ORIGINAL ARTICLE

Prevalence of high-normal blood pressure and associated cardiovascular risk factors among the adult population of Romania: data from the SEPHAR III survey

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Abstract: Objectives – To estimate the prevalence of high normal blood pressure (HNBP) and to find if subjects with HNBP have more often other cardiovascular risk factors. **Methods –** A representative sample of 1970 Romanian adults was enrolled in SEPHAR III survey. Blood pressure measurements were performed according to current guidelines and all subjects were evaluated by a 71-item survey questionnaire together with extensive evaluation for target organ damage. **Results –** Prevalence of HNBP was 11% [45.1% high blood pressure (HBP), 43.9% normal blood pressure (NBP)]. Values of weight, waist circumference, body mass index, total and LDL cholesterol, triglycerides, fasting blood glucose, glycosylated hemoglobin – HbA1c, uric acid, serum creatinine, glomerular filtration rate estimate by CKD-EPI Equation, albumin/creatinine ratio, intimae-media thickness, rates of arterial stiffness and diastolic dysfunction, left ventricular mass, interventricular septum and posterior left ventricle wall thickness, left atrial volume and dilatation were significantly highest in HNBP subjects than in NBP. **Conclusions –** Subjects with HNBP represent ~11% of the population and most of thems had an elevated cardiovascular risk. It's essential to educate the general public and health care providers to be aware of these individuals and of steps that should be taken to treat modifiable cardiovascular risk factors.
Keywords: high normal blood pressure, prevalence, target organ damage, cardiovascular risk factors, high blood pressure.

Rezumat: Obiective – Estimarea prevalenței tensiunii arteriale normal înalte și a agregării factorilor de risc cardiovascular la subiecții cu aceste valori presionale. **Metode –** Un lot reprezentativ de 1970 subiecți au beneficiat de măsurătoarea standardizată a valorilor presionale și au răspuns la un chestionar de 71 de întrebări asociat cu evaluarea afectării organelor țintă. **Rezultate –** Prevalența tensiunii arteriale normal înalte a fost de 11% (45,1% hipertensiune arterială, 43,9% tensiune arterială normală). Valorile greutății corporale, circumferinței abdominale, indicelui de masă corporală, colesterolului total și LDL, trigliceridelor, glicemiei „a jeun", hemoglobinei glicozilate (HbA1c), acidului uric, creatininei serice, filtratului glomerular estimat prin ecuația CKD-EPI, raportului albumină/creatinină, grosimii intimă-medie carotidiene, precum și a frecvenței rigidității arterelor mari, disfuncției diastolice a ventriculului stâng, a masei și dimensiunilor septului și peretelui posterior al acestuia, dar și volumul atriului stâng sunt mai crescute la subiecții cu valori tensionale normal înalte comparativ cu cei care prezintă valori normale sau optimale. **Concluzie –** Subiecții cu valori tensionale arteriale normal înalte se întâlnesc intr-un procent de ~11% în populația adultă din România. Aceștia au frecvent un risc cardiovascular mai crescut și este esențial ca ei sa fie identificați și să beneficieze de măsuri adecvate pentru corectarea sau reducerea factorilor de risc modificabili.
Cuvinte cheie: tensiune arterială normal înaltă, prevalență, afectarea organului țintă, factori de risc cardiovascular, tensiune ridicată.

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INTRODUCTION

In 2017, US guidelines developed jointly by the *American College of Cardiology* (ACC), *American Heart Association* (AHA), and other societies classify the 130 to 139 mmHg /80 to 89 mm Hg range as stage 1 high blood pressure (HBP)[1]. For the same blood pressure (BP) values, the former 2013 and the new 2018 *European Society of Hypertension's* (ESH) / *European Society of Cardiology* (ESC) Guidelines for the management of arterial hypertension consider those with 120–129 mmHg and/or 80–84 mmHg to have normal blood pressure (NBP) and those with 130–139 mmHg and/or 85–89 mmHg to have high normal blood pressure (HNBP), with the intent to alert patients and physicians to provide lifestyle education and sometimes medications[2-7].

