor, circadian and social-behavioural traits [5]. The

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Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) consists of 110 self-reported items and was constructed to evaluate the five subscales of affective temperaments [6]. These temperaments, especially in their more marked appearance, have been hypothesized to be subclinical manifestations or phenotypes of mood disorders that influence the emergence, clinical course and several core features of affective disorders [7–9]. Individual patterns of affective temperaments, for instance, are associated with increased level of hopelessness, which is an important predictor of future depression and lifetime suicide risk [10]. Affective temperament scores are documented independent predictors of lifetime suicide attempt and contribute more to predicting suicidal status than the presence of a major affective disorder [11]. Furthermore, growing evidence supports the impact of affective temperaments on somatic diseases and they are emerging as potential risk factors in cardiovascular (CV) pathology, as well [12–14].

CV diseases remain to be the leading cause of morbidity and mortality in the majority of developed countries worldwide, and hypertension is the leading cause of disability-adjusted life years [15]. Overall, high blood pressure is accountable for more CV deaths than any other modifiable CV risk factor [16]. Left ventricular hypertrophy (LVH), defined as an increase in left ventricular mass (LVM), is an independent predictor of CV morbidity and mortality in hypertensive patients, particularly for stroke, heart failure, and atrial fibrillation [17–20]. Currently, non-invasive methods to quantify LVM include echocardiography, cardiac magnetic resonance imaging (MRI), CT angiography, and single-photon emission CT. Due to its widespread availability, moderate expense, and the lack of radiation exposure, two-dimensional transthoracic echocardiography has been the most commonly used modality for LV measurements, however, it yields limited reproducibility for LVM assessment [21,22]. Coronary CT angiography (CCTA) is a robust, non-invasive modality that permits accurate anatomical visualization of the coronaries and the myocardium, and has recently received class I recommendation for the testing of patients with stable chest pain in the European guidelines [23–25]. Previous studies with large patient cohorts have established CT-based reference values for LVM, with highly reproducible measurements [26,27].

In previous studies, affective temperaments have been associated with various aspects of CV and metabolic disorders [28–31]. Understanding the involvement of such psychological factors together with their genetic, biological, behavioural, cognitive and emotional correlates would not only elaborate our insight into the etiopathological background of such somatic conditions, but would also provide valuable methods for risk screening, prevention, and interventions possibly impacting somatic illness course and outcomes.

The aim of our study was to evaluate the associations between affective temperaments and the presence of LVH in hypertensive patients, as assessed by CCTA. Besides its significant association with coronary atherosclerosis, our previous findings emphasize that cyclothymic temperament yields the most marked associations with elevated blood pressure and the rate of cardiac complications in hypertensive patients [12,32–34]. Furthermore, marked cyclothymic traits have been linked to worse therapeutic adherence [35]. On the other hand, hyperthymic temperament is inversely associated with the increased level of arterial stiffening and the absence of coronary atherosclerosis [12,36]. Therefore, we hypothesized a positive correlation between cyclothymic affective temperament and LVH, as well as an inverse association with hyperthymic temperament.

2. Methods

2.1. Study population

In the present cross-sectional, single center study, 413 consecutive Caucasian patients with chronic hypertension and stable anginal symptoms referred to clinically indicated CCTA were screened with low to intermediate CV risk between February 2020 and March of 2021. All patients agreed to imaging by signing a written consent form prior to the examination. Furthermore, those who wished to participate in the current study completed the self-report temperament questionnaire and provided written consent to data retrieval and analysis before imaging. Patients older than 18 years, who gave approval to data retrieval and analysis met the inclusion criteria. Hypertension was defined as the regular administration of antihypertensive medications. Exclusion criteria included: 1) previous acute myocardial infarction (AMI) / percutaneous coronary intervention (PCI), 2) presence of severe comorbidities potentially impacting the myocardium (congenital heart disease, serious valve disease, heart failure, cardiomyopathy, chronic inflammatory disorders, 3) inadequate CTA image quality, and 4) given that obstructive CAD is a documented predictor of LVH [37,38], patients with significant luminal diameter stenosis [$\geq$70% for epicardial arteries or $\geq$ 50% in case of left main (LM)] in $\geq$1 major coronary artery [LM, left anterior descending (LAD), left circumflex (LCx), right coronary artery (RCA), major side branches: >2 mm luminal diameter] were also excluded. Demographic, anthropometric and medical data of all patients were recorded, and participants were asked to complete the psychometric autoquestionnaire before the examination.

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, the Hungarian Ministry of Health (ETT TUKEB 570/2014) and was carried out in accordance with the tenets of the Declaration of Helsinki.

2.2. Image acquisition

Prospectively triggered axial CTA of the heart was performed using a 256-slice general purpose CT scanner (Philips Brilliance iCT, Best, The Netherlands) or a dedicated CV scanner (CardioGraphe, GE Healthcare, Chicago, USA). Tube voltage and current was adjusted according to patient size. Blood pressure and heart rate were measured once on the left arm in sitting position, one hour prior to the CT examination. Iomeprol contrast material (Iomeron 400, Bracco Ltd., Milan, Italy) through antecubital venous access was used with 85–95 ml contrast agent at a flow rate of 4.5–5.5 ml/s using a four-phasic protocol [39]. In order to obtain proper scan timing, bolus tracking in the left atrium was used.

2.3. Image analysis

Analysis of the CTA datasets were performed on a workstation with dedicated semi-automated software (Philips Healthcare, Cleveland, USA). LV measurements were performed by an experienced reader (with 3 years of experience in CCTA) blinded to the patient's clinical data, while 10 image were re-evaluated by a CV radiologist (with 6 years of experience in CCTA), subsequently, to assess reproducibility of the measurements. LV was initially segmented automatically by the software and epi- and endocardial were adjusted manually, if needed (Fig. 1). Papillary muscles were automatically excluded from the measurements and considered as part of the LV cavity. Myocardial mass was quantified automatically based on the Simpson method. LVMi was calculated by indexing LVM values by the body surface area (BSA), as calculated by the Du Bois formula [40]. Previously published CTA-derived reference values were used to define LVH (men: $\geq$67.2 g/m^2 and women: $\geq$54.7 g/m^2) [41]. Evaluation of the coronaries was performed by expert readers (with 5–10 years of experience in cardiac CT). All readers assessed coronary lesions according to Society of Cardiovascular Computed Tomography (SCCT) guidelines using an 18-segment coronary tree model [42]. Degree of stenosis was categorized as follows: 0%, 1–29%, 30–49%, 50–69%, or $\geq$ 70% stenosis. Segment involvement score (SIS) was defined as the sum of coronary segments with plaque, whereas for the calculation of segment stenosis score (SSS), each coronary segment was graded as having no to severe plaque (scores 0–3) based on the degree of stenosis and the scores of all segments were summed subsequently [43]. We defined severe CAD as the presence of

