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Associations of depression, anxiety and affective temperaments with different hypertension phenotypes

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List of abbreviations

5-HTTLPR	Serotonin-transporter-linked polymorphic region
24-h	Twenty-four hours
ACE	Angiotensin-converting enzyme
ARB	Angiotensin II receptor blocker
ABPM	Ambulatory blood pressure monitoring
baPWV	Brachial-ankle pulse wave velocity
BC	Before Christ
BDI	Beck depression inventory
cfPWV	Carotid-femoral pulse wave velocity
AIx	Augmentation index
BDNF	Brain-derived neurotrophic factor
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CHD	Coronary heart disease
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DBPbrach	Brachial diastolic blood pressure
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GFR-EPI	Glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation
GP	General practitioner
HAM-A	Hamilton anxiety scale
HBPM	Home blood pressure monitoring
HDL	High-density lipoprotein
HF	Heart failure
HMOD	Hypertension-mediated organ damage
HPA	Hypothalamic-pituitary-adrenal

KSH	National Statistical Institute (Központi Statisztikai Hivatal)
LDL	Low-density lipoprotein
LPR	LDL receptor-related protein
MAP	Mean arterial pressure
non-ResHT	Non-resistant hypertensive patients
PP	Pulse pressure
PPbrach	Brachial pulse pressure
PPcent	Central pulse pressure
PWV	Pulse wave velocity
RAAS	Renin-angiotensin-aldosterone system
ResHT	Resistant hypertensive patients
SBP	Systolic blood pressure
SBPbrach	Brachial systolic blood pressure
SBPcent	Central systolic blood pressure
SD	Standard deviation
TEMPS-A	Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto Questionnaire
WHO	World Health Organization
WhHT	White-coat hypertensive patients

1. INTRODUCTION

1.1. The importance of cardiovascular mortality worldwide and in Hungary

Cardiovascular diseases (CVD) including coronary artery disease (CAD), heart failure, peripheral artery disease and stroke are the leading cause of morbidity and mortality in most industrialized countries worldwide, despite the highly effective preventive treatments (1, 2). According to the American Heart Association statistics, in 2020, there were an estimated 19 million deaths from CVDs, with an increase of 18.7% in 10 years (3, 4). Ischemic heart disease was the leading cause of CVD-related health loss globally and in each region of the world, followed by stroke (3, 5). In Central- and Eastern-European countries, including Hungary, CVDs are also the leading cause of mortality (6) (3). Although the overall CVD mortality has been decreased in Hungary over the last 15 years, the prevalence is still high (6). According to the National Statistical Institute (KSH) report in 2019, CVDs caused 49% of deaths in Hungary, which meant more than 64 000 death cases in that year (7).

1.2. The importance of hypertension as a cardiovascular risk factor

A continuous linear relationship between elevated blood pressure and incident cardiovascular (CV) events is well-known at all ages and in all ethnic groups (3, 8, 9). Hypertension is the leading cause of CV mortality and it is in the second place in the list of the preventable causes (e.g. smoking, diabetes, high cholesterol, alcohol consumption, unhealthy lifestyle) of all-cause mortality worldwide, leading to an estimated 10.8 million avoidable deaths each year (8, 10-12). The burden of disease is estimated to contribute to 235 million years of disability and mortality each year (4, 5). Moreover, hypertension and related comorbidities have significant economic cost to patients and their families, health systems and to the national economy, in addition to reducing individual quality of life (4). According to the latest WHO report published in 2023 September, the world population living with hypertension has been doubled between 1990 and 2019, exactly from 650 million to 1.3 billion. Globally, nearly half of people with hypertension are not aware about the condition and only one in five is treated properly. In the European countries the prevalence of high blood pressure among adults is between 30 and 45%, rising with aging (11, 13).

In Hungary, approximately 3.5 million people are suffering from hypertension, its prevalence is almost half of the population aged 30-79 including 56% of men and 41% of women. On average, only 6 out of 10 Hungarian adults with hypertension are diagnosed and only 5 of them are treated, and even among those treated, only one in two have their blood pressure properly controlled (8, 11, 13). In addition, there are non-modifiable (e.g. age, positive family history, male sex) risk factors of CVD which have a complex and interdependent relationship with hypertension. Both the modifiable and non-modifiable CVD risk factors may affect pathophysiological pathways that are also involved in the development of hypertension, such as the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), the cardiac natriuretic peptide system or the endothelial function. Consequently, hypertension can be considered as a result of various adverse processes and not just a simple disease (13-17).

1.3. Definition of different hypertension phenotypes

According to the latest 2023 European Hypertension Guideline (ESH) hypertension is diagnosed when the repeatedly measured office systolic blood pressure (SBP) values are equal or above 140 mmHg and/or the diastolic blood pressure (DBP) values are also equal or above 90 mmHg. According to the level of blood pressure, the duration of hypertension and the number and type of applied antihypertensive medications, 4 main hypertension phenotypes are defined: white-coat hypertension, chronic, non-resistant hypertension, resistant hypertension and masked hypertension (18). The **white-coat hypertension** is defined as elevated blood pressure during the office measurement, where the SBP values are equal or above 140 mmHg and/or the DBP values also equal or above 90 mmHg, but the blood pressure values are within the normal range during a 24-hour (24-h) ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM). It means that the 24-h average is under 130/80 mmHg, the daytime average is lower than 135/85 mmHg, and the nighttime average is lower than 120/70 mmHg in ABPM or lower than 135/85 mmHg in HBPM. Hypertension is **chronic, non-resistant,** when the hypertension duration is longer than 3 months, and treated and controlled with a maximum of 3 antihypertensive agents, such as RAS blockers, calcium channel blockers, beta-blockers, diuretics or any other classes of antihypertensive drugs. **Resistant hypertension is** defined as blood pressure that

remained above 140/90 mmHg during the office measurement despite the concurrent use of three antihypertensive agents of different classes, including a diuretic. In addition, in the United States resistant hypertension also includes those patients, whose blood pressure is controlled with at least four drug classes (19). **Masked hypertension is** defined when the blood pressure is in the normal range during the office measurement, but elevated values are detectable when measured by HBPM or ABPM (18).

1.4. Importance of the measurement of hypertension-mediated organ damage, especially carotid-femoral pulse wave velocity

Hypertension-mediated organ damage (HMOD) refers to structural or functional changes in arteries or in the organs (heart, brain, eyes, and kidney) caused by elevated blood pressure. HMODs are accepted markers of preclinical or asymptomatic CVD (18). HMOD is common in grade 2, 3, or long-standing hypertension, but can also be found in less severe hypertensive conditions. Increased CV risk is associated with the presence of HMOD, and the association is stronger when it affects multiple organs. Therefore, the HMOD assessment in a clinical practice can play a role in exploring the level of CV risk in patients with hypertension (18).

Large artery stiffening is an important pathophysiological determinant of hypertension. Arterial stiffness is a general term that describes the stiffness of the arterial wall. Arterial wall stiffness results from a complex interaction between stable and dynamic changes involving both structural and functional elements of the arterial wall (20-22) Carotid-femoral pulse wave velocity (cfPWV) is the gold standard for measuring large artery stiffness. The cfPWV values above than 10 m/s are considered as significant change in the aortic function, reflecting an increased CV risk in middle-aged hypertensive patients and in the presence of HMOD (18, 23, 24).

Several studies confirmed that elevated PWV is independently associated with the increased risk of CV morbidity and mortality. A meta-analysis of 17 studies, including 16 000 participants followed for 7.7 years, showed that each 1 m/sec increase in PWV increased the rate of CV morbidity, mortality and all-cause death by 15% (25).

1.4.1. Measurement of arterial stiffness with tonometric method

The non-invasive measurement of arterial stiffness in clinical practice is becoming increasingly important using a variety of methods (18, 23, 26). The most commonly used non-invasive, "gold standard" method for assessing arterial stiffness is the use of a tonometer or a mechanotransducer to measure carotid and femoral pulse waveforms. Arterial tonometry is based on the principle of applanation tonometry. The sensor is placed on the skin over the artery, applying moderate pressure. In this way, the artery is slightly compressed by the balance of circumferential forces in the vessel, allowing the sensor to record the pressure at the centre of the compressed artery. However, these devices require a trained operator to make measurements of acceptable quality. This method can be used to determine cfPWV, which is the speed of the pulse wave as it travels from the heart to the carotid and then to the femoral artery (18, 21, 27, 28).

1.4.2. Central hemodynamic and wave reflection parameters

Elastic and muscular arteries adapt differently to the hemodynamic changes caused by the left ventricular structure. The ability of large and elastic arteries that adapt to nonlinear pressure-volume changes caused by pulsatile volume can be characterized by several functional and structural parameters, in particular compliance, distensibility, which provides information about the extrinsic properties of the arteries. The Young's modulus describes the intrinsic elastic properties of the vessel wall. The aortic conduit and Windkessel functions balance the effect of pressure-volume overload that generates central pulse pressure and transmits to peripheral muscular blood vessels with smaller internal diameters, thinner and stiffer vessel walls. Based on these haemodynamic properties, various parameters such as central systolic blood pressure, central pulse pressure, and augmentation index, - which measures the augmentation of the central aortic pressure by the reflected pulse wave-, can be measured and calculated non-invasively with the tonometric method. The cfPWV or brachial-ankle pulse wave velocity (baPWV) calculated from the diameter and pressure waveforms recorded at different points in the arteries, can help assess the stiffness of the large arteries, hence identifying a high-risk subgroup of patients (24).

Arterial stiffness and blood pressure are closely related. Although arterial stiffness has long been regarded as a complication of hypertension, there is now increasing evidence

that arterial stiffness can itself lead to an increase in systolic blood pressure, and in this vicious circle, this increase in blood pressure causes further arterial stiffness (22, 28-30), suggesting that arterial stiffness is both a cause and a consequence of hypertension (24).

These central haemodynamic parameters with PWV all show an impairment with age and CV risk factors such as hypertension, diabetes and hypercholesterolemia and are also strong predictors of CV outcome in different disease conditions (24).

1.4.3. The association of personality traits with arterial stiffness and central hemodynamic parameters

Anger and hostility are two important dimensions in the context of personality traits and have been associated with a number of personality types. Several studies have found that the hostility and anger components of type A behavioural pattern are sensitive predictors of CVDs (such as more aggressive, competitive, hostile, short tempered, more time conscious, constantly preoccupated with deadlines, unable to relax, cynical behaviours) (31-33). Furthermore, type D personality pattern (negative individual affectivity and social inhibition, which are closely associated with neuroticism and introversion) with anxiety has also been found to be a vulnerable marker of CV morbidity by the decrease in cardiac vagal activity and increase in cardiac sympathetic activity with elevation in hearth rate and blood pressure as well (34, 35). In contrast, personality traits such as optimism, conscientiousness, openness, and curiosity have been found to be associated with positive health outcomes of subjects with CVD and hence can be regarded as cardioprotective personality traits (36-39).

In the study of **Aimee J. et al.** anxiety and hostility were found to be associated with elevated PWV values and higher risk of central adiposity (40). Furthermore in a study of **David E. et al.** elevated PWV was found in middle-aged adults with suppressed anger independently from the effects of blood pressure and heart rate (41). Moreover, a study by **Vikram Kumar Y. et al**. revealed significantly higher carotid mean arterial pressure (MAP), baPWV, and arterial stiffness index parameters in individuals with anxiety compared to controls. These findings suggest an important link between reduced vagal and increased sympathetic function, as well as reduced arterial compliance and possible arteriosclerotic changes and increased blood pressure in patients with anxiety

(35). In a prospective study of **Shuyuan Z. et al**., COVID-19-related anxiety was associated with a short-term increase in morning SBP among older patients during a 1-year follow up period and led to a greater risk of CV events (42).

1.4.4. The association of resistant or white-coat hypertension with arterial stiffness and central hemodynamic parameters

In resistant hypertension the association with arterial stiffness and central hemodynamic parameters is well-documented. The elevated PWV and reduced aortic distensibility and Aix are independently linked with hypertension progression and compared to controlled hypertensive patients, to a higher risk of CV events and mortality, as well (43-46). Additionally, a study by **Pabuccu T. et al**. demonstrated that, in resistant hypertensive patients significantly elevated PWV, reduced aortic distensibility and higher AIx values were found compared to normotensive and controlled hypertensive subjects. Moreover, in this study elevated PWV values were independently associated with resistant hypertension, as well (47).

Regarding to white-coat hypertension, a recently published meta-analysis by **Peng C. et al**. including 19 studies with 1538 white-coat hypertensive and 3582 normotensive individuals, reported elevated PWV values in white-coat hypertensive patients compared to normotensive individuals, while the PWV values in juvenile individuals with white-coat hypertension were comparable with normotensive participants (48). However, until now, no studies evaluated cfPWV in healthy subjects, white-coat hypertensive, controlled and resistant hypertensive patients in the same cohort.

1.4.5. The association of white-coat hypertension with cardiovascular morbidity

The association of CV risk with white-coat hypertension is controversial, but data of literature suggested that individuals with white-coat hypertension had higher rates of CV morbidity and mortality but not significantly differed in all-cause mortality and stroke risk, compared with normotensive patients (49-51). In line with these results, in a meta-analysis by **Alexandros B. et al.** the authors found that the white-coat hypertension-associated CV morbidity and mortality may be slightly higher compared with normotension but well-below the risks associated with sustained hypertension (49). In addition, in a meta-analysis by **Mehran A. et al.** CV risk in white-coat hypertensive

individuals without antihypertensive treatment (23 cohorts, 20445 individuals), white-coat hypertensive individuals with antihypertensive treatment (11 cohorts, 8656 individuals) and a mixed population including both treated and untreated subjects (12 cohorts, 21336 individuals) that were assessed and showed an increased CV risk in untreated and mixed population with white-coat hypertension, which was not present in the treated white-coat hypertension individuals (52).

1.5. Mood disorders: a growing public health problem worldwide

Depression and anxiety are considered the most frequent mood disorders worldwide (53, 54). Depression is affecting more than 280 million people and similar number of people have anxiety disorders, often with co-occurring depression according to the WHO 2023 latest report (53, 55). The COVID-19 pandemic has also exacerbated mental health conditions. In the United States from August 2020 to February 2021, the proportion of adults diagnosed with anxiety or depressive disorder increased from 36.4% to 41.5%, with a very marked increase in the 18-29 age group and even higher among people over 60 years old (56, 57). Even before the COVID-19 pandemic, mental disorders were a major burden worldwide (54, 57, 58). While men and women experienced similar rates of mental health disorders overall, depressive, anxiety and eating disorders were more common in women (55). In 2019, depression was the second leading cause of disability globally, and anxiety was ranked eighth, both of them are the most common types of mental health disorders (57, 58). According to WHO's estimation, by 2030 mood disorders, especially depression is expected to be the largest contributor to the disease burden worldwide. In addition, productivity losses due to depression and anxiety alone are estimated to cost the global economy $1 trillion a year, and are projected to reach $16 trillion by 2030 (59).

1.5.1. Hungarian data about depression and anxiety

Nearly 700 000 Hungarians are affected with depression and anxiety. In 2019 the socio-economic direct and indirect burden of depression was 362 billion Hungarian Forints, which is much more than the combined costs of hypertension, asthma, rheumatoid arthritis and osteoporosis (60). The known sex differences in the literature is also present in the Hungarian data: major depression is more common among women (20%

in women compared to 9% in men) (60). Moreover, the onset of the disease in recent years, has been shifting to an even younger age, between 20 and 30 years, and more commonly the first episode appears already in adolescence. Depression and anxiety are often accompanied by the development of comorbidities. These include coronary heart disease, heart attack, stroke, cancer, Parkinson's disease and type 2 diabetes (60). The presence of major depression more than doubles the risk of the development of type 2 diabetes, a factor that alone generates an annual cost of 6.4 billion Hungarian Forints (60). The largest indirect burden of major depression is the loss of working days and productivity of patients. Of these, the indirect costs associated with comorbidities significantly exceed (92%) the direct costs (8%), so the indirect costs for the society are approximately equivalent to the total annual pharmaceutical budget (60).

The above-mentioned statistics have highlighted the urgent need to improve the mental healthcare system, not only in Hungary, but also worldwide, in relation to screening and early treatment of anxiety and depression.

1.5.2. The relationship between depression and anxiety with cardiovascular diseases and hypertension

1.5.2.1. Depression and its connection to hypertension and cardiovascular diseases

There is growing evidence that physical and mental illnesses are not independent of each other. Between 9.3% and 23% of people with one or more chronic physical illnesses have mood disorders, especially depression as a co-morbidity (61). Moreover, in the 12-year-long prospective study with 512 712 included individuals of **Ling M. et al**. found that depression was associated with increased risk of all-cause and CVD mortality particularly in men in Chinese population (62). Moreover, the meta-analysis of prospective cohort studies by **Ling M. et al**. including 22 367 participants and 9.6 years median follow-up found that depression increased the risk of hypertension incidence, which was significantly correlated with the length of follow-up and the prevalence of depression at baseline (63). This study also confirmed depression as an independent risk factor of hypertension and a contributor to CV morbidity and mortality. The literature suggests a complex relationship between depression and CVD. Patients with CVD have more pronounced depression than the general population.

Depressed individuals are more likely to eventually develop CVD and also have a higher mortality rate than the general population (64). Patients with CVD, who are also depressed, have a worse outcome than those patients who are not depressed. The relationship is gradual: the more severe the depression is, the greater risk is present for later death and other CV events (64). Furthermore, depression also plays a detrimental role in coronary heart disease (CHD). In a position paper of the European Society of Cardiology (ESC) working group on coronary pathophysiology and microcirculation, depression was stated to be associated with a 3-4-fold increase of the risk of recurrent cardiac events and mortality in CHD patients (65). Moreover, in people with CHD, depression increases the risk of future cardiac death and morbidity (66). On the other hand, the prevalence of depression in CHD patients is about 3 times higher than in healthy individuals (66). Major depression is three times more common in patients following acute myocardial infarction than in the general population (65). In addition, depression showed a link to hearth failure (HF) as well. According to meta-analysis of **Emily C. et al**. including 18 prospective studies, depression was associated with an increased risk of all-cause mortality in heart failure (HF) patients (66), and even in studies with shorter follow-up periods, the effect of depression was stronger in older adults. This study highlighted that depression in older adults may be predictive of a worse HF outcome (66).