Romania, as previously shown in the three-national representative surveys [SEPHAR I (2005), SEPHAR II (2012)] and SEPHAR III (2016) – Study for the Evaluation of Prevalence of Hypertension and Cardiovascular Risk in Romania], is a high cardiovascular risk East European country with a high prevalence of general HBP around 45.1%[8-11].

Furthermore, with this study, we aimed to know the prevalence of HNBP and to find if these subjects have more often other cardiovascular risk factors than normotensives in order to provide a basis for preventives strategies for HBP and CVD.

METHODS

Detailed SEPHAR III methodology has been previously published; therefore, we briefly present below only those aspects regarding the collection of SEPHAR III data that are the object of this study[10,11]

1. SEPHAR III: sample selection and data collection

The SEPHAR III survey was conducted beetwen 2015/2016 in two stages and for an adult Romanian population of 16,269,839 adult citizens, of which 40.41% are estimated to be hypertensive patients (based on SEPHAR II results), with a maximum error of 2.18% at a confidence level of 95%, the minimum required sample size was 1379 study participants[8]. During the two study visits, scheduled at a 4-day interval, all enrolled individuals were evaluated by the following: 71-item survey questionnaire, anthropometric, and BP measurements, together with investigations for target organ damage, blood, and urine sample collection after proper fasting time (8–14h prior).

2. Blood pressure measurement

BP measurement technique and definitions of hypertensions were in line with 2013 ESH/ESC Guidelines[2].

3. Diagnostic Criteria

The classification of optimal, NHB, HNBP and HBP were done in accordance with the 2013 ESH/ESC Guidelines, unchanged by the 2018 ESH/ESC new release Guidelines[2,3]. The BP category is defined by the highest level of BP, whether systolic or diastolic.

A. Optimal and normal BP – NBP, defined as not being on antihypertensive medication and having for optimal BP an SBP <120 mmHg and/or DBP <80 mmHg, and for normal BP an SBP 120–129 mmHg and/or DBP 80–84mmHg.
B. High normal BP – HNBP, defined as not being on antihypertensive medication and having an SBP of 130–139 mmHg and/or DBP of 85–89mm Hg: Ex, 136/70 mmHg was classified as HNBP but 136/90 mmHg as HBP, 126/70 mmHg was classified as NBP but 126/85 mmHg as HNBP.
C. Hypertension or high BP– HBP, defined as SBP at least 140 mmHg and/or DBP at least 90mmHg at both study visits, using the arithmetic mean of the second and third BP measurement of each study visit (without taking into consideration the first BP measurement from either visit), or previously diagnosed hypertension under treatment during the previous 2 weeks, regardless of BP values.
D. Controlled BP values were defined as SBP less than 140 mmHg and DBP less than 90 mmHg in treated hypertensive patients.

4. Risk factors and diagnostic categories

Detailed SEPHAR III data collection for risk factors and diagnostic categories has been previously published[10,11]. The use of the special medical caravan – SEPHAR BUS – has facilitated the fieldwork of the investigators and for the first time allowed them to perform a complete evaluation of target organ damage in a large number of subjects in a relatively short time interval.

5. Cardiovascular risk classification

Total CV risk estimation was done using SCORE risk estimation system recommended for adults > 40 years of age, unless they are automatically categorized as being at high or very high-risk, based on documented CVD, DM (> 40 years of age), kidney disease or highly elevated single risk factor. We use charts for high risk countries, as recommended for Romania in the 2016

edition of ESC cardiovascular disease prevention guidelines[7].