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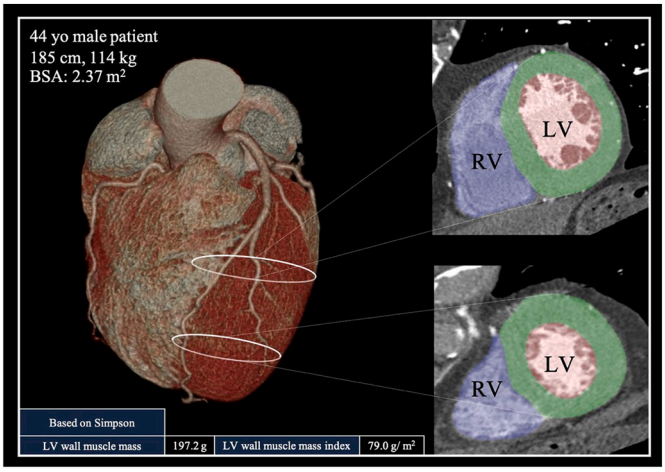

Fig. 1. CCTA confirms LV hypertrophy of a 44-year-old man with hypertension. Representative images showing the result of the semiautomatic short axis segmentation. LV mass measurements were performed in end-diastole by tracing the ventricular cavity and myocardium and was calculated according to Simpson's method.
LV, left ventricle; RV, right ventricle; CCTA, coronary computed tomography angiography.

significant luminal diameter stenosis (≥70% or ≥ 50% in case of LM) in ≥1 major coronary artery (LM, LAD, LCx, RCA) or major side branches: >2 mm luminal diameter).

2.4. Evaluation of affective temperaments and depression

The Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) is an 110-item self-report instrument, developed to assess affective temperaments in depressive, cyclothymic, hyperthymic, irritable, and anxious subscales, requiring "yes" (score 1) or "no" (score 0) answers [6]. The Hungarian validated and standardized version of TEMPS-A was used to assess the point scores in each subscale. The validation of the questionnaire was carried out in 2008 including 1132 individuals, providing national data on reliability and internal consistency [44].

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical variables are expressed as numbers and percentages. Differences between descriptive characteristics, as well as TEMPS-A were compared between groups using unpaired Student's *t*-test or Mann-Whitney test for continuous variables and chi-square test for categorical values. Uni- and multivariate logistic regression analyses were used to assess the determinants of LVH. Each antihypertensive agent and variables that had a $p < 0.10$ value in a univariate setting were entered into further multivariate logistic models to assess independent association with LVH. To determine inter-observer agreement, intra-class correlation coefficient was calculated as indicator of reproducibility.

A two-sided $p < 0.05$ was considered to be significant in all analyses. SPSS (Armonk, NY, USA version 25.0) was used for all calculations.

3. Results

Among a series of 413 consecutive patients who underwent CCTA in the inclusion period, 382 patients agreed to participate in the current study. From this cohort, we excluded 1) 27 patients because of prior AMI/PCI, 2) 19 patients due to severe comorbidity, 3) 2 patients because of inadequate CTA image quality, and 4) 38 patients due to the presence of severe coronary artery stenosis. In total, our study population consisted of 296 patients [(44.9% female; mean age 59.4 ± 10.6 years) (Fig. 2)] and LVH was present in 76 cases (25.7%). The mean age of patients with LVH was significantly lower, as compared to those without: 55.9 ± 10.8 vs 60.9 ± 10.3 years, ($p = 0.01$). Regarding patient anthropometrics, both BMI [30.3 ± 4.4 vs 28.8 ± 3.9 kg/m^2, ($p = 0.005$)] and BSA [2.2 ± 0.3 vs 1.9 ± 0.2 m^2, ($p < 0.001$)] proved to be significantly higher in the LVH group. A significant difference in LVMi could be observed between the LVH and healthy group: 70.3 (62.5–76.8) vs. 53.4 (46.1–61.3) g/m^2, ($p < 0.001$). No statistically significant difference could be observed regarding psychometric parameters. Demographic data, clinical and CTA-derived parameters and scores in the different scales of affective temperaments are summarized in Table 1. Overall, >67% of the hypertensive patients received a beta blocker regularly, while approximately half of them were on ACE-inhibitor. The proportion of patients taking angiotensin receptor blockers was higher in patients with LVH: 70 (30.8%) vs. 35 (46.1%), $p = 0.04$. Overall, 41.9% of patients took diuretics and 36.2% took calcium channel blockers regularly, while approximately 15% of the patients received other antihypertensive medications (alpha-adrenergic receptor blocker or centrally acting agent). Antihypertensive therapy of patients with and without LVH are detailed in Supplementary Table 1.

Overall, 10 datasets were re-evaluated by a second reader in order to assess inter-observer variability of LVM measurements with an intraclass correlation coefficient of 0.91.

In order to determine the predictors of LVH, uni- and multivariate logistic regression analyses were applied. Of all the baseline characteristics, BMI was significantly associated with LVH (OR = 1.07 CI: 1.02–1.13, $p = 0.01$), while the odds of hypertrophy decreased with age (OR = 0.97 CI: 0.94–0.99, p = 0.01). While none of the antihypertensive agents taken regularly presented a significant correlation with the presence of LVH, BMI maintained its association in multivariate analysis, as well (OR = 1.04 CI: 1.01–1.10, $p = 0.04$). Furthermore, cyclothymic affective temperament proved to be an independent predictor of LVH in the multivariate setting (OR = 1.06 CI: 1.00–1.12, p = 0.04). Based on the results, 1 point higher cyclothymic affective temperament score increases the odds of LVH by 7%. Results of the uni- and multivariate analysis are summarized in Table 2.

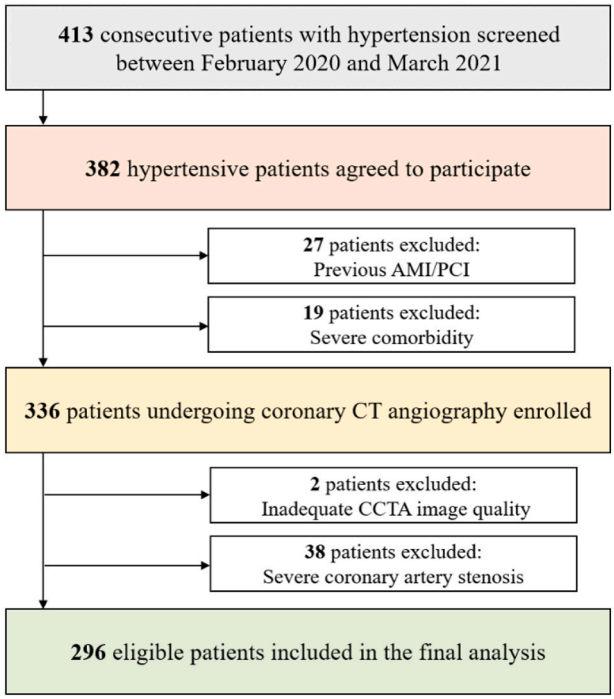

Fig. 2. Flowchart of the study.