1.5.2.2. The pathomechanism between depression and cardiovascular diseases

The pathomechanism explaining the connection between depression and CV diseases is highly investigated and several possible pathways have been found, which can increase the likelihood of vascular disease. These include increased platelet activation, endothelial dysfunction, increased level of inflammatory markers, and decreased heart rate variability (67). Metabolic, immuno-inflammatory and autonomic systems, as well as dysregulation of the hypothalamic-pituitary-adrenal axis, psychosocial and environmental factors are also present both in depression and CVD (68). Furthermore, neurohormonal factors and genetic links, such as the serotonin transporter mechanism (69), as well as behavioral mechanisms are also part of the pathophysiological background linking the two diseases (70). Our working group also revealed new

pathophysiological connections linked to neurotrophic molecules, especially brain-derived neurotrophic factor (17, 71).

1.5.2.3. Anxiety and its connection to hypertension

Several studies demonstrated a positive association between anxiety and prevalent or incident hypertension (72-74). Studies regarding the prevalence of hypertension have been demonstrated a positive, bidirectional association between anxiety and hypertension. Adults with hypertension were more likely to have anxiety and those with anxiety were more likely to have hypertension, independently of other risk factors for hypertension (75). Moreover, anxiety disorders were more prevalent in patients with hypertension (37.9%) than in the general population (12.4%) (76). The level of anxiety also positively affected the hypertension prevalence and resulted in a 15% increase in the presence of comorbidities, as well (77). Moreover, anxiety disorders in the normotensive population increased the risk of developing hypertension by 4-fold during the 1-year follow-up period (78). Resistant hypertensive patients have higher level of anxiety compared with the nonresistant controlled hypertensive patients and anxiety can also contribute to the white-coat effect (79, 80). These studies also revealed that young adults are at a higher risk for developing incident hypertension after the diagnosis of anxiety, which can be accounted to the longer exposure to alterations in autonomic regulatory mechanisms, such as blood pressure variability and reduced baroreflex sensitivity (74). However, both in longitudinal and in cross-sectional studies the impact of anxiety on hypertension has been lost its significance after adjustment for depression (74, 81). These findings may reflect the previously observed associations between depression and hypertension which confounds the link between anxiety and hypertension (74, 81).

1.5.2.4. The pathomechanism between anxiety and hypertension

Anxiety, defined as a negative emotion, characterised by both psychological (e.g., tension and worry) and somatic (e.g., palpitations and chest discomfort) symptoms, can contribute to blood pressure elevation (82). In addition, stress reaction caused by anxiety, which is mediated by the hypothalamic-pituitary-adrenal axis (HPA), alters and increases circulating catecholamine production (83). The catecholamines, including

dopamine, adrenaline and noradrenaline, are the main neurotransmitters that mediate many functions of the central nervous system, such as motoric control, cognition, emotion, memory processing and endocrine modulation and they are responsible for the body's "fight-or-flight" response (84). Changes in circulating catecholamines, together with alterations in autonomic mechanisms cause insulin resistance, endothelial dysfunction, inflammation and hypertension (85). These changes reflect autonomic nervous system dysregulation and result in increased blood pressure variability and reduced baroreflex sensitivity which contribute not only to the onset of hypertension, but also to the progression and severity of HMOD as well (74).

1.5.3. Definition and assessment of affective temperaments

1.5.3.1. Historical background of the personality and affective temperaments

The first human personality concept dates back to centuries before Christ (BC), when Hippocrates (ca. 460 BC - ca. 370 BC) and Aristotle (384-322 BC) based on body fluid habits (called "humors") differentiated four temperamental types: the melancholic, the choleric, the sanguine and the phlegmatic temperament (86). The nowadays used basic concept of affective temperaments was developed by Professor Hagop S. Akiskal, who, by using Kraepelin's four different basic temperament types from 1913, formulated the modern concept of affective temperaments and added a new temperament type, called cyclothymic (86). Since then, we speak about five affective temperaments: depressive, irritable, hyperthymic, cyclothymic and anxious (86). Furthermore, the definition of temperament widened with the term of healthy personality, as well. Thus, the affective temperaments include inherited personality traits which do not necessarily constitute pathology (87).

1.5.3.2. The definition of affective temperaments

Affective temperaments are defined as inherited parts of personality which are stable in adulthood and represent the biological core of emotional reactivity to external stimuli (88). They are also responsible - in their natural mixture - for cultural characteristics on a national level (88, 89). All individuals have their own characteristic temperament profile determining their emotional response to environmental stimuli in the aspects of cognitive, psychomotoric, circadian and social behavioural traits (88).

However, the emotional reactions represented by the different temperaments, especially in their dominant 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 (90-94). The temperament is considered dominant if it scores 2 standard deviations above the mean population average (95).

1.5.3.3. The evaluation of affective temperaments

The affective temperaments can be evaluated with the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto Questionnaire (TEMPS-A) developed by Akiskal and his co-workers on five temperament scales (89). This questionnaire consists of 5 subscales – according to the 5 affective temperaments, requiring only simple "yes" (score 1) or "no" (score 0) answers. The questionnaire was developed in 2005 and since than it is extensively studied, translated and validated into more than 30 languages, including Hungarian (90) (89). The Hungarian standardized version of TEMPS-A has been validated in 2008 including 1132 individuals, providing national data on reliability and internal consistency (95).

1.5.3.4. Features of the different types of affective temperaments

The ***depressive*** temperament can be described as pessimistic, highly self-critical, excessively worrying, lacking assertiveness, self-denying, worrying about personal failure, and striving to live in harmony with others (96). The ***hyperthymic*** temperament is characterized by upbeat, overconfident and overenergetic traits, and shortness of need of sleeping (96). The ***cyclothymic*** temperament shows affective instability with rapid mood shifts and intense emotions, with instable self-estimation (96). The ***irritable*** temperament represents sceptical and critical traits and reacts to negative events with negative emotions, and regarding mood shifting and complaining is closely linked to the cyclothymic (96, 97). The ***anxious*** temperament can be best described by exaggerated worries especially towards family members. This temperament type is unable to relax, stressed, restless and anxious fearing from unhappiness (96).

1.5.3.5. Sex differences in the pattern of affective temperaments and associations between different temperament types

It seems to be obvious that sex differences are present in the pattern of affective temperaments. Women were found to have higher cyclothymic, depressive and anxious temperament scores, while in the case of men higher hyperthymic and irritable temperament scores can be measured (88, 95, 98). The sex differences is therefore a general feature of temperaments which retraceable to ancient evolutional sociocultural origin (96). In contrast, the age does not significantly affect the distribution of temperaments (88, 95). The only exception is depressive temperament, which is more likely to occur in women with ageing (88, 99). Regarding to their associations, studies demonstrated that the five temperaments are not independent form each other (88). Depressive, anxious, irritable and cyclothymic temperaments are associated with each other, with the strongest correlations found between depressive and anxious, cyclothymic and irritable, and anxious and irritable temperaments. In contrast, hyperthymic temperament have been found to be independent from the others (88).

1.5.3.6. Neurobiological background, and differences in affective temperaments

Molecular genetic studies have found strong connection to the central serotonergic regulation in cyclothymic, depressive, irritable and anxious temperaments, while the involvement of dopaminergic regulation seems to be present in hyperthymic temperament (100, 101). The short allele of serotonin-transporter-linked polymorphic region (5-HTTLPR) gene have been found to be responsible for the contribution of depression in case of anxious, depressive, irritable and cyclothymic temperaments, while no association has been observed with hyperthymic temperament (69). Besides the case of affective temperaments, the short allele of the 5-HTTLPR gene showed a strong association with major depression in unipolar and bipolar mood disorders, as well (69, 102). In addition, ADGRB3 gene was found to be associated with depression in anxious affective temperament type (103).

1.5.4. The association of affective temperaments with mood disorders

The relationship between affective temperaments and mood disorders is quite complex. It was demonstrated that bipolar I disorder is related to hyperthymic and, to a lesser

extent, cyclothymic temperament, whereas unipolar major depression is correlated with depressive temperament (104, 105). Hyperthymic temperament is more pronounced in bipolar I patients with a higher prevalence of manic episodes, whereas among those with a predominantly depressive polarity, the depressive temperament is predominant (106). In the case of bipolar II disorder significantly higher prevalence of marked cyclothymic temperament has been found which is also a sensitive precursor of not only the early onset bipolar disorder, but also of bipolar II transformation (97, 105, 107). Moreover, cyclothymic temperament was also found to be associated with atypical depression (108).

1.5.5. The association of affective temperaments with different somatic diseases

Similar to psychiatric disorders, clinical studies have found associations between affective temperaments and different somatic pathologies. In general, depressive, anxious, cyclothymic or irritable temperaments are associated with adverse features of different disorders, while hyperthymic temperament seems to be protective in different ways.

In a study of **Carlos G. et al** the presence of depressive temperament was associated both with impaired psychological attitude and worse metabolic control in type 2 diabetic patients (109). Based on the study of **Scuderi G. et al**. patients with open-angle glaucoma can be divided into 2 clusters according to their TEMPS-A profile; dysthymic and hyperthymic clusters. Dysthymic patients score higher on hopelessness and depressive temperament scales, while lower on well-being scale (110). In a study of **Elena S. et al**. cyclothymic scores were positively associated with binge eating, while hyperthymic temperament showed a protective effect against binge eating and multiple weight cycling in obese patients (111). Moreover, hyperthymic temperament was found to be protective against current or lifetime psychopathologic events in cystic fibrosis patients in a study by **Andrea A. et al** (112). In addition, in the study of **Tulay Y. et al**. depressive, anxious, and cyclothymic temperament scores found higher in patients with ankylosing spondylitis which were also related to psychiatric symptoms, while the anxious temperament was associated with lower life quality in this patient population (113). The protective feature of hyperthymic temperament is missing in drug addicts as according to the results of **David J. et al**. heavy users of cocaine, other stimulants and

alcohol were more likely to have an irritable temperament, while, in contrast, heavy users of opioids were more likely to show depressive and hyperthymic traits (114).

1.5.6. The association of affective temperaments with cardiovascular morbidity

Besides psychopathology, as listed above, growing evidence supports the impact of affective temperaments on somatic diseases but until the last decade limited literature data was available about affective temperaments as potential risk factors of CV pathology. Then, mostly Hungarian researchers, including our working group, started to publish data on this field.

1.5.6.1. The association between affective temperaments and hypertension

According to the European guidelines on CVD prevention in clinical practice, personality has a remarkable impact on CV morbidity (115). Hostility, anxiety and type D personality contribute to the development, clinical course and prognosis of CVD (116). This is due to behavioural risk factors that are predominant in CV disorders, such as unhealthy lifestyle, low adherence to behaviour change recommendations or low medication adherence. Thus, personality patterns and possibly temperaments can be seen as moderators, rather than causes of specific diseases (115-117).

The relationship between affective temperaments and hypertension received increasing attention in the last decade. **Előry A. et al**. demonstrated that dominant cyclothymic temperament is associated independently with the presence of chronic hypertension, suggesting an additional risk factor in CV morbidity (118). Additionally, in another study of **Előry A. et al**., cyclothymic temperament was independently associated with the history of coronary events in chronic hypertensive patients (119). Moreover, in the study of **László A. et al.** cyclothymic temperament score was independently associated with elevated brachial systolic blood pressure, while hyperthymic temperament score was negatively related to augmentation index in chronic hypertensive patients. These results suggest that affective temperaments may play a role in the development of hypertension and arterial stiffening and are potential markers of CV risk (28). **László A. et al.** also found lower serum level of brain-derived neurotrophic factor (BDNF) in chronic hypertensive patients with dominant cyclothymic, depressive, anxious or irritable temperaments, compared with hypertensive patients with non-dominant

affective temperaments (17). In a study of **Nemcsik J. et al**. elevated BDNF level was found in chronic hypertensive patients while the hyperthymic affective temperament score and the presence of hypertension were independent determinants of the BDNF level. In hypertensive patients, the elevation of hyperthymic temperament score was associated with the elevation of BDNF, however, this association was not present in healthy subjects. These findings suggest a possible protective role of hyperthymic affective temperament; furthermore, the elevation in BDNF level in hypertensive patients may consider as a part of a protective compensatory mechanism targeting peripheral neurons and vascular cells (71). Adding to this, **Nemcsik J. et al**. found inverse association between hyperthymic affective temperament and coronary atherosclerosis in patients assessed by coronary computed tomography angiography (CCTA), suggesting a protective role of hyperthymic temperament in coronary atherosclerosis (120). **Kőrösy B. et al**. found independent association between cyclothymic temperament and the onset of hypertension in women. These results suggested that besides traditional risk factors, cyclothymic affective temperament might contribute to the earlier development of hypertension in women (94). In addition to the cyclothymic temperament, a harmful association with other temperaments has also been found in hypertension. **Kőrösy B. et al.** discovered positive association between irritable temperament and nighttime brachial and central systolic blood pressure in untreated men with elevated office blood pressure (121).

The above-mentioned results suggest that affective temperaments have important and complex association not only with psychiatric conditions but also with hypertension. However, hypertension is not a homogenous disease, its different phenotypes can be distinguished. The pattern of affective temperaments and the expression of depression and anxiety in different hypertension phenotypes in the same cohort was not evaluated until our present studies.

2. OBJECTIVES

2.1. The aims of the first study

In the first study, our aims were in healthy subjects, and in different hypertensive phenotypes:

1. to evaluate affective temperament patterns;
2. to evaluate the presence of HMOD.

In our first study, we hypothesized, that white-coat and resistant hypertensive patients have similarities in the patterns of the different types of affective temperaments. We also hypothesized, that HMOD is present in the resistant hypertension group.

2.2. The aims of the second study

In the second study, our aims were in healthy subjects, and in different hypertensive phenotypes to evaluate the severity of:

1. depression;
2. anxiety.

In our second study we hypothesized that in white-coat and resistant hypertensive patients the severity of depression and anxiety are different compared with healthy controls and non-resistant chronic hypertensive patients.

3. PATIENTS AND METHODS

3.1. Study I.: Affective temperaments with haemodynamic and arterial stiffness in healthy controls and in different hypertension phenotypes

In this cross-sectional study Caucasian patients were recruited between August 2012 and January 2019 from three primary care practices in Budapest. Four groups of subjects were investigated; healthy controls (Cont); white-coat hypertensive patients (WhHT); chronic, non-resistant hypertensive patients (non-ResHT); and patients with chronic, resistant hypertension (ResHT).

3.1.1. The definition of the different hypertensive phenotypes

Three different hypertension phenotypes were defined mainly according to the ESH guideline published in 2013 (122). WhHT was defined as elevated office blood pressure (>140/90 mmHg) but normal blood pressure values during 24-h ABPM (24-h average <130/80 mmHg and daytime average <135/85 mmHg and nighttime average <120/70 mmHg). The non-ResHT was defined as the duration of hypertension was longer than 3 months, was treated with antihypertensive drugs and was controlled with a maximum of 3 antihypertensive agents. In the case of ResHT the American consensus document was used which differed from the European guideline in the definition of resistant hypertension (19). ResHT was defined as blood pressure that remained above 140/90 mmHg in the office despite the concurrent use of three antihypertensive agents of different classes, including a diuretic. Additionally, ResHT was also defined in case blood pressure was controlled with the use of more than three medications (19). In the ResHT patients who had uncontrolled office values, the diagnosis was always confirmed by ABPM or by home blood pressure monitoring (HBPM).

In our studies consecutive patients were included within a cardiovascular and psychopathological screening program which were ongoing in general practitioner practices. The program focused on healthy controls over the age of 18 years, subjects with chronic hypertension on medication and subjects with elevated office blood pressure without antihypertensive medication.

Subjects were recruited during the screening visit, when the blood pressure was measured with a validated oscillometric device (Omron M3), and subjects were invited to participate in the study. An Auto Questionnaire for affective temperaments, depression, family and personal history (special attention to CV risk factors and complications) were administered to the subjects including a written informed consent. Patients were asked to bring back the Auto Questionnaires in the morning of the clinical measurements. Within the maximum of a 2-week period an appointment was scheduled for 7.00. a.m. for repeated office blood pressure and cfPWV measurements and also for blood sampling. For untreated patients who had elevated blood pressure during screening (average blood pressure above 140/90 mmHg in repeated office blood pressure measurements), a 24-hour ABPM device (Mobil-O-Graph, I.E.M. GmbH, Germany) was fitted after cfPWV measurement, with the cuff placed on the left arm and blood samples were taken from the right arm. The 24-hour ABPM device was replaced on the following day when both its results and the blood sample were discussed with the patient. At the end of the clinical measurements the Auto Questionnaires were collected and the evaluation of anxiety was completed in the form of a short interview with the examiner, as well.

In this study, exclusion criteria were atrial fibrillation (because of the technical difficulties in cfPWV measurement), dementia posing an obstacle to completing questionnaires or denial of consent. Dementia was excluded on the basis of the medical history and patient examination, and no specific test was applied. Moreover, exclusion criteria included also the history or ongoing treatment of severe depression or anxiety, bipolar disorder or schizophrenia. Patients were classified as severely anxious or depressed if their daily activities, interpersonal relationships, work and sleep patterns were significantly altered by the presence of depression and anxiety for more than two weeks, and they had been hospitalized for suicidal intention or were taking a range of high-dose antidepressants or benzodiazepine-containing medications. For the included patients, the presence of treated depression or anxiety was confirmed by history, medical records, the medications taken by the patient and direct verbal interviews. The moderate use of anxiolytic alprazolam (less than 0.5 mg/day) was not a restrictive criterion, as in a few cases it was part of the hypertension therapy protocol initiated by other specialists. However, in our studies we excluded higher doses of anxiolytics,

sedatives and hypnotics for the treatment of major depression, anxiety and psychiatric disorders. These included benzodiazepines, lithium-containing drugs, SSRI-s, tricyclic and MAO-inhibitor containing antidepressants. Patients using opiate analgesics were also excluded.

All patients gave written informed consent and accepted the participation in this study. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, Hungarian Ministry of Health (ETT TUKEB 842/PI/2011), and was carried out in accordance with the tenets of the Declaration of Helsinki.