STATISTICAL ANALYSES

Statistical analysis was performed with IBM SPSS Statistics 20.0 software at a significance level of $p \leq 0.05$. A descriptive analysis (means, medians, standard deviation and range for continuous data and frequency analysis for categorical data) was performed for all the target variables. Kolmogorov-Smirnov test was used to analyse continuous data distribution, according to which appropriate tests were further used in analysis: independent samples *t*-test or Mann-Whitney U test for differences between means of 2 independent groups, and ANOVA or Kruskal-Wallis test for differences between means of 3 independent groups. Chi-square test was used to analyse differences between categorical data. Binary multiple logistic regression using a stepwise likelihood ratio method including multicollinearity testing (tolerance less than 0.1 and VIF value greater than 10) was used for validation of predictors of HNBP and HBP (as dependent variable). Variables for which statistically significant differences between the 3 study subgroups were highlighted were used as independent variables (predictors) in regression analysis. Data was weighted for region, locality type, age groups and gender.

RESULTS

1. Prevalence of NBP, HNBP and HBP

A total of 1970 subjects were involved in statistical analysis: 1034 were females (52.4%) and 936 males (47.6%), mean age 48.5±17.5 years.

Table 1. Prevalence of NBP, HNBP and HBP accounted for all participants by age

VARIABLES	Total (n)	NBP (n)	HNBP (n)	p[a] (95% CI)	HBP (n)	p[a,b] (95% CI)
TOTAL N, (%)	1970	865 (43.9)	216 (11)	<0.0001 (27.03-37.7)	889 (45.1)	NS[a] <0.0001[b] (28.2-38.9)
MALES N, (%)	936	354 (37.8)	129 (13.8)	<0.0001 (15.4-31.1)	453 (48.4)	<0.002[a] (3.7-17.3) 0.001[b] (26.2-41.3)
FEMALES N, (%)	1034	511 (49.4)	87 (8.4)	<0.0001 (32.1-47.03)	436 (42.2)	<0.02[a] (0.8-13.4) <0.0001[b] (24.8-40.1)
AGE - GROUPS						
18-24 years N, (%)	195	151 (77.4)	14 (7.2)	<0.0001 (44.7-78.5)	30 (15.4)	<0.0001[a] (43.7-72.6) NS[b]
25-34 years N, (%)	319	221 (69.3)	29 (9.1)	<0.0001 (43.2-68.5)	69 (21.6)	<0.0001[a] (34.9-57.5) NS[b]
35-44 years N, (%)	370	197 (53.2)	45 (12.2)	<0.0001 (26.5-50.5)	128 (34.6)	0.001[a] (7.5-28.8) 0.004[b] (7.6-33.2)
45-54 years N, (%)	304	118 (38.8)	33 (10.9)	0.002 (10.8-39.1)	153 (50.3)	0.05[a] (0.4 -22.9) <0.0001[b] (22.5-49.7)
55-64 years N, (%)	329	85 (25.8)	38 (11.6)	0.07 (-1.8 – 26.4)	206 (62.6)	<0.0001[a,b] (24.6-47.08)[a] (35.5-60.2)[b]
65-74 years N, (%)	267	54 (20.3)	26 (9.7)	NS	187 (70)	<0.0001[a,b] (35.3-60.2)[a] (41.9-69.3)[b]
>75 years N, (%)	186	39 (21)	31 (16.7)	NS	116 (62.3)	<0.0001[a,b] (23.7-54.1)[a] (26.9-58.02)[b]

NBP - Optimal and normal blood pressure, HNBP - High normal blood pressure, HBP- hypertension, N & % - numbers and percentage of row, n – numbers of column, NS-without statistical signification
[a] compared with NBP, [b] compared with HNBP, $p < 0.05$
95% CI – confidence interval

Categorized by blood pressure status, 865 (43.9%) subjects had NBP, 216 (11%) subjects had HNBP and 889 (45.1%) subjects had HBP. Individuals with HBP were older (mean age 55.7 ±15.6 years) than those with HNBP (mean age 51.1 ±17.1 years) and NBP (mean age 40.5±15.9 years), p<0.0001 (95% CI 18-85, respectively 18-91) – Table 1.