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Table 1
Demographic parameters, clinical data, and TEMPS-A scores in patients with and without left ventricular hypertrophy.

	Total	Hypertrophy		p
		(−)	(+)	
Number	296	220	76	–
Demographics				
Age (years)	***59.4 ± 10.6***	***60.9 ± 10.3***	***55.9 ± 10.8***	***0.01***
Female sex, n (%)	140 (44.9)	111 (50.5)	29 (38.2)	0.06
BMI (kg/m^2)	***29.6 ± 4.3***	***28.8 ± 3.9***	***30.3 ± 4.4***	***0.005***
BSA (m^2)	***2.0 ± 0.3***	***1.9 ± 0.2***	***2.2 ± 0.3***	***<0.001***
Cardiovascular risk factors				
Duration of hypertension, (years)	12.0 [5.0–21.0]	11.0 [5.0–24.0]	11.0 [6.0–21.0]	0.99
Current smoker, n (%)	41 (13.1)	33 (15.0)	8 (10.5)	0.33
Diabetes mellitus, n (%)	46 (14.7)	33 (14.1)	15 (19.7)	0.24
Dyslipidemia, n (%)	131 (42.0)	100 (45.5)	31 (40.8)	0.48
SBP (mmHg)	157.6 ± 20.3	155.7 ± 19.4	163.6 ± 23.7	0.11
DBP (mmHg)	90.9 ± 12.5	90.5 ± 12.0	93.0 ± 13.9	0.30
CTA-derived parameters				
SSS	4.0 [1.0–7.0]	5.0 [1.0–8.0]	4.0 [1.0–6.0]	0.83
SIS	4.0 [1.0–6.0]	3.0 [1.0–6.0]	3.0 [1.0–6.0]	0.77
LVM (g)	***115.5 [88.4–140.7]***	***100.2 [83.6–100.2]***	***155.1 [121.2–192.2]***	***<0.001***
LVMi (g/ m^2)	***58.4 [47.4–64.2]***	***53.4 [46.1–61.3]***	***70.3 [62.5–76.8]***	***<0.001***
Affective temperaments				
Depressive	6.2 ± 3.3	6.1 ± 3.2	6.2 ± 3.5	0.55
Cyclothymic	4.0 ± 3.9	3.6 ± 3.9	5.2 ± 3.9	0.09
Hyperthymic	12.6 ± 3.5	12.1 ± 3.6	13.9 ± 3.5	0.07
Irritable	4.7 ± 3.6	4.3 ± 3.4	5.5 ± 4.2	0.33
Anxious	6.2 ± 5.4	6.5 ± 5.7	5.1 ± 4.3	0.09

Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical variables are expressed as numbers and percentages.
BMI, Body mass index; BSA, Body surface index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; CTA, Computed tomography angiography; SSS, Segment stenosis score; SIS, Segment involvement score; LVM, Left ventricular mass; LVMi, left ventricular mass index.

Table 2
Uni- and multivariate logistic regression analysis of the association of cardiovascular risk factors, affective temperaments, and left ventricular hypertrophy.

	Univariate			Multivariate		
	OR	95% CI, lower-upper	p	OR	95% CI, lower-upper	p
Age (years)	***0.97***	***0.94–0.99***	***0.01***	1.00	0.95–1.01	0.11
Female sex	0.61	0.36–1.03	0.07	0.77	0.41–1.35	0.38
BMI (kg/m^2)	***1.07***	***1.02–1.13***	***0.01***	***1.04***	***1.01–1.10***	***0.04***
Duration of hypertension, (years)	1.00	0.98–1.03	0.86			
Number of antihypertensive agents, n (%)	1.23	0.92–1.63	0.16			
ACE/ARB	2.50	0.73–8.63	0.15	2.12	0.60–7.50	0.24
Beta blocker	1.03	0.48–2.18	0.63	1.01	0.46–2.18	0.99
Calcium channel blocker	0.83	0.39–1.75	0.83	0.76	0.35–1.65	0.50
Diuretic	1.81	0.89–3.69	0.10	1.62	0.77–3.39	0.20
Alpha-adrenergic receptor blocker	2.08	0.80–5.36	0.13	1.77	0.67–4.68	0.25
Current smoker	0.67	0.29–1.52	0.33			
Diabetes mellitus	1.50	0.76–2.96	0.24			
Dyslipidemia	0.83	0.49–1.40	0.48			
SSS	0.99	0.93–1.05	0.68			
SIS	0.97	0.89–1.07	0.59			
Depressive	0.97	0.89–1.06	0.54			
Cyclothymic	1.06	0.99–1.12	0.09	***1.06***	***1.00–1.12***	***0.04***
Hyperthymic	1.06	1.00–1.13	0.07	1.04	0.98–1.15	0.12
Irritable	1.04	0.96–1.13	0.33			
Anxious	0.96	0.91–1.01	0.10			

Antihypertensive agents and variables with $p < 0.10$ in univariate analysis were entered into the multivariate model.
BMI, Body mass index; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; SSS, Segment stenosis score; SIS, Segment involvement score.

4. Discussion

In our cross-sectional study investigating the association of affective temperaments and LVH in chronic hypertension, we found that cyclothymic temperament independently predicts increased LVM in our cohort of 296 hypertensive patients. Our results further expand the evidence provided by our previous studies concerning the involvement of the biological core of emotional reactivity in somatic and specifically CV illness.

Previous models of temperaments were constructed to describe the healthy personality. The model of affective temperaments, on the other hand, was developed based on data from affective disorder patients and their healthy first-degree relatives to understand their involvement in the development, high risk states, and manifestations of affective illness. Although the biological and genetic basis of temperaments implies a high level of consistency over time, the concept of heritability does not mean lack of change or development, as Kawamura et al. exhibited moderate changes in temperament scores measured by TEMPS-A over a 6-year period (depressive temperament, $r = 0.59$; cyclothymic temperament, $r = 0.68$; hyperthymic temperament, $r = 0.82$; irritable temperament, $r = 0.66$; anxious temperament, $r = 0.74$; $p < 0.01$ for all values) [3].

Extensive evidence is available about the deleterious effect of affective temperaments on psychopathology. Cyclothymic temperament, in particular, has complex associations with affective disorders. Cyclothymic traits appear to lie on a polygenic continuum between excessive temperament and bipolar disorder [45]. Cyclothymic affective temperament shows a central dimension that includes rapid fluctuations in mood and emotional instability and the hallmark of the temperament is the abrupt *endo*-reactive shifts in vigilance, self-esteem, and circadian rhythm [46]. It is the most prevalent temperament in patients with bipolar II disorder [47] and is generally considered the precursor of bipolar disorder often presenting with worse prognosis [48]. Furthermore, cyclothymic temperament seems to be a contributor of suicidality in patients independent of current major depressive episode [49].