3.1.2. Measurement of the office and ambulatory blood pressure

Before the morning of the clinical measurements, patients were asked to fast overnight and refrain from smoking and drinking caffeine-containing beverages before the examination, but their usual antihypertensive medication was asked to be taken in. The blood pressure measurements were performed in a sitting position after 5 minutes of rest. Two brachial blood pressure measurements were taken within a 1-min interval on each arm with an oscillometric device (Omron M3). In the detailed analysis, the arm side with the higher mean values was further applied as brachial systolic (SBPbrach) and diastolic (DBPbrach) blood pressures and heart rate. The calculation of pulse pressure (PPbrach) was also registered as SBPbrach minus DBPbrach. Finally, for blood sampling venipuncture was performed on the right arm. In the case of the untreated subjects with elevated office blood pressure during the screening visit, a 24-h ABPM device (Mobil-O-Graph, I.E.M. GmbH. Germany) was applied for fitting the results. The cuff was placed on the left arm. The 24-h ABPM and blood test results were discussed with the patient on the next day visit. In the case of the treated hypertensive patients with increased office blood pressure the diagnosis of ResHT was defined with the same ABPM device fitted as described above or with HBPM within 2 weeks. ABPM was unfortunately not available for all the treated hypertensive patients because of the shortage of time and healthcare human resources.

3.1.3. Measurement of arterial stiffness

Arterial stiffness measurements were performed on the day of blood sampling, prior to it, between 7:00 and 8:00 a.m. in supine position in a temperature-controlled room, after

the office blood pressure measurement. Patients were equipped with the arterial stiffness measurement device and then rested in supine position for approximately 15 minutes before being measured. Arterial stiffness parameters were evaluated with the gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy). This method provides gold standard measures of cfPWV, central systolic blood pressure (SBPcentr) and central pulse pressure (PPcentr). Two sets of arterial stiffness measurements were performed on each subject and the mean of these values were used for statistical analysis. In the PWV calculations, 80% of the carotid-femoral distance was used, according to a consensus document (123). The intra- and interobserver variability of PWV measurements obtained by the PulsePen device in hypertensive patients was 4.6 and 6.3 %, respectively. Since the PulsePen calculates central blood pressure based on the calibration of brachial diastolic blood pressure, the calculated central diastolic blood pressure is equivalent with the brachial diastolic blood pressure measured in the supine position. Other central hemodynamic or wave reflection parameters were not analyzed in study I.

3.1.4. Questionnaire for evaluation the affective temperaments

3.1.4.1. The Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto Questionnaire

The TEMPS-A was applied to assess the affective temperaments on depressive, cyclothymic, hyperthymic, irritable and anxious subscales, requiring “yes” (score 1) or “no” (score 0) answers. TEMPS-A contains 110 items (109 in the version for males). The questions of the various temperament types are grouped together as follows:

- depressive temperament: question 1 to 21 (21 points)
- cyclothymic temperament: question 22 to 42 (21 points)
- hyperthymic temperament: question 23 to 63 (21 points)
- irritable temperament: question 64 to 84 (21 points in women, 20 in the men’s version)
- anxious temperament: question 85 to 110 (26 points)

3.1.5. Statistical analysis

In Study I. the normality of continuous parameters was tested with the Kolmogorov–Smirnov test. Normally distributed parameters were compared between the four groups (Cont, WhHT, non-ResHT, ResHT) with ANOVA. For post hoc analysis, Tukey's test was used. Nonnormally distributed parameters were compared with the Kruskal–Wallis test. The descriptive data was expressed as mean ± standard deviation or median with interquartile ranges. For the examination of the independent associations of each affective temperament with ResHT, the chronic hypertensive patient groups (non-ResHT plus ResHT) were dichotomized based on the 75% quartile of the affective temperament scores of the patients. Finally, with binary regression analysis, the association of the different affective temperament scores with WhHT and ResHT were studied with adjustment for traditional CV risk factors such as age, smoking, diabetes, body mass index, and total cholesterol. Moreover, affective temperaments with the different hypertensive conditions were studied in the whole population and in males and females separately, but in the case of PWV only the whole population was investigated, where the PWV values were adjusted for age.

In all analyses, $p<0.05$ was considered to be statistically significant. SPSS 22.0 for Windows (IBM Corporation, Armonk, NY, USA) was used for all calculations.

3.2. Study II.: Patients and methods in the study exploring the severity of depression and anxiety in healthy controls and in different hypertension phenotypes

In Study II., the design, the population, and the exclusion criteria were the same like in the Study I. In Study II., we evaluated the severity of depression and anxiety in different hypertension phenotypes.

For the severity of depressive symptoms, the Beck Depression Inventory (BDI) Auto Questionnaire was used, which was handled and collected with the other Auto Questionnaires listed in Study I. For the severity of anxiety, the Hamilton Anxiety Scale (HAM-A) questionnaire was used which was evaluated by the examiner at the end of the clinical measurements.

3.2.1. The Beck Depression Inventory

The BDI is a 21-question multiple-choice self-report questionnaire, created by Aaron T. Beck, and is still widely used in clinical practice for the evaluation of the severity of depression. The questionnaire is created to measure the severity of depressive symptoms, not as a diagnostic instrument. The scale contains 21 items which represent the most common depressive symptoms, such as pessimism, failure, dissatisfaction, sad mood, irritability, social withdrawal, inability to resolve, guilt, crying, insomnia and appetite loss. In a four-point rating scale (from 0 to 3), patients were asked to assesses the claims, where a higher score correlated with more severe depression. The total score of the BDI ranges from 0 to 63 points. However, the cut-off values might differ in various populations, but there are generally accepted thresholds. During the evaluation, scores below 11 points were considered to be normal. Values between 11 and 17 points were regarded as a mild to moderate expression of depressive symptoms. Values of 18 or more were considered as clinically relevant depression (124).

3.2.2. The Hamilton Anxiety Scale

The HAM-A was one of the first rating scales in the clinical application for the evaluation of anxiety. This questionnaire was developed to measure the severity of anxiety symptoms, and nowadays is still widely used both in clinical and research fields. The questionnaire contains 14 items, each defined by a series of symptoms and measures both the psychic anxiety (mental agitation and psychological distress) and the somatic anxiety (physical complaints related to anxiety). Each item is scored on a 0 (not present) to 4 (severe) scale, with a total score range of 0–56, where the points 0-5 indicates lack of anxiety, 6-14 points mild severity of anxiety and points ≥15 severe anxiety (125). The HAM-A questionnaire was completed by a short interview between the examiner and the subject.

All patients also gave their written informed consent and accepted the participation in this study, as well. All the studies were approved by the Scientific and Research Ethics Committee of the Medical Research Council, Hungarian Ministry of Health (ETT TUKEB 842/PI/2011) and were carried out in accordance with the tenets of the Declaration of Helsinki.

3.2.3. Statistical analysis

In Study II., the normality of continuous parameters was tested with Kolmogorov–Smirnov test. For normally distributed parameters to compare differences between the four groups (Cont, WhHT, non-ResHT, ResHT) ANOVA was applied. For post-hoc analysis Tukey's test was performed and the Kruskal–Wallis test was applied to compare non-normally distributed parameters. Descriptive data were expressed as mean ± standard deviation or median with interquartile ranges. To examine the relationship between depression, anxiety and ResHT, groups of patients with chronic hypertension (non-ResHT and ResHT) were dichotomized according to a 75% quartile of patients' depression and anxiety scores. Next, using binary regression analysis the association with ResHT of the patient groups reaching different BDI and HAM-A scores was studied with the adjustment for the most common CV risk factors, such as age, sex, smoking, diabetes, body mass index and total cholesterol. Finally, in the merged group of Cont plus WhHT, with binary regression analysis the association with WhHT of the patients reaching different BDI and HAM-A points was also investigated with the adjustment for sex, smoking and BMI.

In all analyses $p<0.05$ was considered as the border of significance. SPSS 22.0 for Windows (IBM Corporation, Armonk, NY, USA) was used throughout the calculations.

4. RESULTS

4.1. Study I.: Results of affective temperaments and arterial stiffness in different hypertension phenotypes

Altogether 363 Caucasian patients were recruited in this cross-sectional study. Investigations were performed with the subjects divided into four categories, where the number of patients were as follows: Cont: n=82; WhHT: n=44; non-ResHT: n=200; and ResHT: n=37. In Table 1. the demographic parameters and comorbidities, blood test results, current medication and the number of the used antihypertensive medications are summarized. Regarding to the results, the non-ResHT and ResHT patient groups were older, had higher BMI, blood glucose, uric acid and triglyceride levels, and lower total HDL cholesterol compared with the Cont group. In addition, ResHT patients had decreased total and LDL cholesterol levels also compared with Cont, which probably was a consequence of the administration of statins. Finally, the BMI and eGFR were higher in WhHT than in Cont individuals.

Table 1. Baseline characteristics of the study participants

Data are presented as mean ± standard deviation or median (interquartile ranges). Categorical parameters are presented as n (%). Significant differences compared with Cont are signed as bold and italic characters. Cont: healthy controls; WhHT: patients with white-coat hypertension; non-ResHT: chronic, non-resistant hypertensive patients; ResHT: chronic, resistant hypertensive patients; CV diseases: cardiovascular diseases; BMI: body mass index; GFR-EPI: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ACE: Angiotensin converting enzyme; ARB: angiotensin II receptor blocker.

	Cont	**WhHT**	**non-ResHT**	**ResHT**
N (male/female)	82 (31:51)	44 (22:22)	200 (91:109)	37 (14:23)
Age (years)	49.61 ± 18.28	44.12 ±13.36	***59.44 ± 13.24***	***65.55 ± 10.22***
Duration of hypertension (years)	-	-	9.40 ± 9.11	17.44 ± 13.22
Diabetes [n (%)]	-	3 (3.7%)	32 (16%)	16 (43%)
CV disease [n (%)]	-	-	18 (9%)	12 (32%)

Current smoker [n (%)]	12 (15%)	8 (18%)	38 (19%)	7 (19%)
BMI [kg/m^2]	24.35 ± 3.65	***27.70 ± 5.62***	***28.80 ± 4.62***	***30.50 ± 3.45***
Blood glucose [mmol/l]	4.90 (4.60-5.51)	5.15 (4.75-5.40)	5.49 (5.00-6.32)	6.28 (5.26-7.50)
GFR-EPI [ml/min/1.73m^2]	79.31 ± 32.40	***93.31 ± 30.09***	81.69 ± 18.37	72.35 ± 24.24
Uric acid [µmol/l]	295.00 ± 72.97	307.61 ± 68.92	***327.86 ± 81.82***	***351.59 ±101.05***
Total cholesterol [mmol/l]	5.41 ± 1.10	5.54 ± 1.38	5.41 ± 1.15	***4.76 ± 1.33***
LDL [mmol/l]	3.30 ± 0.97	3.56 ± 1.24	3.34 ± 1.03	***2.73 ± 1.24***
HDL [mmol/l]	1.64 ± 0.36	1.47 ± 0.37	***1.38 ± 0.38***	***1.26 ± 0.32***
Triglyceride [mmol/l]	0.96 (0.69-1.30)	1.17 (0.87-1.57)	***1.48 (1.08-2.05)***	***1.53 (1.10-2.47)***
Medication [n (%)]				
ACE-inhibitor	-	-	118 (59%)	24 (64.9%)
ARB [n (%)]	-	-	29 (14.5%)	12 (32.4%)
Calcium channel blocker	-	-	75 (37.5%)	28 (75.6%)
Beta-blocker	-	-	89 (44.5%)	27 (72.9%)
Diuretic	-	-	23 (11.5%)	33 (89.2%)
Alfa-adrenerg receptor blocker	-	-	22 (11%)	19 (51.3%)
Centrally acting agents	-	-	1 (0.5%)	-
Direct acting vasodilators	-	-	1 (0.5%)	5 (13.5%)
Antiplatelet drug	1 (1.2%)	-	42 (21%)	12 (32.4%)
Statin	6 (7.3%)	1 (2.3%)	50 (25%)	12 (32.4%)
Fibrate	-	-	7 (3.5%)	5 (13.5%)
Alprazolam	1 (1.2%)	-	18 (9%)	2 (5.4%)
Number of antihypertensive medications				
0	82 (100%)	44 (100%)	-	-
1	-	-	85 (42.5%)	-
2	-	-	72 (36%)	-
3	-	-	43 (21.5%)	16 (43.2%)
4	-	-	-	9 (24.3%)
5	-	-	-	9 (24.3%)
6	-	-	-	2 (5.4%)
7	-	-	-	1 (2.7%)

Hemodynamic parameters and affective temperament scores are summarized in Table 2. In the WhHT, non-ResHT, and ResHT patients, the SBPbrach and SBPcentr were both higher than in the Cont individuals. The SBPbrach values were higher in ResHT than in non-ResHT patients. DBPbrach was elevated only in WhHT and ResHT patients.

4.2. The differences in affective temperament patterns in healthy subjects and in different hypertensive phenotypes.

In WhHT and in ResHT patients, cyclothymic affective temperament scores were higher than in Cont individuals (p=0.049 and p=0.008, respectively), and they were even higher in ResHT patients than in non-ResHT patients (p=0.032, Table 2). When male and female subjects were studied separately, no significant differences were found (data are not shown).

4.3. The presence of HMOD in healthy subjects and in different hypertensive phenotypes.

In comparison with Cont subjects, the cfPWV was not elevated in WhHT patients, but it was higher in non-ResHT and ResHT patients. Besides Table 2., Figure 1. demonstrates these results graphically. Significant difference (p=0.011) was found in cfPWV between non-ResHT and ResHT patients as well.

Table 2. Hemodynamic parameters and affective temperament scores of the different groups of patients

Data are presented as mean ± standard deviation or median (interquartile ranges). Categorical parameters are presented as n (%). Significant differences compared with Cont are signed as bold and italic characters. Significant differences compared with non-ResHT are signed as bold characters with #. Cont: healthy controls; WhHT: patients with white-coat hypertension; non-ResHT: chronic, non-resistant hypertensive patients; ResHT: chronic, resistant hypertensive patients; SBPbrach: brachial systolic blood pressure; DBPbrach: brachial diastolic blood pressure; PPbrach: brachial pulse pressure; SBPcentr: central systolic blood pressure; PPcentr: central pulse pressure; Age-adj. PWV: age-adjusted carotid-femoral pulse wave velocity.

	Cont	WhHT	non-ResHT	ResHT
Hemodynamic parameters				
Hearth rate [1/min]	72.1 ± 10.7	77.61 ± 11.08	74.1 ± 20.58	73.87 ±13.53
SBPbrach [mmHg]	121.36 ± 11.40	***136.45 ± 12.24***	***131.40 ± 11.9***	***143.96 ± 20.86 #***
DBPbrach [mmHg]	73.18 ± 7.83	**82.91 ± 6.96 #**	76.02 ± 10.21	***79.17 ± 11.19***
PPbrach [mmHg]	47.74 ± 8.94	**47.68 ± 9.46 #**	***53.85 ± 11.30***	***58.02 ± 14.24***
SBPcentr [mmHg]	112.66 ± 10.74	***120.32 ± 10.35***	***122.10 ± 12.97***	***127.55 ± 18.14***
PPcentr [mmHg]	43.25 (38.0-52.38)	**42.88 (38.50-50.50)#**	***49.25 (42.31-58.44)***	***55.0 (45.38-61.50)***
Age-adj. PWV [m/s]	7.76 ± 0.96	8.13 ± 1.39	***8.98 ± 1.25***	***10.18 ± 1.18#***
Affective temperaments				
Depressive	4.0 (4.0-8.0)	6.0 (5.0-8.0)	6.0 (4.0-8.75)	7.0 (5.0-10.0)
Irritable	3.0 (2.0-4.5)	3.0 (3.0-6.0)	3.0 (2.0-5.0)	4.0 (2.0-8.5)
Anxious	4.0 (1.0-7.0)	4.0 (2.0-9.0)	4.0 (1.0-8.0)	6.0 (2.0-13.0)
Hyperthymic	12.0 (8.0-14.0)	11.0 (7.0-13)	9.0 (12.0-14.0)	10.0 (8.0-14.0)
Cyclothymic	2.0 (0-5.0)	***4.0 (2.0-7.0)***	3.0 (1.0-5.0)	***4.0 (2.25-8.0)#***

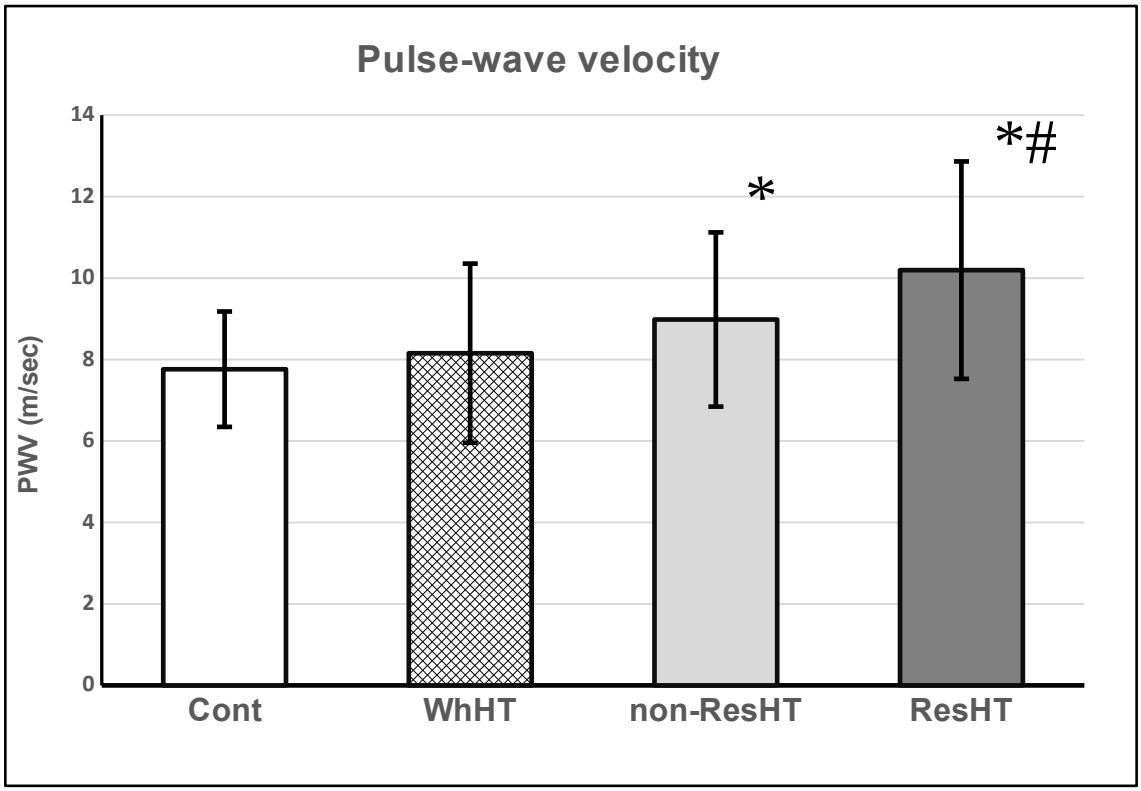


Figure 1. ***Differences between the age-adjusted cfPWV in different hypertension phenotypes: healthy controls (Cont), white-coat hypertensive (WhHT), chronic, non-resistant hypertensive (non-ResHT) and chronic, resistant hypertensive patients (ResHT).***

**p<0.05compared with Cont; #p<0.05 compared with non-ResHT*

Table 3. demonstrates the independent associations of different affective temperament types with resistant hypertension. After adjustment for multiple variables, scores of at least 9 points on the anxious scale, 7 points on the irritable scale and 6 points on the cyclothymic scale were independently associated with ResHT. A score of at least 6 points on the cyclothymic temperament scale was independently associated with WhHT, as well (Beta: 2.378, 95% CI:1.178–4.802, p: 0.016, R^2: 0.041).