Gender prevalence for HNBP was 13.8% in males and 8.4% in females (p = NS, non-significative) and 48.4% vs 42.2% (p=0.06) for HBP individuals. HNBP prevalence is increasing across age groups from 7.2 % in the 18–24 years group up to 12.2 % in the 35-44 years' group and then decreased with increasing age, except for those who were in the more than 75 years' group. Subdividing the population by age and gender showed that in males the prevalence of HNBP peaked at an age of 25–34 years and in females at an age of 35–44 years (Figure 1).

As expected, HBP prevalence is increasing independent of gender across age groups, from 15.4% in the 18–24 years group up to 70 % in more than 65 years' group (Table 1, Figure 1).

Global rate of HBP awareness accounting for a rate of 80.9%.

2. Characteristics of study groups categorized by gender and blood pressure status.

Table 2 shows the characteristics of the three categories of BP groups.

Values of systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, waist circumference, BMI, TC, LDL and HDL cholesterol, TG, fasting blood glucose (FBG), glycated hemoglobin HbA1c, uric acid, serum creatinine, e GFR CKD - EPI and albumin/creatinine ratio were significantly highest in HNBP subjects than in NBP. There is no significant difference for these values between HNBP and HBP subjects.

NBP and HNBP subjects have the biggest number of cigarette smokers in the three groups and there were no differences in the consumption of alcohol.

The prevalence of „no formal" and elementary education increased steadily with the group who had increased BP, while the proportion of "high school" was significantly lower in HNBP and HBP groups.

As expected, salt intake is significantly higher in HBP and HNBP subjects, compared with NBP (13.1 ± 4.1 vs 12.8 ± 3.6 vs 11.2±3.6 g/day, <0.0001), with no significant differences between HBP and HNBP individuals.

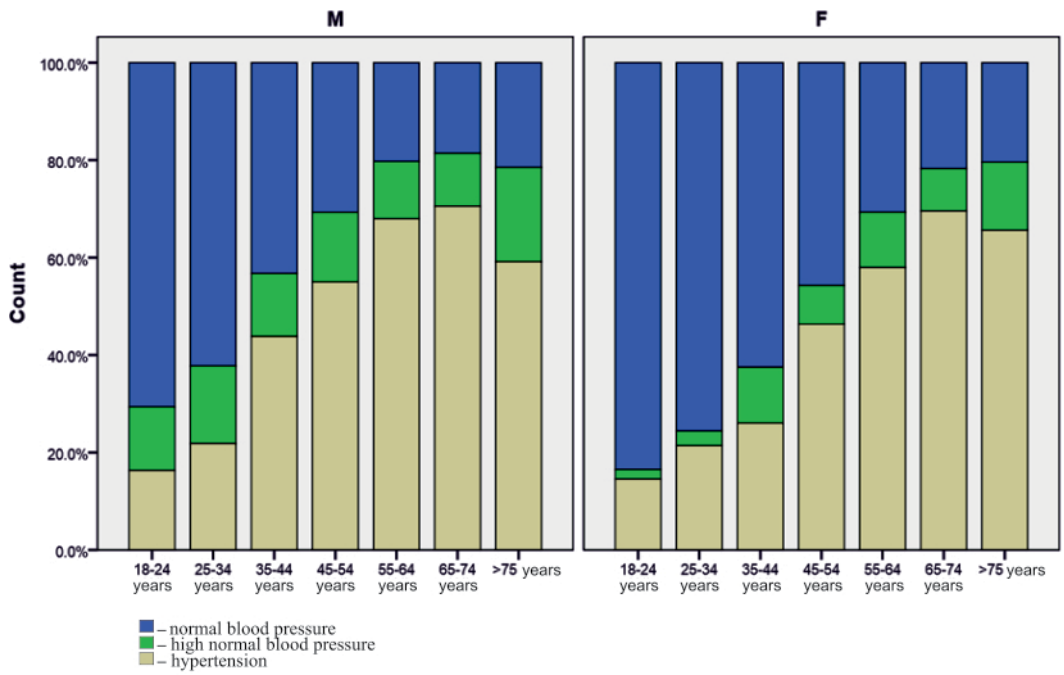

Figure 1. Prevalence of each BP status by gender and age.