The detrimental effect of affective temperaments, however, extends far beyond the field of affective illness, as cumulating evidence confirms their pathoplastic impact on a wide range of somatic diseases. Akiskal's affective temperaments, and especially cyclothymic temperament, are emerging as a helpful tool in identifying the risk components of developing different CV diseases. The association of cyclothymic temperament and accelerated vascular aging has recently been discovered [14]. We have previously reported that higher cyclothymic temperament scores correlated with earlier manifestation of hypertension, and in hypertensive patients, this temperament was associated with coronary events [32,50]. The results of our current study provide further evidence on the impact of cyclothymic affective temperament on CV pathology and may allow for the more precise risk stratification of hypertensive patients. The mediating factors underlying the detrimental effect of cyclothymic temperament on LVM, however, have not been clarified entirely. Cyclothymic scores are higher in patients with resistant

hypertension but it may also be assumed that the BP values of cyclothymic patients are affected by *endo*-reactive shifts, as well, potentially rendering unreliable office blood pressure values [13]. Furthermore, it has recently been documented that cyclothymic temperament is associated with worse medication adherence in patients with type II diabetes and it is plausible that similar tendencies could be observed in hypertensive patients with respect to antihypertensive medication [35]. Affective temperament scores reported on the medical records of patients have the potential of assisting primary care physicians in the timely identification of poor therapeutic adherence and consecutive end-organ damage by drawing attention to patients with marked cyclothymic traits. These patients may require more common check-ups and with further evidence supporting our findings, stricter target BP-values might be set for those with prominent cyclothymic traits. Furthermore, referral of patients with severe symptoms of cyclothymic temperament to a mental health professional substantially increases their chance of improving self-care behaviors in case of an underlying affective disorders. Future prospective studies should be carried out to explore whether the higher LVH prevalence is due to unrepresentative BP levels, insufficient adherence or other confounding factors.

Large population-based studies have confirmed the adverse prognostic influence of LVH [51,52]. Increased LVM is a strong and independent predictor of CV-related death and all-cause mortality in hypertensive patients [53]. LVH is hypothesized to increase the risk of major adverse cardiac events and mortality through a series of unfavorable metabolic, functional, and cardiac structural changes [37,54,55]. Available data delineating the impact of psychometric factors on the development of hypertension-related organ damage are scarce in the literature. Patients with masked hypertension, a documented predictor of end-organ damage associated with hypertension, previously demonstrated lower scores for type A personality [56]. Furthermore, the level of openness, as assessed by the NEO Five-Factor, was lower in subjects with LVH [57]. To the best of our knowledge, no reports have been published on the potential effect of affective temperaments on increased LVM in hypertensive patients.

As compared to invasive coronary angiography, the exquisite negative predictive value of CCTA has established it a highly effective noninvasive alternative to rule out obstructive CAD [58]. Besides the ability to accurately visualise coronary lumen and wall, CCTA yields the potential of precise LVM measurements [59]. Traditionally, cardiac MRI has been considered the gold-standard for the quantification of LV volume and mass [60]. Despite prevailing concerns regarding the requirement of both contrast and radiation [61], previous studies have suggested that CCTA has the potential of performing LV measurements with excellent interreader correlation [62], a finding that we were able to reproduce in our study. As CCTA displays a tendency of overestimating LVM compared to echocardiography [63], we implemented cut-off values specifically determined for CTA-derived measurements [41].

Our findings on the association of cyclothymic temperament and LVH in hypertensive patients, beyond falling in line with previous studies supporting the involvement of affective temperaments in CV pathology, are also useful and utilizable on a clinical level. Besides its potential use for personality-based screening to increase precision of risk prediction and identifying those at risk with an easy-to-apply and low-cost method, further studies should focus on identifying the potential biological, behavioural or cognitive-emotional moderating and mediating factors of the impact of cyclothymic temperament on different aspects of CV illnesses.

Although we previously hypothesized the protective role of hyperthymic temperament, the current study did not confirm this potential association. Hyperthymic individuals engage in exercise more frequently and given that the current investigation did not provide detailed assessment of physical activity, it is plausible that the lack of correlation is due to the under- or overrepresentation of physically active individuals [64]. Further investigations should incorporate levels of physical activity into the multivariate models.

We acknowledge the limitations pertaining to our study. The cross-sectional design precludes causal inference. Although affective temperament was hypothesized as a contributing factor to the development of LVH, a bidirectional relationship between cyclothymic temperaments and end-organ damage cannot be entirely excluded. Nevertheless, considering the previously documented stability of cyclothymic temperaments and the relatively symptom-free course of hypertension, we believe that the impact of LVH on affective temperaments can only be moderate. Taking the self-reporting nature of the standardized autoquestionnaire into account, a complete exclusion of misinterpretations or mistakes by patients is not impossible. Although a widely used and validated instrument for the characterization of individual emotional reactivity, the TEMPS-A questionnaire captures one aspect of personality, and does not reflect on other sociocultural dimensions of the human psyche which may be considered a limitation. Another limitation is that generalizability of our results is limited by the fact that we only enrolled low to intermediate risk patients with stable angina that underwent clinically indicated CCTA. Given that race-specific differences are well-documented in the pattern of affective temperaments, the fact that all of the enrolled patients were Caucasian is a shortcoming. Moreover, blood pressure was only evaluated once prior to CCTA, a practice that did not comply to current guidelines. Blood pressure data was, therefore, not included in the regression analyses.

In conclusion, our findings demonstrated that in chronic hypertensive patients, cyclothymic affective temperament is an independent predictor of LVH. Our results expand evidence on the deleterious role of psychometric parameters on CV diseases, and establishes a novel potential risk factor for the development of LVH in hypertensive patients. According to our results, affective temperaments may provide further potential means of identifying patients with elevated risk for LVH as potential targets for earlier and more aggressive primary intervention. The clarification of the pathophysiological background of this phenomenon remains a topic of focus and possible mediating factors of affective temperaments in CV pathology need to be assessed in future prospective studies.

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Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix A. Supplementary data

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References

[1] K.K. Akiskal, H.S. Akiskal, The theoretical underpinnings of affective temperaments: Implications for evolutionary foundations of bipolar disorder and human nature, J. Affect. Disord. 85 (2005) 231–239, https://doi.org/10.1016/j.jad.2004.08.002.

[2] B. Korosi, A. Laszlo, A. Tabak, D. Batta, L. Lenart, A. Fekete, D. Eorsi, O. Cseprekal, A. Tisler, Z. Nemcsik-Bencze, X. Gonda, Z. Rihmer, J. Nemcsik, The impact of currently recommended antihypertensive therapy on depression and other psychometric parameters: preliminary communication, Neuropsychopharmacol. Hung. 19 (2017) 11–22, http://www.ncbi.nlm.nih.gov/pubmed/28467955.

[3] Y. Kawamura, T. Akiyama, T. Shimada, T. Minato, T. Umekage, Y. Noda, K. Ukawa, C. Hashidume, Y. Sakai, T. Otowa, T. Sasaki, H.S. Akiskal, Six-year stability of affective temperaments as measured by TEMPS-A, Psychopathology. 43 (2010) 240–247, https://doi.org/10.1159/000313522.