Table 3. Associations of chronic hypertensive patients reaching certain points on anxious, irritable or cyclothymic affective temperament subscales with the presence of resistant hypertension. Binary regression analysis, adjusted for multiple confounders.

95% CI, lower-upper: 95% confidence interval, lower and upper values; BMI: body mass index; p<0.05 are signed with bold and italic characters.

Anxious, model R^2: 0.212	***Beta***	**95% CI, lower-upper**		**p**
Age	1.022	0.985	1.061	0.241
Sex	0.933	0.407	2.135	0.869
Diabetes	2.485	1.023	6.045	***0.045***
Smoking	1.573	0.551	4.490	0.397
BMI	1.100	1.009	1.200	***0.031***
Total cholesterol	0.673	0.455	0.996	***0.047***
Anxious score min. 9	2.575	1.081	6.135	***0.033***
Irritable, model R^2: 0.224	***Beta***	**95% CI, lower-upper**		**p**
Age	1.026	0.988	1.065	0.176
Sex	1.309	0.562	3.051	0.532
Diabetes	2.43	0.955	5.749	0.063
Smoking	1.417	0.494	4.063	0.516
BMI	1.101	1.009	1.201	***0.031***
Total cholesterol	0.714	0.485	1.052	0.088
Irritable score min. 7	3.168	1.306	7.687	***0.011***
Cyclothymic, model R^2: 0.217	***Beta***	**95% CI, lower-upper**		**p**
Age	1.029	0.990	1.069	0.146
Sex	1.029	0.453	2.337	0.945
Diabetes	2.025	0.836	4.903	0.118
Smoking	1.596	0.563	4.524	0.379
BMI	1.102	1.010	1.202	***0.029***
Total cholesterol	0.724	0.491	1.065	0.101
Cyclothymic score min. 6	2.591	1.162	5.774	***0.020***

4.4. Study II.: Results of depression and anxiety points in healthy controls and in different hypertension phenotypes

As in Study II., the involved patients were similar with Study I., demographic parameters, comorbidities, laboratory parameters, current medication and the number of the used antihypertensive medications are summarized in Table1. BDI and HAM-A points are summarized in Table 4.

Table 4. Depression and anxiety scores of the different groups of patients

Data are presented as mean ± standard deviation or median (interquartile ranges). Categorical parameters are presented as n (%). Significant differences compared with Cont are signed as bold and italic characters. Significant differences compared with non-ResHT are signed as bold characters with #. Cont: healthy controls; WhHT: patients with white-coat hypertension; non-ResHT: chronic, non-resistant hypertensive patients; ResHT: chronic, resistant hypertensive patients; BDI: Beck Depression Inventory; HAM-A: Hamilton Anxiety Scale.

	Cont	WhHT	non-ResHT	ResHT
BDI	3.0 (1.0-6.0)	***7.0 (3.0-11.0)****	4 (2.0-8.0)	***6.0 (3.0-11.5)****
HAM-A	4.0 (1.0-7.0)	***8.0 (5.0-15.0)**#***	5.0 (2.0-10.0)	***10.5 (5.25-18.75)**#***

4.4.1. The range of depression in healthy subjects and different hypertensive phenotypes

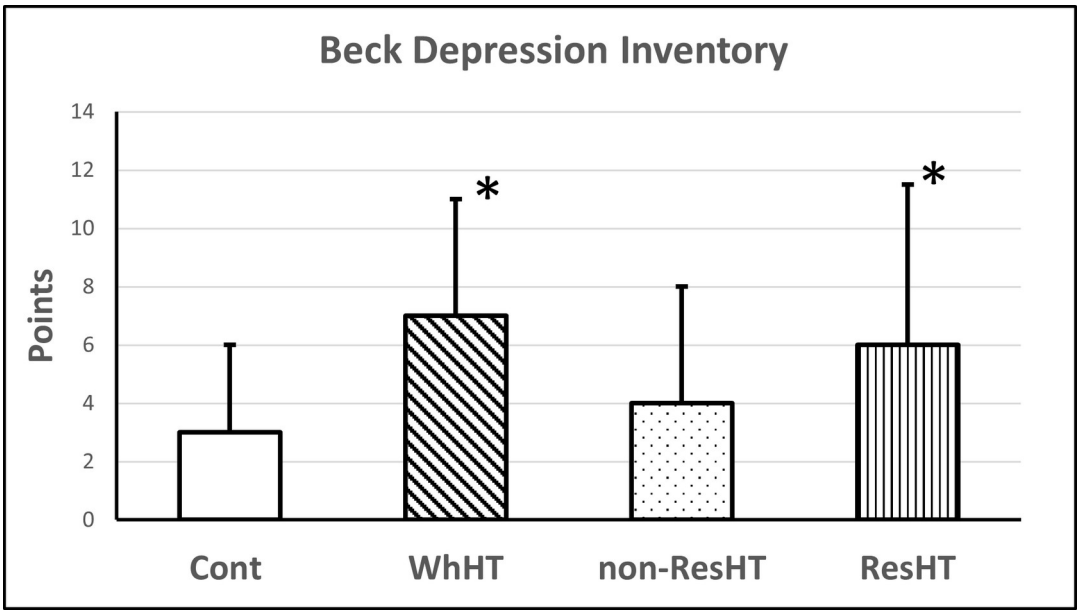
Regarding depression, in WhHT and ResHT groups BDI points were significantly higher ($p<0.05$) compared with the Cont group.

4.4.2. The range of anxiety in healthy subjects and different hypertensive phenotypes

The HAM-A points in WhHT and ResHT groups were elevated compared with Cont, and these two groups of patients had higher HAM-A points compared with non-ResHT patients, as well ($p<0.05$).

Figure 2. also demonstrates the differences in the depression and anxiety points between the different study groups.

A



B

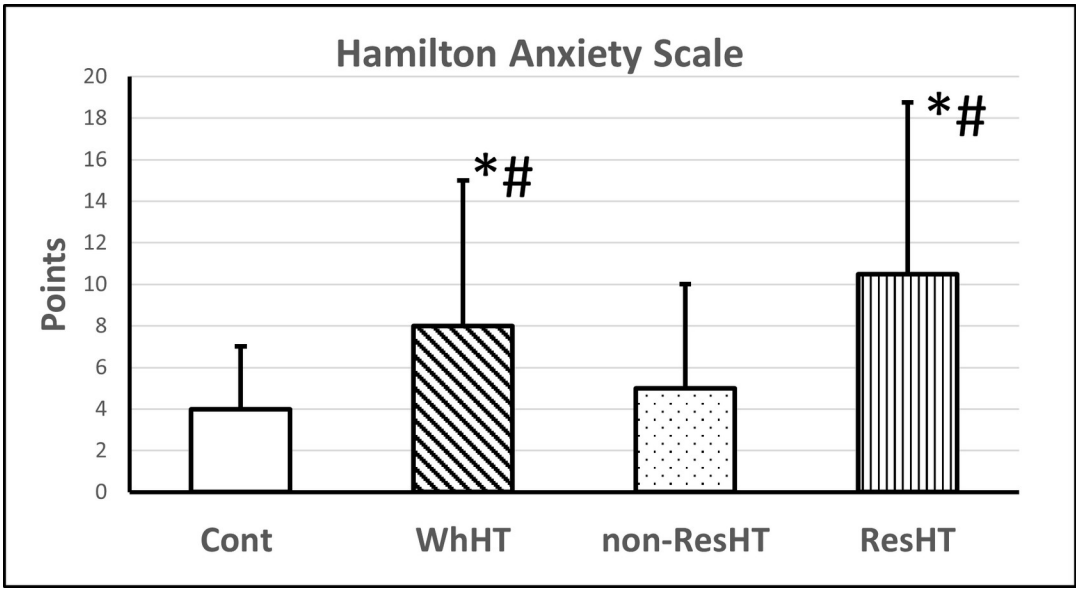


Figure 2. *Differences between healthy controls (Cont), white-coat hypertensive (WhHT), chronic, non-resistant hypertensive (non-ResHT) and chronic, resistant hypertensive patients (ResHT) in the degree of depression (A) and anxiety (B). *p<0.05 compared with Cont; #p<0.05 compared with non-ResHT*

Table 5. demonstrates the independent association of depression with white-coat hypertension. After the adjustment of multiple variables in the final model, white-coat hypertension was associated with BDI scale equal or above 5 (Beta=2.888, 95% CI 1.170–7.126) points.

Table 5. Association of depression with the presence of white-coat hypertension in healthy controls and white-coat hypertensive patients (n=126). Binary regression analysis, adjusted for multiple confounders.

95% CI, lower-upper: 95% confidence interval, lower and upper values; p<0.05 are signed with bold and italic characters. BMI: body mass index; GFR-EPI: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; BDI: Beck Depression Inventory.

	B	**Beta**	**95% CI**		**p**
			Lower	**Upper**	
Age	-0.012	0.989	0.954	1.024	0.525
Sex	-0.194	0.824	0.320	2.124	0.688
Smoking	0.332	1.394	0.429	4.525	0.581
BMI	0.146	1.157	1.025	1.307	***0.019***
Total cholesterol	0.168	1.183	0.803	1.742	0.396
GFR- EPI	0.026	1.026	0.995	1.059	0.100
BDI min. 5 points	1.060	2.888	1.170	7.126	***0.021***

Table 6. demonstrates the independent association of anxiety with white-coat and resistant hypertension. After the adjustment of multiple variables, in the final model, white-coat hypertension was associated with HAM-A scale equal or above 2 points (Beta=4.701, 95% CI 1.165–18.973, Table 4. A), while resistant hypertension was associated with HAM-A scale equal or above 3 points (Beta=3.804, 95% CI 1.204–12.015, Table 4. B).

Table 6. Association of anxiety with the presence of white-coat hypertension in healthy controls and white-coat hypertensive patients (A, n=126) and with the presence of resistant hypertension in chronic hypertensive patients (B, n=237). Binary regression analysis, adjusted for multiple confounders.

95% CI, lower-upper: 95% confidence interval, lower and upper values; p<0.05 are signed with bold and italic characters. BMI: body mass index; GFR-EPI: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; HAM-A: Hamilton Anxiety Scale.

A

	B	Beta	95% CI		p
			Lower	Upper	
Age	-0.014	0.986	0.951	1.022	0.444
Sex	-0.203	0.817	0.320	2.085	0.672
Smoking	0.198	1.22	0.367	4.053	0.746
BMI	0.136	1.145	1.012	1.295	0.031
Total cholesterol	0.160	1.174	0.787	1.751	0.431
GFR- EPI	0.027	1.028	0.995	1.061	0.095
HAM-A min. 2 points	1.548	4.701	1.165	18.973	***0.030***

B

	B	Beta	95% CI		p
			Lower	Upper	
Age	0.017	1.018	0.975	1.062	0.425
Sex	-0.058	0.944	0.405	2.197	0.893
Diabetes	0.855	2.352	0.952	5.809	0.064
Smoking	0.598	1.818	0.626	5.280	0.272
BMI	0.101	1.106	1.011	1.210	***0.027***
Total cholesterol	-0.281	0.755	0.516	1.106	0.149
GFR- EPI	-0.013	0.987	0.965	1.010	0.252
HAM-A min. 3 points	1.336	3.804	1.204	12.015	***0.023***

5. DISCUSSION

In Study I. first in the literature we evaluated the affective temperament patterns of patients with different hypertension phenotypes in the same cohort. We found, that both white-coat and resistant hypertensive patients had elevated cyclothymic scores. In addition, we also identified the thresholds of affective temperament scores (anxious, irritable, and cyclothymic) that are associated independently with resistant hypertension. In white-coat and resistant hypertensive individuals a similar association with cyclothymic scores was discovered with the same threshold limit (6 points). In resistant hypertensive patients the HMOD marker cfPWV values were also elevated, reflecting an increased CV risk.

In Study II. the levels of depression and anxiety were evaluated in different hypertension phenotypes and was demonstrated, that white-coat and resistant hypertensive individuals scored higher points compared with healthy controls on BDI scale. In the case of HAM-A scale white-coat and resistant hypertensive individuals had elevated points compared with healthy subjects and also compared with non-resistant hypertensive patients. Scoring at least 2 or 3 points on HAM-A scale were independently associated with white-coat or resistant hypertension, respectively. Scoring at least 5 points on BDI scale was independently associated with white-coat hypertension. These results suggest psychopathological similarities between white-coat and resistant hypertension regarding both the affective temperaments patterns and level of depression and anxiety.

5.1. Affective temperaments: cumulating data of their influence on CV pathology

Cumulating data confirm the association of affective temperaments with CV pathology, especially with hypertension. Besides previous findings regarding cyclothymic temperament, which has been associated with CV events in the history, elevated systolic blood pressure and earlier onset of hypertension in women (28, 94, 126), our working group published novel data in this field since the publication of papers involved into this thesis. Vascular ageing is a complex process which is associated with CV outcome (127). Cyclothymic temperament was found to be independently associated with

accelerated vascular aging in women after adjustment of multiple risk factors, including depression (128). CCTA enables to detect and quantify coronary artery atherosclerosis on a very exact manner. Cyclothymic affective temperament was independently associated with severe coronary artery disease and also with left ventricular hypertrophy in chronic hypertensive patients assessed by CCTA (126, 129). Adding to the previous findings, our current results confirm the hypothesis, that cyclothymic temperament may play a deleterious role in contributing to CV morbidity in individuals with hypertension and in those in prehypertensive state. A link between cyclothymic temperament and CV complications can be the drug adherence. In the study of **Tetsuya Y. et al**. it was found that cyclothymic temperament is associated with lower level of drug adherence in patients with type 2 diabetes (130). Furthermore, a very recent meta-analysis by **Szabo G. et al**. also revealed, that both in psychiatric and non-psychiatric samples higher scores on the cyclothymic, irritable and depressive temperament scales are associated with worse medical adherence (131).

In our Study I., in the case of resistant hypertension independent associations were found with cyclothymic temperament points at least 6, irritable temperament points at least 7 and anxious temperament point at least 9. In line with our findings in the study of **Amir R. et al.** in pregnant women it was found that scoring at least 9 points on anxious temperament scale was independently associated with gestational hypertension (132). Furthermore, in the study published by **Gyöngyösi H. et al**. another connection was explored between affective temperaments and hypertension. The authors found independent association between depressive, cyclothymic and irritable temperaments with arterial stiffness index in hypertensive patients suggesting a link with the presence of hypertensive target organ damage in patients with pronounced presence of these temperaments (133).

In the study of **Szabo G. et al.,** it was found that in ladies who underwent infertility treatment scoring at least 4 points on cyclothymic scale and at least 9-9 points on depressive and anxious scales, respectively, were independently associated with significantly decreased odds of clinical pregnancy (134). Furthermore, in another study of **Szabo G. et al**., it was also found that, elevated anxious and depressive temperament points were directly associated with the lower odds of achieving clinical pregnancy, while the elevated cyclothymic scores both directly and indirectly affected negatively

the odds of clinical pregnancy. Elevated irritable temperament scores indirectly decreased the odds of clinical pregnancy through reduced dietary recommendation adherence (135). Finally, in a very recent publication, the role of affective temperaments was investigated by **Sipos B. et al** in connection with the severity and extent of CAD in patients examined with CCTA. According to their results, in addition to traditional risk factors, affective temperaments proved to be an independent predictor of the severity and extent of CAD. In the case of men, significant inverse association were found between hyperthymic temperament and clinical plaque burden scores. However, in the female population, the elevated irritable temperament scores independently predicted the extent and the severity of CAD (136). These results also confirm the association between affective temperaments and cardiovascular disease and, like previous results of our working group, also confirm the protective role of hyperthymic temperament against cardiovascular morbidity (28, 71, 120, 126). These data suggest that affective temperaments are associated with a wide aspect of somatic disorders with more and more exactly defined threshold limits. It suggests that in the future affective temperaments can be used for screening subjects who are prone to develop different psychiatric and non-psychiatric disorders which can lead to better prevention and to a more improved, personalized therapy.

At present, we have only hypotheses about possible therapeutic interventions for cardiovascular prevention in patients with different affective temperaments. These might include beneath individual patient communication and strategies to support lifestyle change, for example, task-oriented therapy for individuals with depressive temperaments, meditation and cognitive behavioural therapies for individuals with anxious temperaments, art and relaxation therapies for patients with cyclothymic temperaments, and stress reduction and cognitive behavioural therapies for individuals with irritable temperaments, in addition to individual patient communication and lifestyle change strategies. Alongside these, closer monitoring of medication adherence may also be effective. These interventions would be in line with the recent hypertension guidelines' lifestyle changes recommendations (18, 137, 138), but requires evidence in relation of affective temperaments.

5.2. Management of white-coat hypertension considering depression and anxiety

The findings of Study I. and Study II. suggest as a novel hypothesis an association between white-coat and resistant hypertension, providing a new approach of white-coat hypertension. Until the very recent years white-coat hypertension was considered as a harmless condition, however, data are conflicting. In 2022 **Mancia et al**. published outcomes of the PAMELA study with the median follow-up of 29 years, which discovered that white-coat hypertension with or without organ damage is associated with elevated CV and all-cause mortality risk compared with normotension (139). In contrast, in the study of **Staplin N et al.**, which was recently published in the Lancet including 59 124 patients with the median follow-up of 9.7 years, no association was found between all-cause or CV mortality and white-coat hypertension (140).