Table 2. Characteristics of study groups categorized by BP status

VARIABLES	NBP	HNBP	p[a] (95%CI)	HBP	p[a,b] (95%CI)
Total – n, %	865 (43.9)	216 (11)	<0.0001 (27.03-37.7)	889 (45.1)	NS[a] <0.0001[b] (28.2-38.9)
Mean age, years	40.5±15.9	51.1±17.1	<0.0001 (8.1-13.01)	55.7±15.6	<0.0001[a,b] (13.7-16.6)[a] (2.2-6.9)[b]
Males - %	37.8	13.8	<0.0001 (17.8-29.1)	48.4	<0.0001[a] (5.9-15.1)[a] 0.001[b] (28.4-39.7)[b]
Female - %	49.4	8.4	<0.0001 (35.4-45.4)	42.2	0.002[a] (2.5-11.2) <0.0001[b] (35.4-45.4)
SBP, mmHg	118.4±11.2	136.6±7.1	<0.0001 (16.6-19.7)	142.1±20.3	<0.0001[a,b] (22.1-25.2)[a] (2.7-8.2)[b]
DBP, mmHg	75.4±7.3	85.4±5.6	<0.0001 (8.9-11.06)	86.1±11.4	<0.0001[a] (9.8-11.6) NS[b]
Heart rate, bpm	74.3±9.9	74.2±10.7	NS	74.4±10.8	NS[a,b]
Height, cm	166.8±9.5	167.8±10.3	NS	166.2±9.8	NS[a,b]
Weight, kg	72.4±15.4	82.4±16	<0.0001 (7.6-12.2)	83.01±18.2	<0.0001[a] (9.02-12.1) NS[b]
Waist circumference, cm	89.1±13.3	99.05±13.2	<0.0001 (7.9-11.9)	100.3±14.6	<0.0001[a] (9.8-12.5) NS[b]
Body mass index	25.9±4.9	29.3±5.3	<0.0001 (2.6-4.1)	30±5.9	<0.0001[a] (3.5-4.6) NS[b]
Obesity, %	24,6	32,7	0.01 (1.4-15.1)	47	<0.0001[a,b] (17.9-26.6)[a] (17-26.06)[b]
Daily Alcohol use, %	45	43	NS	43	NS[a,b]
Current Cigarette smokers %	28	25	NS	17	<0.0001[a] (7.1-14.9)[a] 0.006[b] (2.1-14.6)[b]
Depression state, %	13	16	NS	17	0.01[a] (0.7-7.3) NS[b]
No formal education, %	0	1	0.003 (0.2-3.4)	2	<0.0001[a] (1.1-3.1) NS[b]
Elementary school, %	14	14	NS	21	0.0001[a] (3.4-10.5)[a] 0.02[b] (1.2-11.9)[b]
High school, %	41	37	NS	26	<0.0001[a] (10.6-19.3)[a] 0.001[b] (4.2-18.2)[b]
Family history of CVD (including HBP) %	24	30.5	0.04 (0.03-13.4)	29	0.01[a] (0.9-9.1) NS[b]