[4] G.H. Vázquez, L. Tondo, L. Mazzarini, X. Gonda, Affective temperaments in general population: a review and combined analysis from national studies, J. Affect. Disord. 139 (2012) 18–22, https://doi.org/10.1016/j.jad.2011.06.032.

[5] H.S. Akiskal, G.F. Placidi, I. Maremmani, S. Signoretta, A. Liguori, R. Gervasi, G. Mallya, V.R. Puzantian, TEMPS-I: delineating the most discriminant traits of the cyclothymic, depressive, hyperthymic and irritable temperaments in a nonpatient population, J. Affect. Disord. 51 (1998) 7–19, https://doi.org/10.1016/S0165-0327(98)00152-9.

[6] H.S. Akiskal, K.K. Akiskal, R.F. Haykal, J.S. Manning, P.D. Connor, TEMPS-A: progress towards validation of a self-rated clinical version of the temperament evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire, J. Affect. Disord. 85 (2005) 3–16, https://doi.org/10.1016/j.jad.2004.12.001.

[7] Z. Rihmer, K.K. Akiskal, A. Rihmer, H.S. Akiskal, Current research on affective temperaments, Curr. Opin. Psychiatry. 23 (2010) 12–18, https://doi.org/10.1097/YCO.0b013e32833299d4.

[8] G. Perugi, C. Toni, I. Maremmani, G. Tusini, S. Ramacciotti, A. Madia, M. Fornaro, H.S. Akiskal, The influence of affective temperaments and psychopathological traits on the definition of bipolar disorder subtypes: a study on Bipolar i Italian National sample, J. Affect. Disord. 136 (2012), https://doi.org/10.1016/j.jad.2009.12.027.

[9] M. Pompili, Z. Rihmer, H. Akiskal, M. Amore, X. Gonda, M. Innamorati, D. Lester, G. Perugi, G. Serafini, L. Telesforo, R. Tatarelli, P. Girardi, Temperaments mediate suicide risk and psychopathology among patients with bipolar disorders, Compr. Psychiatry. 53 (2012) 280–285, https://doi.org/10.1016/j.comppsych.2011.04.004.

[10] M. Pompili, Z. Rihmer, H. Akiskal, M. Amore, X. Gonda, M. Innamorati, D. Lester, G. Perugi, G. Serafini, L. Telesforo, R. Tatarelli, P. Girardi, Temperaments mediate suicide risk and psychopathology among patients with bipolar disorders, Compr. Psychiatry. 53 (2012) 280–285, https://doi.org/10.1016/j.comppsych.2011.04.004.

[11] R.J. Baldessarini, M. Innamorati, D. Erbuto, G. Serafini, A. Fiorillo, M. Amore, P. Girardi, M. Pompili, Differential associations of affective temperaments and diagnosis of major affective disorders with suicidal behavior, J. Affect. Disord. 210 (2017) 19–21, https://doi.org/10.1016/j.jad.2016.12.003.

[12] A. Laszlo, A. Tabak, B. Korosi, D. Eorsi, P. Torzsa, O. Cseprekal, A. Tisler, G. Reusz, Z. Nemcsik-Bencze, X. Gonda, Z. Rihmer, J. Nemcsik, Association of affective temperaments with blood pressure and arterial stiffness in hypertensive patients: a cross-sectional study, BMC Cardiovasc Disord. 16 (2016) 158, https://doi.org/10.1186/s12872-016-0337-9.

[13] B. Kőrösi, H. Gyöngyösi, D. Batta, A. László, I. Kovács, A. Tislér, O. Cseprekál, Z. Nemcsik-Bencze, X. Gonda, Z. Rihmer, J. Nemcsik, Evaluation of affective temperaments and arterial stiffness in different hypertension phenotypes, Hypertens. Res. (2020), https://doi.org/10.1038/s41440-020-0513-2.

[14] M. Vecsey-Nagy, B. Szilveszter, M. Kolossváry, M. Boussoussou, B. Vattay, X. Gonda, Z. Rihmer, B. Merkely, P. Maurovich-Horvat, J. Nemcsik, The association between accelerated vascular aging and cyclothymic affective temperament in women, J. Psychosom. Res. 145 (2021), 110423, https://doi.org/10.1016/j.jpsychores.2021.110423.

[15] S.S. Lim, T. Vos, A.D. Flaxman, G. Danaei, K. Shibuya, H. Adair-Rohani, M. Amann, H.R. Anderson, K.G. Andrews, M. Aryee, C. Atkinson, L.J. Bacchus, A.N. Bahalim, K. Balakrishnan, J. Balmes, S. Barker-Collo, A. Baxter, M.L. Bell, J.D. Blore, F. Blyth, C. Bonner, G. Borges, R. Bourne, M. Boussinesq, M. Brauer, P. Brooks, N. G. Bruce, B. Brunekreef, C. Bryan-Hancock, C. Bucello, R. Buchbinder, F. Bull, R. T. Burnett, T.E. Byers, B. Calabria, J. Carapetis, E. Carnahan, Z. Chafe, F. Charlson, H. Chen, J.S. Chen, A.T.A. Cheng, J.C. Child, A. Cohen, K.E. Colson, B.C. Cowie, S. Darby, S. Darling, A. Davis, L. Degenhardt, F. Dentener, D.C. Des Jarlais, K. Devries, M. Dherani, E.L. Ding, E.R. Dorsey, T. Driscoll, K. Edmond, S.E. Ali, R. E. Engell, P.J. Erwin, S. Fahimi, G. Falder, F. Farzadfar, A. Ferrari, M.M. Finucane, S. Flaxman, F.G.R. Fowkes, G. Freedman, M.K. Freeman, E. Gakidou, S. Ghosh, E. Giovannucci, G. Gmel, K. Graham, R. Grainger, B. Grant, D. Gunnell, H. R. Gutierrez, W. Hall, H.W. Hoek, A. Hogan, H.D. Hosgood, D. Hoy, H. Hu, B. J. Hubbell, S.J. Hutchings, S.E. Ibeanusi, G.L. Jacklyn, R. Jasrasaria, J.B. Jonas, H. Kan, J.A. Kanis, N. Kassebaum, N. Kawakami, Y.H. Khang, S. Khatibzadeh, J. P. Khoo, C. Kok, F. Laden, R. Lalloo, Q. Lan, T. Lathlean, J.L. Leasher, J. Leigh, Y. Li, J.K. Lin, S.E. Lipshultz, S. London, R. Lozano, Y. Lu, J. Mak, R. Malekzadeh, L. Mallinger, W. Marcenes, L. March, R. Marks, R. Martin, P. McGale, J. McGrath, S. Mehta, G.A. Mensah, T.R. Merriman, R. Micha, C. Michaud, V. Mishra, K. M. Hanafiah, A.A. Mokdad, L. Morawska, D. Mozaffarian, T. Murphy, M. Naghavi, B. Neal, P.K. Nelson, J.M. Nolla, R. Norman, C. Olives, S.B. Omer, J. Orchard, R. Osborne, B. Ostro, A. Page, K.D. Pandey, C.D.H. Parry, E. Passmore, J. Patra, N. Pearce, P.M. Pelizzari, M. Petzold, M.R. Phillips, D. Pope, C.A. Pope, J. Powles, M. Rao, H. Razavi, E.A. Rehfuess, J.T. Rehm, B. Ritz, F.P. Rivara, T. Roberts, C. Robinson, J.A. Rodriguez-Portales, I. Romieu, R. Room, L.C. Rosenfeld, A. Roy, L. Rushton, J.A. Salomon, U. Sampson, L. Sanchez-Riera, E. Sanman, A. Sapkota, S. Seedat, P. Shi, K. Shield, R. Shivakoti, G.M. Singh, D.A. Sleet, E. Smith, K. R. Smith, N.J.C. Stapelberg, K. Steenland, H. Stöckl, L.J. Stovner, K. Straif, L. Straney, G.D. Thurston, J.H. Tran, R. Van Dingenen, A. Van Donkelaar, J. L. Veerman, L. Vijayakumar, R. Weintraub, M.M. Weissman, R.A. White, H. Whiteford, S.T. Wiersma, J.D. Wilkinson, H.C. Williams, W. Williams, N. Wilson, A.D. Woolf, P. Yip, J.M. Zielinski, A.D. Lopez, C.J.L. Murray, M. Ezzati, A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010, Lancet. 380 (2012) 2224–2260, https://doi.org/10.1016/S0140-6736(12)61766-8.