In white-coat hypertension regular antihypertensive medication might cause hypotension and based on the recent European hypertension guideline antihypertensive drug therapy might be considered besides HMOD and high CV risk (recommendation II/C) (18). However, the results of the present thesis highlight a different approach for clinicians to pay more attention for the depression and anxiety of white-coat hypertensive patients and their management (mostly with lifestyle changes, like meditation, relaxation) might provide new therapeutic possibilities.

As the untreated white-coat hypertensive patients in our study were much younger than the resistant hypertensive patients, these results can hypothesize, that those white-coat hypertensive patients, are prone to develop resistant hypertension. Theoretically this can be an explanation for the findings of the PAMELA study, when the 29-year risk for CV mortality was elevated in white-coat hypertension (139). Certainly, this hypothesis requires long-term prospective studies to be confirmed.

Our results are in line with previous studies where the depression and stress were also found to be associated both with white-coat and resistant hypertension. In the previous studies depression was pronounced in association with the CHD and risk of incidence of hypertension (141, 142). Furthermore, in a recently published study depressive symptoms were associated with masked hypertension suggesting that depressive symptoms may be considered as risk factors for masked hypertension, as well (143). In addition, according to the very recent 4 years follow-up prospective cohort study by

Tokioka S. et al. depressive symptoms were also found to be associated with early onset of hypertension as well, which confirms the detrimental role of depression in the development of hypertension (144).

Anxiety have also an important pathophysiological role both in resistant and in white-coat hypertensive condition. It was found to be associated with the white-coat effect, and was independently associated with prevalent or incident hypertension and resulted 15% increased risk in the presence of co-morbidities, as well (74). A very recent study by **Gulmer Y. et al.** unveiled a potential association between white-coat hypertension and death anxiety, as well. In this study asymptomatic normotensive or white-coat hypertensive patients with positive familial history of sudden cardiac death or acute myocardial infarction within the last year were enrolled. According to their results, the Templer's Death Anxiety Scale points were significantly elevated in white-coat hypertension compared with normotensive individuals suggesting an association between white-coat hypertension and death anxiety (145).

In line with our results, higher level of anxiety and depression was demonstrated in resistant hypertension compared to not-resistant hypertensive patients (146). These results were confirmed in a very recent study by **Handan D. et al**. as well, where higher levels of depression and anxiety were found in resistant hypertensive patients (147). Resistant hypertensive patients also had higher BMI and CRP levels, while in a multivariate analysis besides anxiety and depression scores, BMI and CRP levels were independent predictors of resistant hypertension. These results suggest that psychopathological factors and inflammation contribute to the development of resistant hypertension (147).

5.3. Evaluation of depression, anxiety and affective temperaments in the clinical practice

The evaluation of depression, anxiety and affective temperaments in the future can play an important role in the preventive tasks of general practitioners (GPs). The screening of depressive symptoms (with the short version of BDI, which consist 9 questions) is already part of the reimbursed preventive activities of Hungarian GP communities. In the future, besides the screening of anxiety, which is still not reimbursed, the evaluation of affective temperaments could also be part of the evaluation of psychometric

parameters for preventive reasons. An advantage of the evaluation of the affective temperaments is that in contrast with depression and anxiety, which are relatively unstable conditions and can change with lifestyle changes and different medications, temperaments are stable in adults. It means that their evaluation in adult patients can be enough only once and does not require temporal repeated measures.

The evaluation of depression has high clinical importance regarding the CV outcome of the patients as the medical treatment of depression improves CV outcome, as well (148). The evidence in this field is so strong that in the 2021 European Cardiovascular Prevention Guideline the use of selective serotonin reuptake inhibitors is recommended (with the strength of IIa/B) in those coronary artery disease patients who have major mood disorder (115).

Affective temperaments cannot be modified by medications, but probably the temperament-associated behaviours could be targeted. It was demonstrated that patients with a marked cyclothymic and irritable temperament have a higher tendency to smoke (149). In relation to morbid obesity, a predominant cyclothymic, irritable and anxious temperament has been found with higher prevalence compared to healthy controls (150). In alcohol dependence, alcoholics had higher scores on cyclothymic, depressive and irritable scales (151). Furthermore, in another recent study, cyclothymic and irritable scales were also found to be higher in alcoholics (152).

Besides the 110 item-long TEMPS-A questionnaire the short version of TEMPS-A was also published and a version containing 40 items was developed in Hungarian language in 2018. The authors tested the short version on two cohorts including 1651 and 206 participants, respectively and found excellent internal reliability on each temperament scales (153). This version after further clinical validations could make the screening of affective temperaments much easier and less time consuming (153).

5.4. The position of arterial stiffness measurement in the clinical practice

Measurement of arterial stiffness in our study confirmed the increased CV risk of ResHT patients, as their mean cfPWV was above 10 m/s, which is the threshold for HMOD. In contrast, cfPWV was normal in WhHT patients which means, that in line with the literature HMOD was not present in these patients.

The evaluation of HMOD with arterial stiffness measurement was present with different strength of recommendation in previous guidelines. The cfPWV measurement was first recommended as a marker of subclinical organ damage with the value >12 m/s in 2007, in the hypertension management guideline of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (154). In the next ESH-ESC hypertension guideline in 2013 cfPWV was recommended to be evaluated as a measure of asymptomatic organ damage with the strength of class **IIa**, level of evidence **B** (24, 122). In the ESC- Artery Society 2015 position paper, the evaluation of cfPWV as a vascular biomarker was recommended as a class **IIa**, level of evidence **A** method (24, 155). Furthermore, the recommendation of cfPWV measurement was also present in the ESC- European Association for the Study of Diabetes guideline, as a useful CV risk marker, adding predictive value to the usual risk estimate (156). In addition, the American College of Cardiology Foundation-American Heart Association task force document published in 2015 also highlighted the importance of cfPWV and arterial stiffness measurement to provide incremental information beyond standard CV disease risk factors in the prediction of future CV disease events with the recommendation of class **IIa**, level of evidence **A** (24, 157). In the recent 2023 ESH hypertension management guideline the measurement of PWV is recommended for HMOD detection, however without graded level of evidence (18). Numerous studies have proven that the assessment of large artery stiffness using cfPWV or baPWV is clinically useful in hypertensive patients. Evidences from the Framingham cohort and also in European studies have shown that an increase in arterial stiffness is highly prevalent in the hypertensive population (18, 155, 158, 159). Furthermore, cfPWV was found to be higher in masked and white-coat hypertension than in normotension, but was still lower compared to sustained hypertensive subjects, which means that increased PWV in patients with normal office BP may identify those in whom out-of-office BP monitoring should be performed to identify this higher CV risk condition (160). Moreover, in two meta-analyses, cfPWV or baPWV were able to more accurately classify CV risk compared to traditional risk-based scores, with a particularly important advantage for young and middle-aged patients at low to moderate risk (161, 162). Adding cfPWV to traditional Framingham CV risk factors resulted in a 27% net reclassification index for CV mortality, while adding baPWV to the model incorporating the Framingham risk

score improved the net reclassification index by 24.7%. Increased cfPWV and baPWV values were found in apparently healthy adolescents, young and middle-aged people to predict an increased risk of new-onset hypertension (18, 22, 163, 164).

Finally, because of its relationship with age, PWV is considered a key element in the assessment of vascular ageing, which is currently the subject of huge scientific interest (165). Although cfPWV measurement is the gold standard for arterial stiffness estimation, the PWV estimation method was also developed as a namely estimated PWV (ePWV) which requires only age and mean arterial blood pressure in the formula (166). ePWV was a predictor of the outcome of the SPRINT trial independently of the Framingham Risk Score (167) suggesting that it is a simple and promising method which can be applied for a population-based cohort, as well.

In the future the measurement or the estimation of PWV will probably find its place in the clinical practice. An incoming consensus document aiming to guide clinicians for the use of PWV in everyday practice is under construction by the committee of the Artery Society, which might provide clear recommendations in this field.

5.5. Limitation of the studies

Our studies have some limitations. Although standardized questionnaires were used and patients with dementia were excluded, the possibility of misinterpretations or mistakes during the completion of the questionnaires could not have been totally excluded. Another limitation was the cross-sectional design, which limits us to make causal inferences. In addition, all participants were from Caucasian race it provides another limitation as race-specific differences are supposed to be present in the pattern of affective temperaments. Moreover, as ABPM was not performed in those patients or healthy participants who had normal office blood pressure values, we were unable to diagnose masked hypertension and to analyse affective temperaments, depression and anxiety in this hypertension phenotype. Finally, as tonometric cfPWV was used, patients with atrial fibrillation were excluded from the studies which is also an obstacle of the generalizability of our results.

In our present cross-sectional studies, we did not investigate further potential interactions of affective temperaments with other psychological or sociodemographic factors. Furthermore, our studies have only revealed primary statistical associations with

affective temperaments, hypertension phenotypes, depression and anxiety. A prospective phase of our study is ongoing, in which we are investigating progression of hypertension, all-cause and cardiovascular mortality. We also aim to use mediation analysis for more detailed exploration of pathophysiological pathways.

6. CONCLUSIONS

In conclusion, in resistant hypertensive patients compared with healthy controls we found significant differences in affective temperament patterns, in depression, anxiety and also in HMOD measured with arterial stiffness. Moreover, we found psychopathological similarities between white-coat and resistant hypertensive patients regarding affective temperament patterns and depression and anxiety scores, as well. In the case of affective temperaments, we found similar associations with cyclothymic score in white-coat and resistant hypertensive patients. We also identified thresholds of anxious, irritable and cyclothymic temperament scores and HAM-A scores that are independently associated with resistant hypertension. Additionally, we identified thresholds of cyclothymic temperament score and BDI, HAM-A scores that are independently associated with white-coat hypertension. In the light of our results, the evaluation of affective temperaments, depression and anxiety can contribute to a more personalized approach of the care of white-coat and resistant hypertensive patients which might be helpful in the future to prevent the development or the progression of HMOD and consequently, CV events.

7. SUMMARY

In our first cross-sectional study, we evaluated affective temperaments in different hypertension phenotypes. We found that both the white-coat and resistant hypertensive patients have similarly elevated cyclothymic points. We identified the thresholds of affective temperament scores that are independently associated with white-coat or resistant hypertension. Carotid-femoral pulse wave velocity measurement verified hypertension-mediated organ damage in resistant hypertension.

In our second study, we also found that the level of depression and anxiety is altered in different hypertension phenotypes. We found similarly higher results on the depression and anxiety points in white-coat and resistant hypertensive patient groups compared with controls. In addition, almost similar threshold limits were found regarding the anxiety scale in the association of white-coat and resistant hypertension.

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8. PUBLICATION SUMMARY

8.1. Publications related to the thesis

1. Kőrösi B, Gyöngyösi H, Batta D, László A, Kovács I, Tislér A, Cseprekál O, **Nemcsik-Bencze Zs**, Gonda X, Rihmer Z, Nemcsik J. Evaluation of affective temperaments and arterial stiffness in different hypertension phenotypes. Hypertension Research 44pp 47-54. (2021) **(IF: 5.525)**

2. **Zsófia Nemcsik Bencze**, Beáta Kőrösi, Helga Gyöngyösi, Dóra Batta, Andrea László, Péter Torzsa, Illés Kovács, Zoltán Rihmer, Xénia Gonda and János Nemcsik. Depression and anxiety in different hypertension phenotypes: a cross sectional study. Annals of General Psychiatry 21: (1). (2022) **(IF: 3.7)**

8.2. Publications not directly related to the thesis

1. Cseprekál O, Egresits J, Tabák Á, Nemcsik J, Járai Z, Babos L, Fodor E, Farkas K, Godina G, Kárpáthi K, Kerkovits L, Marton A, Németh Z, **Nemcsik-Bencze Z**, Sallai L, Kiss I, Tislér A. The significance of micro- and macrovascular biomarkers on cardiovascular outcome in chronic kidney disease - Prospective cohort study. Journal of Human Hypertension 30:449-455. (2016) **(IF: 2.797)**

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13. Gyöngyösi Helga, Kőrösi Beáta Zita, Batta Dóra, László Andrea, Kovács Illés, Tislér András, Cseprekál Orsolya, **Nemcsik-Bencze Zsófia**, Gonda Xénia, Rihmer Zoltán, Nemcsik János. Az affektív temperamentumok vizsgálata egészségesekben és különböző fenotípusú hypertoniás kórállapotokban. Hypertonia és Nephrologia. 26(03) (2022)

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15. Helga Gyöngyösi, Dóra Batta, Andrea László, Péter Torzsa, Beáta Kőrösi, **Zsófia Nemcsik-Bencze**, Orsolya Cseprekál, András Tislér, János Nemcsik. Evaluation of Office and Ambulatory Central Blood Pressure and Augmentation Index by Two Methods and Their Changes After Lifestyle or Medical

Interventions in Hypertension. Artery Research, Volume 30, article number 2, (2024) **(IF: 0.9)**

Cumulative impact factor of the candidate's publications related to the thesis: **IF: 9.225**
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APPENDIX

Tempermant Scale of Memphis, Pisa, Paris and San Diego – Autoquestionnaire Version (TEMPS-A)

Circle T (True) for all items that are true about you for <u>much of your life.</u>
Circle F (False) for all the rest that don't apply to you for much of your life.

1. T F I'm a sad, unhappy person.
2. T F People tell me I am unable to see the lighter side of things.
3. T F I have suffered a lot in life
4. T F I think things often turn out for the worst.
5. T F I give up easily.
6. T F For as long as I can remember, I've felt like a failure.
7. T F I have always blamed myself for what others might consider no big deal.
8. T F I don't seem to have as much energy as other people.
9. T F I'm the kind of person who doesn't like change very much.
10. T F In a group, I would rather hear others talk.
11. T F I often give in to others.
12. T F I feel very uneasy meeting new people.
13. T F My feelings are easily hurt by criticism or rejection.
14. T F I am the kind of person you can always depend on.
15. T F I put the needs of others above my own.
16. T F I am a hard working person.
17. T F I would rather work for someone else than be the boss.
18. T F It is natural for me to be neat and organized.
19. T F I'm the kind of person who doubts everything.
20. T F My sex drive has always been low.
21. T F I normally need more than 9 hours of sleep.
22. T F I often feel tired for no reason.
23. T F I get sudden shifts in mood and energy.
24. T F My moods and energy are either high or low, rarely in between.
25. T F My ability to think varies greatly from sharp to dull for no apparent reason.

26. T F I can really like someone a lot, and then completely lose interest in them.
27. T F I often blow up at people and then feel guilty about it.
28. T F I often start things and then lose interest before finishing them.
29. T F My mood often changes for no reason.
30. T F I constantly switch between being lively and sluggish.
31. T F I sometimes go to bed feeling down, but wake up in the morning feeling terrific.
32. T F I sometimes go to bed feeling great, and wake up in the morning feeling life is not worth living.
33. T F I am told that I often get pessimistic about things, and forget previous happy times.
34. T F I go back and forth between feeling overconfident and feeling unsure of myself.
35. T F I go back and forth between being outgoing and being withdrawn from others.
36. T F I feel all emotions intensely.
37. T F My need for sleep varies a lot from just a few hours to more than 9 hours.
38. T F The way I see things is sometimes vivid, but at other times lifeless.
39. T F I am the kind of person who can be sad and happy at the same time.
40. T F I daydream a great deal about things that other people consider impossible to achieve.
41. T F I often have a strong urge to do outrageous things.
42. T F I am the kind of person who falls in and out of love easily.
43. T F I'm usually in an upbeat or cheerful mood.
44. T F Life is a feast which I enjoy to the fullest.
45. T F I like telling jokes, people tell me I'm humorous.
46. T F I'm the kind of person who believes everything will eventually turn out all right.
47. T F I have great confidence in myself.
48. T F I often get many great ideas.
49. T F I am always on the go.

50. T F I can accomplish many tasks without even getting tired.
51. T F I have a gift for speech, convincing and inspiring to others.
52. T F I love to tackle new projects, even if risky.
53. T F Once I decide to accomplish something, nothing can stop me.
54. T F I am totally comfortable, even with people I hardly know.
55. T F I love to be with a lot of people.
56. T F People tell me that I often get my nose into others' business.
57. T F I am known to be generous, and spend a lot of money on other people.
58. T F I have abilities and expertise in many areas.
59. T F I feel I have the right and privilege to do as I please.
60. T F I am the kind of person who likes to be the boss.
61. T F When I disagree with someone, I can get into a heated argument.
62. T F My sex drive is always high.
63. T F Normally I can get by with less than 6 hours of sleep.
64. T F I am a grouchy (irritable) person.
65. T F I am by nature a dissatisfied person.
66. T F I complain a lot.
67. T F I am highly critical of others.
68. T F I often feel on edge.
69. T F I often feel wound up.
70. T F I am driven by an unpleasant restlessness that I don't understand.
71. T F I often get so mad that I will just trash everything.
72. T F When crossed, I could get into a fight.
73. T F People tell me I blow up out of nowhere.
74. T F When angry, I snap at people.
75. T F I like to tease people, even those I hardly know.
76. T F My biting humor has gotten me into trouble.
77. T F I can get so furious I could hurt someone.
78. T F I am so jealous of my spouse (or lover), that I cannot stand it.
79. T F I am known to swear a lot.
80. T F I have been told that I become violent with just a few drinks.
81. T F I am a very skeptical person.

82. T F I could be a revolutionary.

83. T F My sex drive is often so intense that it is truly unpleasant.

84. T F (Women only): I have attacks of uncontrollable rage right before my period.

85. T F I have been a worrier for as long as I can remember.

86. T F I'm always worrying about one thing or another.

87. T F I keep on worrying about daily matters that others consider minor.

88. T F I cannot help worrying.

89. T F Many people have told me not to worry so much.

90. T F When stressed, my mind often goes blank.

91. T F I am unable to relax.

92. T F I often feel jittery inside.

93. T F When stressed, my hands often tremble.

94. T F I often have an upset stomach.

95. T F When I'm nervous, I may have diarrhea.

96. T F When I'm nervous, I often feel nauseous.

97. T F When I'm nervous, I have to go to the bathroom more often.

98. T F When someone is late coming home, I fear they have had an accident.

99. T F I am often fearful of someone in my family coming down with a serious disease.

100. T F I'm always thinking someone might break bad news to me about a family member.

101. T F My sleep is not restful.

102. T F I frequently have difficulty falling asleep.

103. T F I am, by nature, a very cautious person.

104. T F I often wake up at night afraid that burglars are in the house.

105. T F I easily get headaches when stressed.

106. T F When stressed, I get an uncomfortable feeling in my chest.

107. T F I'm an insecure person.

108. T F Even minor changes in routine, stress me highly.

109. T F While driving, even when I haven't done anything wrong, I fear that the police may stop me.

110. T F Sudden noises startle me easily.

Interpreting the TEMPS-A

depressive temperament: questions 1 to 21 (21 points)
cyclothymic temperament: questions 22 to 42 (21 points)
hyperthymic temperament: questions 23 to 63 (21 points)
irritable temperament: questions 64 to 84 (21 points in women, 20 in the men's version)
anxious temperament: questions 85 to 110 (26 points).