[16] G. Danaei, E.L. Ding, D. Mozaffarian, B. Taylor, J. Rehm, C.J. Murray, M. Ezzati, The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors, PLoS Med. 6 (2009), e1000058, https://doi.org/10.1371/journal.pmed.1000058.

[17] G. de Simone, J.S. Gottdiener, M. Chinali, M.S. Maurer, Left ventricular mass predicts heart failure not related to previous myocardial infarction: the Cardiovascular Health Study, Eur. Heart J. 29 (2008) 741–747, https://doi.org/10.1093/eurheartj/ehm605.

[18] S.R. Heckbert, W. Post, G.D.N. Pearson, D.K. Arnett, A.S. Gomes, M. Jerosch-Herold, W.G. Hundley, J.A. Lima, D.A. Bluemke, Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis, J. Am. Coll. Cardiol. 48 (2006) 2285–2292, https://doi.org/10.1016/j.jacc.2006.03.072.

[19] R.V. Milani, C.J. Lavie, M.R. Mehra, H.O. Ventura, J.D. Kurtz, F.H. Messerli, Left ventricular geometry and survival in patients with normal left ventricular ejection fraction, Am. J. Cardiol. 97 (2006) 959–963, https://doi.org/10.1016/j.amjcard.2005.10.030.

[20] C.J. Lavie, R.V. Milani, H.O. Ventura, F.H. Messerli, Left ventricular geometry and mortality in patients >70 years of age with normal ejection fraction, Am. J. Cardiol. 98 (2006) 1396–1399, https://doi.org/10.1016/j.amjcard.2006.06.037.

[21] T.H. Marwick, T.C. Gillebert, G. Aurigemma, J. Chirinos, G. Derumeaux, M. Galderisi, J. Gottdiener, B. Haluska, E. Ofili, P. Segers, R. Senior, R.J. Tapp, J. L. Zamorano, Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE)†, Eur. Hear. Journal. Cardiovasc. Imaging. 16 (2015) 577–605, https://doi.org/10.1093/ehjci/jev076.

[22] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F. A. Flachskampf, E. Foster, S.A. Goldstein, T. Kuznetsova, P. Lancellotti, D. Muraru, M.H. Picard, E.R. Rietzschel, L. Rudski, K.T. Spencer, W. Tsang, J.-U. Voigt, Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr. 28 (2015) 1–39.e14, https://doi.org/10.1016/j.echo.2014.10.003.

[23] C. Celeng, R.A.P. Takx, M. Ferencik, P. Maurovich-Horvat, Non-invasive and invasive imaging of vulnerable coronary plaque, Trends Cardiovasc. Med. 26 (2016) 538–547, https://doi.org/10.1016/j.tcm.2016.03.005.

[24] P. Maurovich-Horvat, M. Ferencik, S. Voros, B. Merkely, U. Hoffmann, Comprehensive plaque assessment by coronary CT angiography, Nat Rev Cardiol. 11 (2014) 390–402, https://doi.org/10.1038/nrcardio.2014.60.

[25] J. Knuuti, W. Wijns, A. Saraste, D. Capodanno, E. Barbato, C. Funck-Brentano, E. Prescott, R.F. Storey, C. Deaton, T. Cuisset, S. Agewall, K. Dickstein, T. Edvardsen, J. Escaned, B.J. Gersh, P. Svitil, M. Gilard, D. Hasdai, R. Hatala, F. Mahfoud, J. Masip, C. Muneretto, M. Valgimigli, S. Achenbach, J.J. Bax, 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes, Eur. Heart J. 41 (2020) 407–477, https://doi.org/10.1093/eurheartj/ehz425.

[26] S.S. Mao, D. Li, D.G. Rosenthal, M. Cerilles, I. Zeb, H. Wu, F. Flores, Y. Gao, M. J. Budoff, Dual-standard reference values of left ventricular volumetric parameters by multidetector CT angiography, J. Cardiovasc. Comput. Tomogr. 7 (2013) 234–240, https://doi.org/10.1016/j.jcct.2013.08.001.

[27] D. Juneau, F. Erthal, O. Clarkin, A. Alzahrani, A. Alenazy, A. Hossain, J.R. Inacio, G. Dwivedi, A.J. Dick, F.J. Rybicki, B.J.W. Chow, Mid-diastolic left ventricular volume and mass: normal values for coronary computed tomography angiography, J. Cardiovasc. Comput. Tomogr. 11 (2017) 135–140, https://doi.org/10.1016/j.jcct.2017.01.011.

[28] A. László, L. Babos, Z. Kis-Igari, A. Pálfy, P. Torzsa, A. Eory, L. Kalabay, X. Gonda, Z. Rihmer, O. Cseprekál, A. Tislér, J. Hodrea, L. Lénárt, A. Fekete, J. Nemcsik, Identification of hypertensive patients with dominant affective temperaments might improve the psychopathological and cardiovascular risk stratification: a pilot, case-control study, Ann. Gen. Psychiatry. 14 (2015) 1–8, https://doi.org/10.1186/s12991-015-0072-0.

[29] B. Amann, R. Mergl, C. Torrent, G. Perugi, F. Padberg, N. El-Gjamal, G. Laakmann, Abnormal temperament in patients with morbid obesity seeking surgical treatment, J. Affect. Disord. 118 (2009) 155–160, https://doi.org/10.1016/j.jad.2009.01.020.

[30] A. Eory, X. Gonda, Z. Lang, P. Torzsa, J. Kalman, L. Kalabay, Z. Rihmer, Personality and cardiovascular risk: association between hypertension and affective temperaments-A cross-sectional observational study in primary care settings, Eur. J. Gen. Pract. 20 (2014) 247–252, https://doi.org/10.3109/13814788.2013.868431.

[31] C. Gois, A. Barbosa, A. Ferro, A.L. Santos, F. Sousa, H. Akiskal, K. Akiskal, M. L. Figueira, The role of affective temperaments in metabolic control in patients

with type 2 diabetes, J. Affect. Disord. 134 (2011) 52–58, https://doi.org/10.1016/j.jad.2011.05.021.
[32] A. Eory, S. Rozsa, P. Torzsa, L. Kalabay, X. Gonda, Z. Rihmer, Affective temperaments contribute to cardiac complications in hypertension independently of depression, Psychother. Psychosom. 83 (2014) 187–189, https://doi.org/10.1159/000357364.
[33] M. Vecsey-Nagy, B. Szilveszter, M. Kolossváry, M. Boussoussou, B. Vattay, X. Gonda, Z. Rihmer, B. Merkely, P. Maurovich-Horvat, J. Nemcsik, The association between accelerated vascular aging and cyclothymic affective temperament in women, J. Psychosom. Res. 145 (2021), 110423, https://doi.org/10.1016/j.jpsychores.2021.110423.
[34] M. Vecsey-Nagy, B. Szilveszter, M. Kolossváry, M. Boussoussou, B. Vattay, X. Gonda, Z. Rihmer, B. Merkely, P. Maurovich-Horvat, J. Nemcsik, Association between affective temperaments and severe coronary artery disease, J. Affect. Disord. 295 (2021) 914–919, https://doi.org/10.1016/j.jad.2021.08.063.
[35] T. Yamamoto, K. Sakurai, M. Watanabe, I. Sakuma, N. Kanahara, A. Shiina, T. Hasegawa, H. Watanabe, M. Iyo, R. Ishibashi, Cyclothymic temperament is associated with poor medication adherence and disordered eating in type 2 diabetes patients: a case-control study, Diabetes Ther. Res. Treat. Educ. Diabetes Relat. Disord. 12 (2021) 2611–2624, https://doi.org/10.1007/s13300-021-01121-y.
[36] J. Nemcsik, M. Vecsey-Nagy, B. Szilveszter, M. Kolossváry, J. Karády, A. László, B. Kőrösi, Z. Nemcsik-Bencze, X. Gonda, B. Merkely, Z. Rihmer, P. Maurovich-Horvat, Inverse association between hyperthymic affective temperament and coronary atherosclerosis: a coronary computed tomography angiography study, J. Psychosom. Res. 103 (2017) 108–112, https://doi.org/10.1016/j.jpsychores.2017.10.013.
[37] S. Kishi, T.A. Magalhaes, R.T. George, M. Dewey, R.J. Laham, H. Niinuma, L. A. Friedman, C. Cox, Y. Tanami, J.D. Schuijf, A.L. Vavere, K. Kitagawa, M.Y. Chen, C.H. Nomura, J.A. Brinker, F.J. Rybicki, M.F. Di Carli, A. Arbab-Zadeh, J.A. C. Lima, Relationship of left ventricular mass to coronary atherosclerosis and myocardial ischaemia: the CORE320 multicenter study, Eur. Hear. Journal. Cardiovasc. Imaging. 16 (2015) 166–176, https://doi.org/10.1093/ehjci/jeu217.
[38] M.M. Ciccone, P. Scicchitano, A. Zito, L. Agati, M. Gesualdo, S. Mandolesi, R. Carbonara, F. Ciciarello, F. Fedele, Correlation between coronary artery disease severity, left ventricular mass index and carotid intima media thickness, assessed by radio-frequency, Cardiovasc. Ultrasound. 9 (2011) 1–8, https://doi.org/10.1186/1476-7120-9-32.
[39] J. Karády, A. Panajotu, M. Kolossváry, B. Szilveszter, Á.L. Jermendy, A. Bartykowszki, M. Károlyi, C. Celeng, B. Merkely, P. Maurovich-horvat, The effect of four-phasic versus three-phasic contrast media injection protocols on extravasation rate in coronary CT angiography: a randomized controlled trial, Eur. Radiol. 27 (2017) 4538–4543, https://doi.org/10.1007/s00330-017-4866-0.
[40] E.F. Du Bois, D. Du Bois, A formula to estimate the approximate surface area if height and weight be known, Arch. Intern. Med. 17 (1916) 863–871.
[41] S.S. Mao, D. Li, D.G. Rosenthal, M. Cerilles, I. Zeb, H. Wu, F. Flores, Y. Gao, M. J. Budoff, Dual-standard reference values of left ventricular volumetric parameters by multidetector CT angiography, J. Cardiovasc. Comput. Tomogr. 7 (2013) 234–240, https://doi.org/10.1016/j.jcct.2013.08.001.
[42] S. Abbara, P. Blanke, C.D. Maroules, M. Cheezum, A.D. Choi, B.K. Han, M. Marwan, C. Naoum, B.L. Norgaard, R. Rubinshtein, P. Schoenhagen, T. Villines, J. Leipsic, SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee, J. Cardiovasc. Comput. Tomogr. 10 (2016) 435–449, https://doi.org/10.1016/j.jcct.2016.10.002.
[43] G.A. Rodriguez-Granillo, P. Carrascosa, A. Deviggiano, C. Capunay, M.C. De Zan, A. Goldsmit, R. Campisi, Pericardial fat volume is related to atherosclerotic plaque burden rather than to lesion severity, Eur. Hear. Journal. Cardiovasc. Imaging. 18 (2017) 795–801, https://doi.org/10.1093/ehjci/jew139.
[44] S. Rózsa, Z. Rihmer, X. Gonda, I. Szili, A. Rihmer, N. Ko, A. Németh, P. Pestality, G. Bagdy, O. Alhassoon, K.K. Akiskal, H.S. Akiskal, A study of affective temperaments in Hungary: Internal consistency and concurrent validity of the TEMPS-A against the TCI and NEO-PI-R, J. Affect. Disord. 106 (2008) 45–53, https://doi.org/10.1016/j.jad.2007.03.016.
[45] H.S. Akiskal, A.H. Djenderedjian, R.H. Rosenthal, M.K. Khani, Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group, Am. J. Psychiatry. 134 (1977) 1227–1233, https://doi.org/10.1176/ajp.134.11.1227.
[46] H.S. Akiskal, M.V. Mendlowicz, G. Jean-Louis, M.H. Rapaport, J.R. Kelsoe, J. C. Gillin, T.L. Smith, TEMPS-A: validation of a short version of a self-rated instrument designed to measure variations in temperament, J. Affect. Disord. 85 (2005) 45–52, https://doi.org/10.1016/j.jad.2003.10.012.