Those reaching the mean+2 SD level or higher in each subscale are considered to have dominant affective temperaments.

Beck's Depression Inventory

This depression inventory can be self-scored. Select one of the four responses for each of the 21 points.

1.

0 I do not feel sad.

1 I feel sad

2 I am sad all the time and I can't snap out of it.

3 I am so sad and unhappy that I can't stand it.

2.

0 I am not particularly discouraged about the future.

1 I feel discouraged about the future.

2 I feel I have nothing to look forward to.

3 I feel the future is hopeless and that things cannot improve.

3.

0 I do not feel like a failure.

1 I feel I have failed more than the average person.

2 As I look back on my life, all I can see is a lot of failures.

3 I feel I am a complete failure as a person.

4.

0 I get as much satisfaction out of things as I used to.

1 I don't enjoy things the way I used to.

2 I don't get realsatisfaction out ofanything anymore.

3 I am dissatisfied or bored with everything.

5.

0 I don't feel particularly guilty

1 I feel guilty a good part of the time.

2 I feel quite guilty most of the time.

3 I feel guilty all of the time.

6.

0 I don't feel I am being punished.

1 I feel I may be punished.

2 I expect to be punished.

3 I feel I am being punished.

7.

0 I don't feel disappointed in myself.

1 I am disappointed in myself.

2 I am disgusted with myself.

3 I hate myself.

8.

0 I don't feel I am any worse than anybody else.

1 I am critical of myself for my weaknesses or mistakes.

2 I blame myself all the time for my faults.

3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.

1 I have thoughts of killing myself, but I would not carry them out.

2 I would like to kill myself.

3 I would kill myself if I had the chance.

10.

0 I don't cry any more than usual.

1 I cry more now than I used to.

2 I cry all the time now.

3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.

1 I am slightly more irritated now than usual.

2 I am quite annoyed or irritated a good deal of the time.

3 I feel irritated all the time.

12.

0 I have not lost interest in other people.

1 I am less interested in other people than I used to be.

2 I have lost most of my interest in other people.

3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.

1 I put off making decisions more than I used to.

2 I have greater difficulty in making decisions more than I used to.

3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.

1 I am worried that I am looking old or unattractive.

2 I feel there are permanent changes in my appearance that make me look unattractive

3 I believe that I look ugly.

15.

0 I can work about as well as before.

1 It takes an extra effort to get started at doing something.

2 I have to push myself very hard to do anything.

3 I can't do any work at all.

16.

0 I can sleep as well as usual.

1 I don't sleep as well as I used to.

2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.

1 I get tired more easily than I used to.

2 I get tired from doing almost anything.

3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.

1 My appetite is not as good as it used to be.

2 My appetite is much worse now.

3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.

1 I have lost more than five pounds.

2 I have lost more than ten pounds.

3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.

1 I am worried about physical problems like aches, pains, upset stomach, or

constipation.

2 I am very worried about physical problems and it's hard to think of much else.

3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I have almost no interest in sex.

3 I have lost interest in sex completely.

Interpreting the Beck Depression Inventory

Total Score	Levels of Depression
1-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
over 40	Extreme depression

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe).

	Not present	Mild	Moderate	Severe	Very Severe
1. **Anxious Mood** Worries, anticipation of the worst, fearful anticipation, irritability.					
2. **Tension** Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.					
3. **Fears** Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.					
4. **Insomnia** Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.					
5. **Intellectual** Difficulty in concentration, poor memory.					
6. **Depressed Mood** Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.					
7. **Somatic (muscular)** Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.					
8. **Somatic (sensory)** Tinnitus, blurring of vision, hot and					

cold flushes, feelings of weakness, pricking sensation.					
9. **Cardiovascular Symptoms** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.					
10. **Respiratory Symptoms** Pressure or constriction in chest, choking feelings, sighing, dyspnea.					
11. **Gastrointestinal Symptoms** Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.					
12. **Genitourinary Symptoms** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of rigidity, premature ejaculation, loss of libido, impotence.					
13. **Autonomic Symptoms** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.					
14. **Behavior at Interview** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.					

Interpreting HAMA-A

Sum the scores from all 14 parameters.

0-5= No anxiety

6-14= Mild anxiety

>15= Severe anxiety

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ARTICLE

Evaluation of affective temperaments and arterial stiffness in different hypertension phenotypes

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Abstract

Affective temperaments (depressive, anxious, irritable, hyperthymic, and cyclothymic) are stable parts of personality and describe emotional reactivity to external stimuli. Their relation to psychopathological conditions is obvious, but less data are available on their relationship with cardiovascular disorders. The aim of this study was to evaluate affective temperaments and hemodynamic and arterial stiffness parameters in healthy subjects (Cont), in white-coat hypertensive (WhHT) patients, and in non-resistant (non-ResHT) and resistant hypertensive (ResHT) patients. In this cross-sectional study, 363 patients were included: 82 Cont, 44 WhHT, 200 non-ResHT, and 37 ResHT. The patients completed the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A), and arterial stiffness was examined with tonometry (PulsePen). Significant differences were found between the Cont, WhHT, non-ResHT and ResHT groups in pulse wave velocity (7.76 ± 0.96, 8.13 ± 1.39, 8.98 ± 1.25, and 10.18 ± 1.18 m/s, respectively, $p < 0.05$ between Cont and non-ResHT/ResHT; $p < 0.05$ between non-ResHT and ResHT). Cyclothymic affective temperament points (4 (2.25–8)) were higher ($p < 0.05$) in the ResHT group than in the Cont (2 (0–5)) and non-ResHT (3 (1–5)) groups. The cyclothymic temperament points of the WhHT group (4 (2–7)) were also higher than those in the Cont group. ResHT was independently associated with a cyclothymic scale score above 6 (beta = 2.59 (95% CI: 1.16–5.77)), an irritable scale score above 7 (beta = 3.17 (95% CI: 1.3–7.69)) and an anxious scale score above 9 (beta = 2.57 (95% CI: 1.08–6.13)) points. WhHT was also independently associated with cyclothymic scale scores above 6 points (beta = 2.378, 95% CI: 1.178–4.802). In conclusion, white-coat and ResHT patients have specific affective temperament patterns, and the evaluation of these patterns can help to understand the psychopathological background of these conditions.

Keywords Affective temperaments · Arterial stiffness · Resistant hypertension · White-coat hypertension

Introduction

Cardiovascular (CV) diseases are the leading cause of morbidity and mortality in most industrialized countries worldwide, and hypertension is responsible for more CV

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deaths than any other modifiable CV risk factor [1]. A continuous linear relationship between elevated blood pressure and CV events is present at all ages and in different ethnic groups as well [2–6]. Different hypertension phenotypes have been described, such as white-coat hypertension (WhHT), chronic nonresistant hypertension (non-ResHT) and chronic, resistant hypertension (ResHT). WhHT, which is characterized as elevated blood pressure during office measurement but normotension in out-of-office conditions, is thought to be a benign condition [7]. Patients with both controlled and uncontrolled ResHT are definitely at higher risk than those with non-ResHT [8]. In hypertensive patients, the evaluation of hypertension-mediated organ damage (HMOD) helps determine the exact CV risk. Among the different tools, the measurement of carotid-femoral pulse wave velocity (cfPWV) is one of the methods recommended for the detection of HMOD with a threshold limit of 10 m/s [9].

Temperament is regarded as an inherited part of personality [10, 11]. Affective temperaments characterize the emotional reactivity to external stimuli and are classified into five types: depressive, irritable, anxious, hyperthymic, and cyclothymic [12]. These affective temperaments can be measured by the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A), which contains 110 items [13]. Depressive temperament is characterized as self-denying, striving to live in harmony with others and sensitive to suffering, while irritable temperament incorporates skeptical and critical traits. Anxious temperament can best be explained by exaggerated worries, especially toward family members. Hyperthymic temperament is characterized by upbeat, overconfident and overenergetic traits, while cyclothymic temperament shows affective instability with rapid mood shifts and intense emotions [11, 14, 15]. It is well known that there are sex differences in the patterns of affective temperaments [16, 17].

Associations between affective temperaments and different psychopathological conditions are increasingly obvious [18]. Specific affective temperament types can be antecedents of minor and major mood disorders [12], where hyperthymic affective temperament is inversely related to depression [19]. Fewer data are available in relation to CV diseases, especially hypertension, but cyclothymic temperament is presumably detrimental in the context of this condition, while hyperthymic temperament might be protective [17, 20, 21].

The aim of our study was to evaluate affective temperaments in individuals with different hypertension phenotypes and in healthy subjects and to screen HMOD with the measurement of cfPWV. We hypothesized that cfPWV is elevated in ResHT patients and that patients with ResHT have different affective temperament patterns than non-ResHT patients and controls.

Methods

Patients

In the present cross-sectional study, 363 Caucasian patients were enrolled between August 2012 and January 2019 in three primary care practices in the capital of Hungary, Budapest. Healthy controls (Cont, $n = 82$), patients with white-coat hypertension (WhHT, $n = 44$), patients with chronic non-resistent hypertension (non-ResHT, $n = 200$) and patients with chronic resistant hypertensive (ResHT, $n = 37$) were involved in the study. WhHT was defined as elevated office blood pressure (>140/90 mmHg) but normal blood pressure values during 24-h ambulatory blood pressure measurement (ABPM, 24-h average <130/80 mmHg, daytime average <135/85 mmHg, night-time average <120/70 mmHg). ResHT was defined as blood pressure that remained above 140/90 mmHg in the office despite the concurrent use of three antihypertensive agents of different classes, including a diuretic, or as a blood pressure controlled with the use of more than three medications [22]. In the ResHT patients who had uncontrolled office values, the diagnosis was always confirmed by ABPM or by home blood pressure monitoring (HBPM). Non-ResHT was defined as chronic (>3 months) hypertension that is treated and controlled with a maximum of 3 antihypertensive agents.

Patients with atrial fibrillation, treated depression or other psychiatric diseases (schizophrenia, bipolar disorder) or with dementia potentially interfering with the completion of questionnaires were excluded. Patients on moderate doses of alprazolam (<0.5 mg/day) were not excluded.

During the screening visit, blood pressure was measured with a validated oscillometric device (Omron M3), and subjects were invited to participate in the study. An autoquestionnaire was administered to the subjects and included a written informed consent form and a questionnaire for the evaluation of family and personal history and affective temperaments. Patients were asked to bring back the autoquestionnaires in the morning of the clinical measurements.

For the included patients, within two weeks after the screening visit, an appointment was scheduled for 7.00. a.m. for arterial stiffness (cfPWV) measurement and for blood sampling. For untreated patients who had elevated office blood pressure during the screening visit, after the cfPWV measurement, a 24-h ABPM device (Mobil-O-Graph, I.E.M. GmbH, Germany) was fitted with the cuff placed on the left arm, and a blood sample was taken from the right arm. The 24-h ABPM device was brought back on the following day, when its results and of the blood sample analysis were discussed with the patient. For treated patients who had elevated office blood pressure, ResHT was confirmed within 2 weeks with HBPM or with ABPM, similar to the procedure for the untreated patients.

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 842/PI/2011), and was carried out in accordance with the tenets of the Declaration of Helsinki.

Evaluation of affective temperaments

The 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 [13]. The TEMPS-A contains 110 items (109 in the version for males), and the questions of the various temperament types are grouped together as follows:

1. Depressive temperament: questions 1–21 (21 points)
2. Cyclothymic temperament: questions 22–42 (21 points)
3. Hyperthymic temperament: questions 23–63 (21 points)
4. Irritable temperament: questions 64–84 (21 points for women, 20 for men)
5. Anxious temperament: questions 85–110 (26 points).

TEMPS-A has been extensively studied, has been translated into more than 25 languages and has been 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 [16].

Blood pressure and arterial stiffness measurements

Patients were required to fast overnight and refrain from smoking and drinking caffeine-containing beverages before the procedure but were instructed to take their usual blood pressure medication. Upon arrival and after 5 min of rest, two brachial blood pressure measurements were taken on each arm with the patients in a sitting position with a validated oscillometric blood pressure device (Omron M3). The mean values of the arm with the higher readings of brachial systolic (SBPbrach) and diastolic (DBPbrach) blood pressures and heart rate were used. Brachial pulse pressure (PPbrach) was also calculated from these data. The subjects were next fitted with an arterial stiffness measurement device and were asked to rest in the supine position for ~15 min before being measured. Arterial stiffness parameters were evaluated with the gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy) [23]. This method provides estimates of cfPWV, central systolic blood pressure (SBPcentr), and central pulse pressure (PPcentr). In each subject, two sequences of arterial stiffness measurements were performed, and their means were used for statistical analysis. In the PWV calculations, 80% of the carotid-femoral distance was used, according to the consensus [24]. The intra- and interobserver variability in PWV measurements obtained by the PulsePen device in hypertensive patients was 4.6% and 6.3%, respectively. Since PulsePen calculates pressures based on brachial diastolic blood pressure calibration, the calculated central diastolic blood pressure is identical to the brachial diastolic blood pressure assessed in the supine position [23].

Statistical analysis

Descriptive data are expressed as the mean ± standard deviation or median with interquartile range. The normality of continuous parameters was tested with the Kolmogorov–Smirnov test. Normally distributed parameters were compared between the four groups (Cont, WhHT, non-ResHT, ResHT) with ANOVA. For post hoc analysis, Tukey's test was used. Nonnormally distributed parameters were compared with the Kruskal–Wallis test.

As age is an important determinant of PWV [25] and there were significant differences in age between the groups studied, we adjusted values of PWV for age.

Based on the literature, sex differences are common in psychopathological conditions [26] and in the pattern of affective temperaments [16]; therefore, the associations of affective temperaments with the different hypertensive conditions were studied in the whole population and in males and females separately.

For the examination of the independent association of each affective temperament with ResHT, the chronic hypertensive patient groups (non-ResHT plus ResHT) were dichotomized based on the 75% quartile of the affective temperament scores of the patients. Next, with binary regression analysis, the association of the different affective temperament scores with ResHT was studied with adjustment for traditional CV risk factors such as age, sex, smoking, diabetes, body mass index, and total cholesterol. Finally, the association of the different affective temperament scores with WhHT was also studied with adjustment for sex, smoking, and BMI.

In all analyses, $p < 0.05$ was considered to be statistically significant. SPSS 22.0 for Windows was used for all calculations.

Results

Baseline demographic and laboratory parameters, current medication, and the number of antihypertensive medications used are summarized in Table 1. Compared with Cont individuals, non-ResHT and ResHT patients were older; had higher BMI, blood glucose, uric acid, and triglyceride levels; and had lower HDL cholesterol levels. Compared

Table 1 Baseline characteristics of the study participants

	Cont	WhHT	non-ResHT	ResHT
N (male/female)	82 (31:51)	44 (22:22)	200 (91:109)	37 (14:23)
Age (years)	49.61 ± 18.28	44.12 ± 13.36	***59.44 ± 13.24***	***65.55 ± 10.22***
Duration of hypertension (years)	–	–	9.40 ± 9.11	17.44 ± 13.22
Diabetes [*n* (%)]	–	3 (3.7%)	32 (16%)	16 (43%)
CV disease [*n* (%)]	–	–	18 (9%)	12 (32%)
Current smoker [*n* (%)]	12 (15%)	8 (18%)	38 (19%)	7 (19%)
BMI [kg/m^2]	24.35 ± 3.65	***27.70 ± 5.62***	***28.80 ± 4.62***	***30.50 ± 3.45***
Blood glucose [mmol/l]	4.90 (4.60–5.51)	5.15 (4.75–5.40)	5.49 (5.00–6.32)	6.28 (5.26–7.50)
GFR-EPI [ml/min/1.73 m^2]	79.31 ± 32.40	***93.31 ± 30.09***	81.69 ± 18.37	72.35 ± 24.24
Uric acid [μmol/l]	295.00 ± 72.97	307.61 ± 68.92	***327.86 ± 81.82***	***351.59 ± 101.05***
Total cholesterol [mmol/l]	5.41 ± 1.10	5.54 ± 1.38	5.41 ± 1.15	***4.76 ± 1.33***
LDL [mmol/l]	3.30 ± 0.97	3.56 ± 1.24	3.34 ± 1.03	***2.73 ± 1.24***
HDL [mmol/l]	1.64 ± 0.36	1.47 ± 0.37	***1.38 ± 0.38***	***1.26 ± 0.32***
Triglyceride [mmol/l]	0.96 (0.69–1.30)	1.17 (0.87–1.57)	***1.48 (1.08–2.05)***	***1.53 (1.10–2.47)***
Medication [*n* (%)]				
ACE- inhibitor	–	–	118 (59%)	24 (64.9%)
ARB [*n* (%)]	–	–	29 (14.5%)	12 (32.4%)
Calcium channel blocker	–	–	75 (37.5%)	28 (75.6%)
Beta-blocker	–	–	89 (44.5%)	27 (72.9%)
Diuretic	–	–	23 (11.5%)	33 (89.2%)
Alfa-adrenerg receptor blocker	–	–	22 (11%)	19 (51.3%)
Centrally acting agents	–	–	1 (0.5%)	–
Direct acting vasodilatators	–	–	1 (0.5%)	5 (13.5%)
Antiplatelet drug	1 (1.2%)	–	42 (21%)	12 (32.4%)
Statin	6 (7.3%)	1 (2.3%)	50 (25%)	12 (32.4%)
Fibrate	–	–	7 (3.5%)	5 (13.5%)
Alprazolam	1 (1.2%)	–	18 (9%)	2 (5.4%)
Number of antihypertensive medications				
0	82 (100%)	44 (100%)	–	–
1	–	–	85 (42.5%)	–
2	–	–	72 (36%)	–
3	–	–	43 (21.5%)	16 (43.2%)
4	–	–	–	9 (24.3%)
5	–	–	–	9 (24.3%)
6	–	–	–	2 (5.4%)
7	–	–	–	1 (2.7%)

Cont healthy controls, *WhHT* patients with white-coat hypertension, *non-ResHT* chronic, nonresistant hypertensive patients, ResHT chronic, resistant hypertensive patients, *CV* diseases cardiovascular diseases, *BMI* body mass index, *GFR-EPI* glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ACE* angiotensin converting enzyme, *ARB* angiotensin II receptor blocker

Data are presented as mean ± standard deviation or median (interquartile ranges). Categorical parameters are presented as *n* (%). Significant differences compared with Cont are signed as bold and italic characters

with Cont individuals, ResHT patients had lower total and LDL cholesterol levels, probably due to the administration of statins. BMI and eGFR were higher in WhHT patients than in Cont individuals.

Hemodynamic parameters and affective temperament scores for the whole population are summarized in Table 2. SBPbrach and SBPcentr were both higher in the WhHT, non-ResHT, and ResHT groups than in the Cont group.

Table 2 Hemodynamic parameters and affective temperament scores of the different groups of patients

	Cont	WhHT	non-ResHT	ResHT
Hemodyn. parameters				
Hearth rate [1/min]	72.1 ± 10.7	77.61 ± 11.08	74.1 ± 20.58	73.87 ± 13.53
SBPbrach [mmHg]	121.36 ± 11.40	***136.45 ± 12.24***	***131.40 ± 11.9***	***143.96 ± 20.86 #***
DBPbrach [mmHg]	73.18 ± 7.83	**82.91 ± 6.96 #**	76.02 ± 10.21	***79.17 ± 11.19***
PPbrach [mmHg]	47.74 ± 8.94	**47.68 ± 9.46 #**	***53.85 ± 11.30***	***58.02 ± 14.24***
SBPcentr [mmHg]	112.66 ± 10.74	***120.32 ± 10.35***	***122.10 ± 12.97***	***127.55 ± 18.14***
PPcentr [mmHg]	43.25 (38.0–52.38)	**42.88 (38.50–50.50)#**	***49.25 (42.31–58.44)***	***55.0 (45.38–61.50)***
Age-adj. PWV [m/s]	7.76 ± 0.96	8.13 ± 1.39	***8.98 ± 1.25***	***10.18 ± 1.18#***
Affective temperaments				
Depressive	4.0 (4.0–8.0)	6.0 (5.0–8.0)	6.0 (4.0–8.75)	7.0 (5.0–10.0)
Irritable	3.0 (2.0–4.5)	3.0 (3.0–6.0)	3.0 (2.0–5.0)	4.0 (2.0–8.5)
Anxious	4.0 (1.0–7.0)	4.0 (2.0–9.0)	4.0 (1.0–8.0)	6.0 (2.0–13.0)
Hyperthymic	12.0 (8.0–14.0)	11.0 (7.0–13)	9.0 (12.0–14.0)	10.0 (8.0–14.0)
Cyclothymic	2.0 (0–5.0)	***4.0 (2.0–7.0)***	3.0 (1.0–5.0)	***4.0 (2.25–8.0)#***

Data are presented as mean ± standard deviation or median (interquartile ranges). Categorical parameters are presented as *n* (%). Significant differences compared with Cont are signed as bold and italic characters. Significant differences compared with non-ResHT are signed as bold characters with #

Cont healthy controls, *WhHT* patients with white-coat hypertension, *non-ResHT* chronic, nonresistant hypertensive patients, *ResHT* chronic, resistant hypertensive patients, *SBPbrach* brachial systolic blood pressure, *DBPbrach* brachial diastolic blood pressure, *PPbrach* brachial pulse pressure, *SBPcentr* central systolic blood pressure, *PPcentr* central pulse pressure, Age-adj. *PWV* age-adjusted carotid-femoral pulse wave velocity

BrachSBP was higher in ResHT than in non-ResHT. DBPbrach was elevated only in WhHT and ResHT patients. Compared with Cont individuals, cfPWV was not elevated in WhHT patients, but it was higher in non-ResHT and ResHT patients. A significant difference ($p = 0.011$) was found between non-ResHT and ResHT patients as well (Table 2).

In the total population, cyclothymic affective temperament scores were higher in WhHT and in ResHT patients than in Cont individuals ($p = 0.049$ and $p = 0.008$, respectively), and they were even higher in ResHT patients than in non-ResHT patients ($p = 0.032$, Table 2). When male and female subjects were studied separately, no significant differences were found (data not shown).

Table 3 demonstrates the independent associations of different affective temperament types with resistant hypertension. After adjustment for multiple variables, scores of at least 9 points on the anxious scale, 7 points on the irritable scale and 6 points on the cyclothymic scale were independently and strongly associated with ResHT. A score of at least 6 points on the cyclothymic temperament scale was independently associated with WhHT (Beta: 2.378, 95% CI: 1.178–4.802, *p*: 0.016, R^2: 0.041).

Discussion

To the best of our knowledge, this is the first study to evaluate the affective temperament patterns of patients with different hypertension phenotypes. We found that both WhHT and ResHT patients had elevated cyclothymic scores. In ResHT patients, cfPWV, a marker of HMOD, was also elevated, reflecting an increased CV risk, and we identified thresholds of affective temperament scores (anxious, irritable, and cyclothymic) that are strongly associated with resistant hypertension. In WhHT patients where a similar association with cyclothymic scores was discovered, we did not find any significant differences from Cont individuals in the presence of HMOD measured with cfPWV.

Resistant hypertensive patients have increased CV risk independent of the actual measurements of controlled or uncontrolled blood pressure [8]. Previously, it was demonstrated that ResHT patients have higher levels of anxiety than nonresistant uncontrolled hypertensive patients [27], and depression is also an important comorbidity in this condition and can influence treatment resistance [28]. In contrast with depression and anxiety, which are not stable conditions and can significantly change not only as a result of psychotherapy or medications but also as a result of interventions, such as renal denervation [29], affective temperaments are relatively stable after adolescence [30]. Therefore, our finding that scores of at least nine points on the anxious scale, seven points on the irritable scale or six points on the cyclothymic scale are associated with the presence of resistant hypertension independent of multiple confounders including age and sex can be important for the identification of this the subgroup of hypertensive patients

Table 3 Association of chronic hypertensive patients reaching certain points on anxious, irritable, or cyclothymic affective temperament subscales with the presence of resistant hypertension. Binary regression analysis, adjusted for multiple confounders

Anxious, model R^2: 0.212	*Beta*	95% CI, lower-upper		*p*
Age	1.022	0.985	1.061	0.241
Sex	0.933	0.407	2.135	0.869
Diabetes	2.485	1.023	6.045	***0.045***
Smoking	1.573	0.551	4.490	0.397
BMI	1.100	1.009	1.200	***0.031***
Total cholesterol	0.673	0.455	0.996	***0.047***
Anxious score min. 9	2.575	1.081	6.135	***0.033***
Irritable, model R^2: 0.224	*Beta*	95% CI, lower-upper		*p*
Age	1.026	0.988	1.065	0.176
Sex	1.309	0.562	3.051	0.532
Diabetes	2.43	0.955	5.749	0.063
Smoking	1.417	0.494	4.063	0.516
BMI	1.101	1.009	1.201	***0.031***
Total cholesterol	0.714	0.485	1.052	0.088
Irritable score min. 7	3.168	1.306	7.687	***0.011***
Cyclothymic, model R^2: 0.217	*Beta*	95% CI, lower-upper		*p*
Age	1.029	0.990	1.069	0.146
Sex	1.029	0.453	2.337	0.945
Diabetes	2.025	0.836	4.903	0.118
Smoking	1.596	0.563	4.524	0.379
BMI	1.102	1.010	1.202	***0.029***
Total cholesterol	0.724	0.491	1.065	0.101
Cyclothymic score min. 6	2.591	1.162	5.774	***0.020***

95% CI, lower-upper: 95% confidence interval, lower and upper values; $p < 0.05$ are signed with bold and italic characters

BMI body mass index

with increased CV risk, even before the development of resistant hypertension and HMOD. A very recent paper is in line with our findings regarding the threshold of anxious temperament; similar to our results, during pregnancy, scores of at least nine points on the anxious scale were independently associated with gestational hypertension [31].

Interestingly, in WhHT patients, cyclothymic affective temperament scores were elevated compared with those in Cont individuals, were similar to those in ResHT patients and did not differ significantly from those in non-ResHT patients. Another similarity between white-coat and ResHT patients was that scores of least six points on the cyclothymic scale were associated with both conditions. White-coat hypertensive patients are at an increased risk of becoming sustained hypertensive patients, which requires treatment in the future [9]. As previously found in hypertensive patients, cyclothymic temperament was associated with CV events [32], with elevated systolic BP [20] and with the earlier development of hypertension in women [17]. Our present findings confirm our previous hypothesis that cyclothymic temperament can play a deleterious role in individuals with hypertension and in those in a prehypertensive state.

In addition to the similar cyclothymic pattern of white-coat and ResHT patients, based on the literature, there are other psychopathological similarities between the two groups. Anxiety is associated with resistant hypertension and can also lead to the white-coat effect [27, 33], and depression and stress are also associated with both the white-coat effect and resistant hypertension [28, 34, 35]. These data suggest a novel hypothesis; compared with nonResHT patients, an increased proportion of ResHT patients 60–70 years of age could have had white-coat hypertension at 30–40 years of age. Although after this study, during recent control visits, some ResHT patients reported experiencing the white-coat effect decades previously (data not shown), this information was not obtained from all patients, as this question was not part of the study design, and exploring this hypothesis requires follow-up studies.

Another finding requires discussion: the cyclothymic score of non-ResHT patients was similar to that of controls and was not elevated as it was in WhHT and ResHT patients. However, a proportion of WhHT patients progress to non-ResHT, and a proportion of non-ResHT patients progress to ResHT. Resistant hypertension has been reported in ~8–13% of the hypertensive population [36, 37], while the prevalence of white-coat hypertension is ~30% in patients with elevated clinical blood pressure readings; [9, 38] therefore, we think that the relatively low proportion of these conditions does not markedly influence the median cyclothymic score of the whole nonResHT population. In addition, not all WhHT patients progress to real hypertension, which can also decrease the impact on average psychometric scores in the nonResHT population.

Arterial stiffness measurement also confirmed the elevated CV risk in our ResHT patients, as the mean cfPWV was above 10 m/s, the threshold of HMOD, which is in line with the literature [39]. In contrast, we found no difference in the presence of HMOD in WhHT patients compared with the healthy subjects. White-coat hypertension in untreated subjects is supposed to be a benign phenomenon, as previous reports found the associated CV risk to be similar to that of normotension [7, 40] or to be between those of normotension and hypertension [41, 42]. Therefore, our results confirm the present knowledge of CV risk based on HMOD of both WhHT and ResHT patients.

There are some limitations of our study. Although we used standardized autoquestionnaires and excluded patients with dementia, we cannot exclude the possibility of some

misinterpretations or mistakes by the patients. Furthermore, the cross-sectional design of the study does not allow us to make causal inferences. In addition, all of the involved patients were of Caucasian race. As race-specific differences are supposed to be present in the pattern of affective temperaments, this can be a limitation of the generalizability of our result. Next, as there has been a lack of capacity to perform ABPM for those patients or healthy subjects who had normal clinical blood pressure values and did not report elevated results during HBPM, we were unable to diagnose masked hypertension and to analyze the affective temperament pattern of this hypertension phenotype. Finally, as tonometric cfPWV was part of the protocol, patients with atrial fibrillation were excluded from the study, which also limits the generalizability of our results.

In conclusion, compared with healthy controls and non-resistant chronic hypertensive patients, we found marked differences in patients with resistant hypertension both in affective temperament patterns and HMOD measured with arterial stiffness. In addition, we identified thresholds of anxious, irritable and cyclothymic temperament scores that are independently associated with resistant hypertension. White-coat hypertensive patients had similar cyclothymic scores as ResHT patients, and similar associations were found between cyclothymic score and white-coat hypertension and resistant hypertension. Our results suggest that the evaluation of affective temperaments can help to understand the psychopathological background of white-coat and resistant hypertension, which might be helpful in the future when designing interventions to prevent the development of HMOD and CV events.

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Compliance with ethical standards

Conflict of interest XG is a recipient of the János Bolyai Research Fellowship of the Hungarian Academy of Sciences. This study was supported by the Hungarian Society of Hypertension. However, these grants did not influence the data analysis or the interpretation of the results.

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RESEARCH

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Depression and anxiety in different hypertension phenotypes: a cross-sectional study

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Abstract

Background: Hypertension is a major risk factor of cardiovascular mortality. Mood disorders represent a growing public health problem worldwide. A complex relationship is present between mood disorders and cardiovascular diseases. However, less data is available about the level of depression and anxiety in different hypertension phenotypes. The aim of our study was to evaluate psychometric parameters in healthy controls (Cont), in patients with white-coat hypertension (WhHT), with chronic, non-resistant hypertension (non-ResHT), and with chronic, treatment-resistant hypertension (ResHT).

Methods: In a cross-sectional study setup 363 patients were included with the following distribution: 82 Cont, 44 WhHT, 200 non-ResHT and 37 ResHT. The patients completed the Beck Depression Inventory (BDI) and the Hamilton Anxiety Scale (HAM-A).

Results: BDI points were higher in WhHT (7 (3–11)) and ResHT (6 (3–11.5)) compared with Cont (3 (1–6), $p < 0.05$). Similarly, HAM-A points were higher in WhHT (8 (5–15)) and ResHT (10.5 (5.25–18.75)) compared with Cont (4 (1–7), $p < 0.05$) and also compared with non-ResHT (5 (2–10), $p < 0.05$). ResHT was independently associated with HAM-A scale equal or above 3 points (Beta = 3.804, 95%CI 1.204–12.015). WhHT was independently associated with HAM-A scale equal or above 2 points (Beta = 7.701, 95%CI 1.165–18.973) and BDI scale equal or above 5 points (Beta = 2.888, 95%CI 1.170–7.126).

Conclusions: Our results suggest psychopathological similarities between white-coat hypertension and resistant hypertension. As recently it was demonstrated that white-coat hypertension is not a benign condition, our findings can have relevance for future interventional purposes to improve the outcome of these patients.

Keywords: Depression, Anxiety, Resistant hypertension, White-coat hypertension

Background

Hypertension is considered as the leading cause of cardiovascular (CV) mortality and based on American data, it is in the second place in the list of the preventable causes of all-cause mortality as well [1, 2]. Mood disorders such as depression and anxiety represent a growing public health problem and their association with adverse CV outcome is well-established [3–5].

The association between hypertension, depression and anxiety are controversially discussed in diverse studies [6, 7]. The background of this observation can be based on the differences of the studied patient populations, the application of different psychometric measures, the heterogenous pathophysiological background

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of hypertension or the presence of different hypertension phenotypes in the cohorts. Such phenotypes are white-coat hypertension (WhHT), masked hypertension, chronic, treatment-resistant hypertension (ResHT) and chronic, non-resistant hypertension (non-ResHT). In WhHT patients blood pressure is increased in office, but normal during out-of office measurements. In masked hypertension home results are elevated, while in the office, blood pressure is normal [8]. In ResHT blood pressure is above 140/90 mmHg in the office in spite of the use of 3 antihypertensive drugs of different classes including a diuretic. ResHT also includes patients whose blood pressure is controlled with the use of more than 3 medications [9]. It was demonstrated that both controlled and uncontrolled ResHT are accompanied with higher CV risk compared with non-ResHT [10].

Anxiety was found to be associated with white-coat effect during blood pressure measurement [11, 12], while resistant hypertension was also associated with anxiety [13]. Recently we described similarities in affective temperament patterns between WhHT and ResHT [14]. However, until now the level of depression and anxiety was not evaluated in a cohort of individuals with different hypertension phenotypes.

The aim of our study was to measure depression and anxiety in healthy controls, in untreated subjects with white-coat effect and in chronic hypertension with or without the presence of resistant hypertension. Based on our recent findings we hypothesized similarities between subjects with white-coat and resistant hypertension.

Methods.

Our present results are part of an additional analysis of a previously published cohort [14], including the results of the depression and anxiety questionnaires.

Patients

In the setup of a cross-sectional study, altogether 363 Caucasian patients were involved between August 2012 and January 2019, in three primary care practices in Budapest, Hungary. Four categories of the enrolled subjects were defined: healthy controls (Cont, $n=82$); white-coat hypertensive patients (WhHT, $n=44$); chronic, non-resistant hypertensive patients (non-ResHT, $n=200$); and patients with chronic, resistant hypertension (ResHT, $n=37$). The diagnosis of resistant hypertension was always confirmed by ambulatory blood pressure monitoring (ABPM) or by home blood pressure monitoring (HBPM). The definition of non-resistant hypertension required the following criteria: chronic (the onset is longer than 3 months), treated (with the maximum use of 3 antihypertensive agents) and controlled hypertension.

As in this cohort carotid–femoral pulse wave velocity was also measured (data are not shown in the present publication), patients with atrial fibrillation were excluded from the study. Other exclusion criteria were treated depression, anxiety, or other psychiatric conditions (bipolar disorder, schizophrenia) and also dementia to avoid mistakes or misunderstanding of the questionnaires. The chronic, moderate use of alprazolam (< 0.5 mg/day) was not an exclusion criterion when it was added to the hypertension therapy protocol by other specialists, without the diagnosis of anxiety.

Subjects were recruited into the study during the screening visit when blood pressure was measured with a validated oscillometric device (Omron M3) and written informed consent was collected. At the end of the screening visit an autoquestionnaire was handed out to the subjects including a questionnaire for the evaluation of family and personal history and also for depression. The autoquestionnaires were collected from the patients in the day of the clinical measurements.

After the screening visit within the maximum of a 2-week period an appointment was scheduled for 7.00. a.m. for repeated office and/or ambulatory blood pressure measurement and also for blood sampling. Finally the evaluation of anxiety was completed in the form of an interview with the examiner.

Evaluation of depression and anxiety

The *Beck Depression Inventory* (BDI) was used to evaluate the severity of depression. It is one of the most widely used instruments including a 21-question multiple-choice self-report questionnaire with ratings on a four-point scale, where a higher score correlates with more severe depression [15].