[47] H.S. Akiskal, E.G. Hantouche, J.F. Allilaire, Bipolar II with and without cyclothymic temperament: "dark" and "sunny" expressions of soft bipolarity, J. Affect. Disord. 73 (2003) 49–57, https://doi.org/10.1016/S0165-0327(02)00320-8.
[48] H.S. Akiskal, Validating "hard" and "soft" phenotypes within the bipolar spectrum: Continuity or discontinuity? J. Affect. Disord. 73 (2003) 1–5, https://doi.org/10.1016/S0165-0327(02)00390-7.
[49] E.G. Hantouche, H.S. Akiskal, S. Lancrenon, J.F. Allilaire, D. Sechter, J.M. Azorin, M. Bourgeois, J.P. Fraud, L. Châtenet-Duchêne, Systematic clinical methodology for validating bipolar-II disorder: Data in mid-stream from a french national multi-site study (EPIDEP), J. Affect. Disord. 50 (1998) 163–173, https://doi.org/10.1016/S0165-0327(98)00112-8.
[50] B. Kőrösi, M. Vecsey-Nagy, M. Kolossváry, Z. Nemcsik-Bencze, B. Szilveszter, A. László, D. Batta, X. Gonda, B. Merkely, Z. Rihmer, P. Maurovich-Horvat, D. Eörsi, P. Torzsa, J. Nemcsik, Association between cyclothymic affective temperament and age of onset of hypertension, Int. J. Hypertens 2019 (2019) 1–6.
[51] W.B. Kannel, T. Gordon, W.P. Castelli, J.R. Margolis, Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham study, Ann. Intern. Med. 72 (1970) 813–822, https://doi.org/10.7326/0003-4819-72-6-813.
[52] D. Levy, R.J. Garrison, D.D. Savage, W.B. Kannel, W.P. Castelli, Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study, N. Engl. J. Med. 322 (1990) 1561–1566, https://doi.org/10.1056/NEJM199005313222203.
[53] M.J. Koren, R.B. Devereux, P.N. Casale, D.D. Savage, J.H. Laragh, Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension, Ann. Intern. Med. 114 (1991) 345–352, https://doi.org/10.7326/0003-4819-114-5-345.
[54] M.L. Muiesan, M. Salvetti, A. Paini, C. Monteduro, G. Galbassini, B. Bonzi, P. Poisa, E. Belotti, C. Agabiti Rosei, D. Rizzoni, M. Castellano, E. Agabiti Rosei, Inappropriate left ventricular mass changes during treatment adversely affects cardiovascular prognosis in hypertensive patients, Hypertens. (Dallas, Tex. 1979) 49 (2007) 1077–1083, https://doi.org/10.1161/HYPERTENSIONAHA.107.087320.
[55] M.P. Turakhia, N.B. Schiller, M.A. Whooley, Prognostic significance of increased left ventricular mass index to mortality and sudden death in patients with stable coronary heart disease (from the Heart and Soul Study), Am. J. Cardiol. 102 (2008) 1131–1135, https://doi.org/10.1016/j.amjcard.2008.06.036.
[56] A.S. Konstantopoulou, P.S. Konstantopoulou, I.K. Papargyriou, S.T. Liatis, G. S. Stergiou, D.E. Papadogiannis, Masked, white coat and sustained hypertension: comparison of target organ damage and psychometric parameters, J. Hum. Hypertens. 24 (2010) 151–157, https://doi.org/10.1038/jhh.2009.55.
[57] L. Popiołek, O. Siga, A. Dzieża-Grudnik, I. Popiołek, M. Moląg, J. Królczyk, T. Grodzicki, J. Walczewska, K. Rutkowski, Personality traits and hypertension-mediated organ damage, Psychiatr. Pol. 53 (2019) 1003–1020, https://doi.org/10.12740/PP/108453.
[58] M.J. Budoff, D. Dowe, J.G. Jollis, M. Gitter, J. Sutherland, E. Halamert, M. Scherer, R. Bellinger, A. Martin, R. Benton, A. Delago, J.K. Min, Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease. Results from the prospective multicenter ACCURACY (Assessment by Coro), J. Am. Coll. Cardiol. 52 (2008) 1724–1732, https://doi.org/10.1016/j.jacc.2008.07.031.
[59] A. Fuchs, M.R. Mejdahl, J.T. Kühl, Z.R. Stisen, E.J.P. Nilsson, L.V. Køber, B. G. Nordestgaard, K.F. Kofoed, Normal values of left ventricular mass and cardiac chamber volumes assessed by 320-detector computed tomography angiography in the Copenhagen General Population Study, Eur. Hear. Journal. Cardiovasc. Imaging. 17 (2016) 1009–1017, https://doi.org/10.1093/ehjci/jev337.
[60] K. Nasir, R. Katz, S. Mao, J. Takasu, C. Bomma, J.A.C. Lima, D.A. Bluemke, R. Kronmal, J.J. Carr, M.J. Budoff, Comparison of left ventricular size by computed tomography with magnetic resonance imaging measures of left ventricle mass and volumes: the multi-ethnic study of atherosclerosis, J. Cardiovasc. Comput. Tomogr. 2 (2008) 141–148, https://doi.org/10.1016/j.jcct.2008.01.003.
[61] S. Natori, S. Lai, J.P. Finn, A.S. Gomes, W.G. Hundley, M. Jerosch-Herold, G. Pearson, S. Sinha, A. Arai, J.A.C. Lima, D.A. Bluemke, Cardiovascular function in multi-ethnic study of atherosclerosis: normal values by age, sex, and ethnicity, AJR Am. J. Roentgenol. 186 (2006) S357–S365, https://doi.org/10.2214/AJR.04.1868.
[62] P.M. Madaj, S.R. Pagali, Y.S. Hamirani, S. Raina, S. Nair, I. Zeb, S. Mao, M. J. Budoff, Coronary artery calcium and plaque association with left ventricular mass, assessed by multi-row detector computed tomography, Coron. Artery Dis. 21 (2010) 428–434, https://doi.org/10.1097/MCA.0b013e32833db521.
[63] J.W. Lee, K.J. Nam, J.Y. Kim, Y.J. Jeong, G. Lee, S.M. Park, S.J. Lim, K.S. Choo, Simultaneous assessment of left ventricular function and coronary artery anatomy by third-generation dual-source computed tomography using a low radiation dose, J. Cardiovasc. Imaging. 28 (2020) 21–32, https://doi.org/10.4250/jcvi.2019.0066.
[64] C. Krumm-Merabet, T.D. Meyer, Leisure activities, alcohol, and nicotine consumption in people with a hypomanic/hyperthymic temperament, Pers. Individ. Dif. 38 (2005) 701–712, https://doi.org/10.1016/j.paid.2004.05.024.