The *Hamilton Anxiety Scale* (HAM-A) was used to study the severity of anxiety. During the evaluation the examiner reports the subject. Its scale consists 14 items, each item is scored on a scale of 0 (not present) to 4 (severe anxiety) [16].

Office and ambulatory blood pressure measurement

Before the clinical measurements overnight fasting, refrain from smoking and drinking caffeine-containing beverages were required, but patients were asked to take their usual antihypertensive medication. In sitting position after 5 min of rest, two brachial blood pressure measurements were taken in 1-min interval on each arm with an oscillometric device (Omron M3, validated). In the detailed analysis the mean value of the higher side of arms was further used as brachial systolic (SBP) and diastolic (DBP) blood pressures and heart rate. Pulse pressure (PP) was also calculated as SBP minus DBP. Next, untreated subjects, who had elevated office blood pressure during the screening visit, were fitted with a 24-h ABPM device (Mobil-O-Graph, I.E.M. GmbH,

Germany). The cuff was placed on the left arm. Finally venipuncture was performed on the right arm for blood sampling. The 24-h ABPM and blood test results were discussed with the patient on the following day. In case of treated hypertensive patients with increased office blood pressure, where the diagnosis of ResHT was considered, it was confirmed within 2 weeks with HBPM or with ABPM.

Statistical analysis

Descriptive data are expressed as mean ± standard deviation or median with interquartile ranges. Kolmogorov–Smirnov test was used test the normality of continuous parameters. ANOVA was applied for normally distributed parameters to compare differences between the four groups (Cont, WhHT, non-ResHT, ResHT). Tukey's test was used for post-hoc analysis. Kruskal–Wallis test was applied to compare non-normally distributed parameters.

To study the association of depression and anxiety with ResHT, chronic hypertensive patient groups (non-ResHT plus ResHT) were dichotomized based on the 75% quartile of the depression and anxiety scores of the patients. Next, with binary regression analysis, the association with ResHT of the patient groups reaching different BDI and HAM-A scores was studied with the adjustment for traditional CV risk factors, such as age, sex, smoking, diabetes, body mass index and total cholesterol. Finally, in the merged group of Cont plus WhHT, with binary regression analysis the association with WhHT of the patients reaching different BDI and HAM-A points was also studied with the adjustment for sex, smoking and BMI.

In all analyses $p < 0.05$ was considered as the border of significance. SPSS 22.0 for Windows was used throughout the calculations.

Results

Demographic parameters and comorbidities, results of blood sampling, current medication and the number of the used antihypertensive medications are summarized in Table 1.

Compared with Cont, non-ResHT and ResHT patients had elevated age, higher BMI, blood glucose, uric acid and triglyceride levels, and lower HDL cholesterol. ResHT patients had decreased total and LDL cholesterol levels compared with Cont probably as a consequence of the administration of statins. BMI and eGFR were higher in WhHT compared with Cont.

Hemodynamic parameters and the results of BDI and HAM-A questionnaires are summarized in Table 2.

Compared with Cont SBP was higher in WhHT, non-ResHT and ResHT groups. SBP in ResHT was even higher than in non-ResHT. Compared with Cont, DBP was higher only in WhHT and ResHT. BDI points of WhHT and ResHT groups were significantly higher compared with Cont ($p < 0.05$). Similarly, compared with Cont, HAM-A points of WhHT and ResHT were also higher, but these two groups of patients had higher HAM-A points compared with non-ResHT as well ($p < 0.05$). Figure 1 also demonstrates the differences in the depression and anxiety points between the different study groups.

Table 3 demonstrates the independent association of depression with white-coat hypertension.

After the adjustment of multiple variables white-coat hypertension was associated with BDI scale equal or above 5 (Beta = 2.888, 95% CI 1.170–7.126) points.

Table 4 demonstrates the independent association of anxiety with white-coat and resistant hypertension.

After the adjustment of multiple variables white-coat hypertension was associated with HAM-A scale equal or above 2 points (Beta = 4.701, 95% CI 1.165–18.973, Table 4A), while resistant hypertension was associated with HAM-A scale equal or above 3 points (Beta = 3.804, 95% CI 1.204–12.015, Table 4B).

Discussion

In our study we demonstrated that the level of depression and anxiety can vary in different hypertension phenotypes. Patients with white-coat and resistant hypertension scored higher points compared with healthy controls in BDI scale, and also compared with non-resistant hypertensive patients in HAM-A scale. In addition, almost similar threshold limits were found in respect of HAM-A scale with the independent association of white-coat and resistant hypertension.

Our results are in line with our recent findings on the same cohort, where cyclothymic affective temperament points were similarly higher in white-coat and resistant hypertension compared with healthy controls and cyclothymic affective temperament points equal or above 6 were independently associated both with white-coat and resistant hypertension [14]. Therefore, in addition to cyclothymic affective temperament, another psychopathological similarities, namely, the level of depression and anxiety, are also present between white-coat and resistant hypertensive patients. As in our study patients with untreated white-coat hypertension were much younger compared with the resistant hypertensive ones, these results suggest that those white-coat hypertensive patients who progress to sustained hypertension, are prone to develop resistant hypertension, which is a novel hypothesis and requires long-lasting prospective studies to confirm. However, we suppose that in the present stage our results are enough to encourage clinicians to

Table 1 Baseline characteristics of the study participants

	Cont	WhHT	non-ResHT	ResHT
N (male/female)	82 (31:51)	44 (22:22)	200 (91:109)	37 (14:23)
Age (years)	49.61 ± 18.28	44.12 ± 13.36	***59.44 ± 13.24***	***65.55 ± 10.22***
Duration of hypertension (years)	–	–	9.40 ± 9.11	17.44 ± 13.22
Diabetes [*n* (%)]	–	3 (3.7%)	32 (16%)	16 (43%)
CV disease [*n* (%)]	–	–	18 (9%)	12 (32%)
Current smoker [*n* (%)]	12 (15%)	8 (18%)	38 (19%)	7 (19%)
BMI (kg/m^2)	24.35 ± 3.65	***27.70 ± 5.62***	***28.80 ± 4.62***	***30.50 ± 3.45***
Blood glucose (mmol/l)	4.90 (4.60–5.51)	5.15 (4.75–5.40)	5.49 (5.00–6.32)	6.28 (5.26–7.50)
GFR–EPI (ml/min/1.73m^2)	79.31 ± 32.40	***93.31 ± 30.09***	81.69 ± 18.37	72.35 ± 24.24
Uric acid (μmol/l)	295.00 ± 72.97	307.61 ± 68.92	***327.86 ± 81.82***	***351.59 ± 101.05***
Total cholesterol (mmol/l)	5.41 ± 1.10	5.54 ± 1.38	5.41 ± 1.15	***4.76 ± 1.33***
LDL (mmol/l)	3.30 ± 0.97	3.56 ± 1.24	3.34 ± 1.03	***2.73 ± 1.24***
HDL (mmol/l)	1.64 ± 0.36	1.47 ± 0.37	***1.38 ± 0.38***	***1.26 ± 0.32***
Triglyceride (mmol/l)	0.96 (0.69–1.30)	1.17 (0.87–1.57)	***1.48 (1.08–2.05)***	***1.53 (1.10–2.47)***
Medication [*n* (%)]				
ACE-inhibitor	–	–	118 (59%)	24 (64.9%)
ARB [*n* (%)]	–	–	29 (14.5%)	12 (32.4%)
Calcium channel blocker	–	–	75 (37.5%)	28 (75.6%)
Beta-blocker	–	–	89 (44.5%)	27 (72.9%)
Diuretic	–	–	23 (11.5%)	33 (89.2%)
Alfa-adrenergic receptor blocker	–	–	22 (11%)	19 (51.3%)
Centrally acting agents	–	–	1 (0.5%)	–
Direct acting vasodilators	–	–	1 (0.5%)	5 (13.5%)
Antiplatelet drug	1 (1.2%)	–	42 (21%)	12 (32.4%)
Statin	6 (7.3%)	1 (2.3%)	50 (25%)	12 (32.4%)
Fibrate	–	–	7 (3.5%)	5 (13.5%)
Alprazolam	1 (1.2%)	–	18 (9%)	2 (5.4%)
Number of antihypertensive medications				
0	82 (100%)	44 (100%)	–	–
1	–	–	85 (42.5%)	–
2	–	–	72 (36%)	–
3	–	–	43 (21.5%)	16 (43.2%)
4	–	–	–	9 (24.3%)
5	–	–	–	9 (24.3%)
6	–	–	–	2 (5.4%)
7	–	–	–	1 (2.7%)

Data are presented as mean ± standard deviation or median (interquartile ranges)

Cont: healthy controls, *WhHT*: patients with white-coat hypertension, *non-ResHT*: chronic, non-resistant hypertensive patients, *ResHT*: chronic, resistant hypertensive patients, *CV* diseases: cardiovascular diseases, *BMI*: body mass index, *GFR–EPI*: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation, *LDL*: low-density lipoprotein, *HDL*: high-density lipoprotein, *ACE*: Aangiotensin converting enzyme, *ARB*: angiotensin II receptor blocker

Categorical parameters are presented as *n* (%). Significant differences compared with Cont are signed as bold and italic characters

pay more attention for the psychopathological features of white-coat hypertensive patients, which is particularly important in the light of a very recent study. Until now untreated white-coat hypertension was supposed to be a benign phenomenon, but the study of Mancia et al. on PAMELA cohort with the median follow-up of 29 years demonstrated that white-coat hypertension with or without organ damage is associated with elevated CV and all-cause mortality risk compared with normotension [17]. These results will probably modify the recommendations about the clinical management of white-coat hypertension and based on the results of our present study as target of intervention, depression and anxiety might be considered.

Table 2 Hemodynamic parameters, depression and anxiety scores of the different groups of patients

	Cont	WhHT	non-ResHT	ResHT
Hemodyn. parameters				
Hearth rate (1/min)	72.1 ± 10.7	77.61 ± 11.08	74.1 ± 20.58	73.87 ± 13.53
SBP (mmHg)	121.36 ± 11.40	***136.45 ± 12.24***	***131.40 ± 11.9***	***143.96 ± 20.86 #***
DBP (mmHg)	73.18 ± 7.83	***82.91 ± 6.96 #***	76.02 ± 10.21	***79.17 ± 11.19***
PP (mmHg)	47.74 ± 8.94	***47.68 ± 9.46 #***	***53.85 ± 11.30***	***58.02 ± 14.24***
BDI	3.0 (1.0–6.0)	***7.0 (3.0–11.0)****	4 (2.0–8.0)	***6.0 (3.0–11.5)****
HAM-A	4.0 (1.0–7.0)	***8.0 (5.0–15.0)*#***	5.0 (2.0–10.0)	***10.5 (5.25–18.75)*#***

Data are presented as mean ± standard deviation or median (interquartile ranges)

Cont: healthy controls, *WhHT*: patients with white-coat hypertension, *non-ResHT*: chronic, non-resistant hypertensive patients, *ResHT*: chronic, resistant hypertensive patients, *SBP*: brachial systolic blood pressure, *DBP*: brachial diastolic blood pressure, *PP*: brachial pulse pressure, *BDI*: Beck Depression Inventory, *HAM-A*: Hamilton Anxiety Scale

Categorical parameters are presented as *n* (%). Significant differences compared with Cont are signed as bold and italic characters. Significant differences compared with non-ResHT are signed as bold characters with #

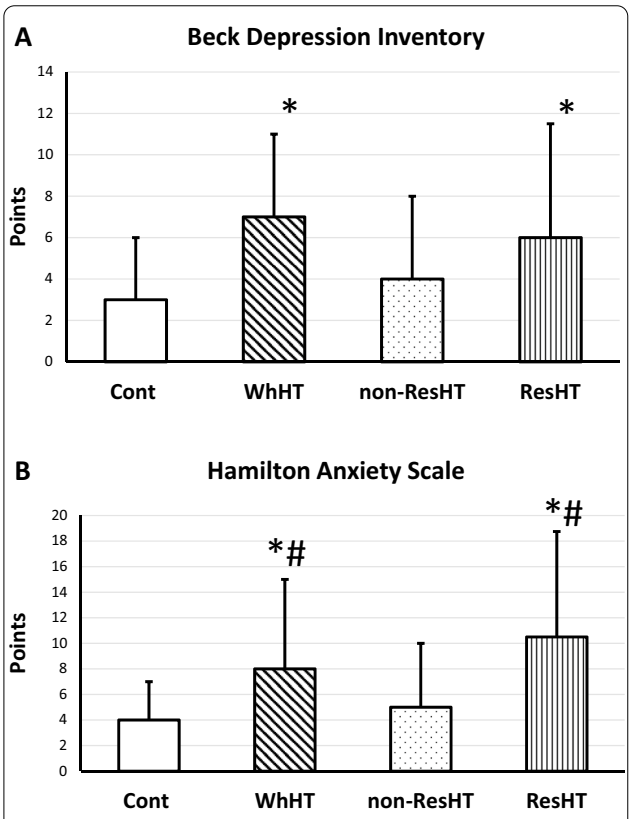

Fig. 1 Differences between healthy controls (Cont), white-coat hypertensive (WhHT), chronic, non-resistant hypertensive (non-ResHT) and chronic, resistant hypertensive patients (ResHT) in the degree of depression (**A**) and anxiety (**B**). *$p < 0.05$ compared with Cont; #$p < 0.05$ compared with non-ResHT

However, it is the first study which evaluated the level of depression and anxiety in different hypertension phenotypes in one cohort, in the literature some data are already available about the similarities between white-coat and resistant hypertension. Anxiety has a pathophysiological role in both conditions as it was found to be associated with white-coat effect [12] and was also more pronounced in resistant hypertension compared with uncontrolled, but not resistant hypertensive patients [13]. Depression and stress were also found to be associated both with white-coat and resistant hypertension [18–20]. Our results are in line with these previous studies and confirm the importance of the evaluation of mood disorders in hypertension, especially as proper medical intervention of mood disorders might improve hypertensive conditions as well [21].

Table 3 Association of depression evaluated with the presence of white-coat hypertension in healthy controls and white-coat hypertensive patients ($n = 126$). Binary regression analysis, adjusted for multiple confounders

	B	Beta	95% CI		*p*
			Lower	Upper	
Age	−0.012	0.989	0.954	1.024	0.525
Sex	−0.194	0.824	0.320	2.124	0.688
Smoking	0.332	1.394	0.429	4.525	0.581
BMI	0.146	1.157	1.025	1.307	0.019
Total cholesterol	0.168	1.183	0.803	1.742	0.396
GFR–EPI	0.026	1.026	0.995	1.059	0.100
BDI min. 5 points	1.060	2.888	1.170	7.126	***0.021***

95% CI, lower–upper: 95% confidence interval, lower and upper values; $p < 0.05$ are signed with bold and italic characters. *BMI*: body mass index; *GFR–EPI*: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; *BDI*: Beck Depression Inventory

A limitation of our study was that although standardized autoquestionnaires were used and patients with dementia were excluded, the possibility of misinterpretations or mistakes during the completion of the questionnaires could not have been totally excluded. Next, the cross-sectional design of the study limits us to make

Table 4 Association of anxiety with the presence of white-coat hypertension in healthy controls and white-coat hypertensive patients (**A**, $n=126$) and with the presence of resistant hypertension in chronic hypertensive patients (**B**, $n=237$). Binary regression analysis, adjusted for multiple confounders

(A)					
	B	**Beta**	**95% CI**		***p***
			Lower	**Upper**	
Age	−0.014	0.986	0.951	1.022	0.444
Sex	−0.203	0.817	0.320	2.085	0.672
Smoking	0.198	1.22	0.367	4.053	0.746
BMI	0.136	1.145	1.012	1.295	0.031
Total cholesterol	0.160	1.174	0.787	1.751	0.431
GFR–EPI	0.027	1.028	0.995	1.061	0.095
HAM-A min. 2 points	1.548	4.701	1.165	18.973	***0.030***
(B)					
Age	0.017	1.018	0.975	1.062	0.425
Sex	−0.058	0.944	0.405	2.197	0.893
Diabetes	0.855	2.352	0.952	5.809	0.064
Smoking	0.598	1.818	0.626	5.280	0.272
BMI	0.101	1.106	1.011	1.210	0.027
Total cholesterol	−0.281	0.755	0.516	1.106	0.149
GFR–EPI	−0.013	0.987	0.965	1.010	0.252
HAM-A min. 3 points	1.336	3.804	1.204	12.015	***0.023***

95% CI, lower–upper: 95% confidence interval, lower and upper values; $p<0.05$ are signed with bold and italic characters

BMI: body mass index, *GFR–EPI*: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation, *HAM-A*: Hamilton Anxiety Scale

causal inferences. Furthermore, as all of participants were from Caucasian race it limits the generalizability of our results for other races. Finally, as ABPM was not performed in those patients or healthy participants who had normal office blood pressure values and did not report elevated values during home blood pressure monitoring, we were unable to diagnose masked hypertension and to analyze the level of depression and anxiety of this hypertension phenotype.

Conclusions

Psychopathological similarities are present between white-coat and resistant hypertensive patients. In light of the recent evidence as white-coat hypertension is not a harmless condition, our findings can have relevance for future interventional purposes to improve the outcome of these patients.

Abbreviations

ACE-inhibitor: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; BDI: Beck Depression Inventory; BMI: Body mass index; CV: Cardiovascular; CKD–EPI GFR: Glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; DBP: Brachial diastolic blood pressure; HAM-A: Hamilton Anxiety Scale; HDL: High-density lipoprotein; PP: Brachial pulse pressure; SBP: Brachial systolic blood pressure; TEMPS-A: The Temperament Evaluation of Memphis Pisa, Paris and San Diego questionnaire.

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Author contributions

ZsN-B uploaded the questionnaires into Excel, helped in data analysis and wrote a draft of the manuscript. BK, HGy, DB and LA performed the clinical measurements and helped in the questionnaires and clinical data collection. PT helped in patient recruitment and reviewed critically the manuscript. IK helped in study planning and statistical analysis. XG helped in the psychiatric part of the study with choosing the proper questionnaires and she helped in their analysis. ZR supervised the psychiatric part of the study and reviewed critically the manuscript. JN planned and supervised the study, helped in patient recruitment and completed the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, Hungarian Ministry of Health (ETT TUKEB 842/PI/2011) and carried out in accordance with the tenets of the Declaration of Helsinki. All patients gave written informed consent to their participation.

Availability of data and materials

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to reasons pertaining to patient privacy.

Competing interests

There has been no role of these grants in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

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