Total cholesterol, mg/dL	190.01±43.07	198.9±41.7	0.006 (2.5-15.2)	201.3±45.5	<0.0001[a] (16.1-24.4) NS[b]
LDL cholesterol, mg/dL	123.8±39.2	132.09±38.7	0.005 (2.4-14.1)	133.8±41.7	<0.0001[a] (6.2-13.7) NS[b]
HDL cholesterol, mg/dL	56.7±15.9	55.1±17.1	NS	55.8±16.2	NS[a,b]
Triglycerides, mg/dL	103.3±83.7	133.5±115.6	<0.0001 (16.6-43.7)	135.8±93.8	<0.0001[a] (24.1-40.8) NS[b]
Dyslipidemia, %	72.3	77,6	NS	83.2	<0.0001[a] (7.02-14.7) 0.05[b] (0.08-12.04)
Fasting blood glucose, mg/dL	96.3±18.4	106.3±29.3	<0.0001 (6.8-13.1)	110.4±31.8	<0.0001[a] (11.6-16.5) 0.08[b] (0.5-8.7)
HbA1c, %	5.2±0.6	5.6±0.8	<0.0001 (0.3-0.5)	5.7±0.9	<0.0001[a] (0.4-0.5) NS[b]
DM, %	7,8	11,5	0.08 (0.4-8.9)	17,5	<0.0001[a] (6.6-12.7) 0.03[b] (0.5-10.4)
Uric acid, mg/dL	4.5±1.1	5.1±1.4	<0.0001 (0.4-0.7)	5.2±1.4	<0.0001[a] (0.5-0.8) NS[b]
Serum creatinine, mg/dl	0.8±0.1	0.9±0.3	<0.0001 (0.07-0.12)	0.9±0.4	<0.0001[a] (0.07-0.13) NS[b]
eGFR CKDEPI, ml/min	113.8±18.5	101.4±20	<0.0001 (-15.1/ -9.9)	98.1±20.4	<0.0001[a] (-17.5/-13)[a] 0.03[b] (-6.3/-0.2)[b]
Albumine/Creatinine ratio mg/ mmol	8.3±26.4	31.5±288.3	0.02 (3.6-42.7)	29.8±211.2	0.003[a] (7.3-35.6) NS[b]
Salt intake/ Kawasaki formula, g/day	11.2±3.6	12.8±3.6	<0.0001 (1.06-2.1)	13.1±4.1	<0.0001[a] (1.5-2.2) NS[b]
Ao- PWV, m/s	7.8±1.9	9.2±2.2	<0.0001 (1.1-1.6)	9.6±2.4	<0.0001[a] (1.6-2)[a] 0.02[b] (0.04-0.7)[b]
ABI <0.9, %	`1.1	0.1	NS	1.9	NS[a] 0.05[b] (0.1-2.9)
cIMT, mm	0.5±0.1	0.6±0.1	<0.0001 (0.08-0.1)	0.7±0.1	<0.0001[a,b] (0.1-0.2)[a] (0.08-1.05)[b]
cIMT > 0.9, %	1	0.6	NS	3.6	0.0003[a] (1.2-4.1) 0.02[b] (0.5-4.5)[b]
Instable Carotids plaques, %	0.9	0.6	NS	2.8	0.003[a] (0.6-3.2) 0.05[b] (0.1-3.5)
LVMI, g/m^2	74.9±21.6	87.4±25.8	<0.0001 (9.1-15.8)	91.9±28.8	<0.0001[a] (14.6-19.3) 0.03[b] (0.3-8.7)

LVH, %	4	2.4	NS	12.4	<0.0001[a,b] (5.8-10.9)[a] (6.3-12.7)[b]
ISV, mm	6.8±1.1	7.5±1.2	<0.0001 (0.5-0.8)	8.05±1.1	<0.0001[a,b] (1.1-1.3)[a] (0.3-0.7)[b]
PV, mm	6.6±0.9	7.3±1.07	<0.0001 (0.5-0.8)	7.5±1.05	<0.0001[a] (0.8-1)[a] 0.01[b] (0.04-0.3)[b]
LA volume, ml	36.3±12.6	42.4±17.8	<0.0001 (4,04-8,1)	46±15.7	<0.0001[a] (8.3-11.04)[a] 0.003[b] (1.2-6)[b]
LA dilatation, %	9	18	0.0001 (4-14.9)	23	<0.0001[a] (10.6-17.4) NS[b]
Delayed relaxation, %	31	41	0.005 (2.9-17.3)	44	<0.0001[a] (8.5-17.4) NS[b]
Sistolic dysfunction (FE ≤50%), %	1	2	NS	5	<0.0001[a] (2.5-5.7) <0.05[b] (0.1-5)

NBP - optimal and normal blood pressure, HNBP - high normal blood pressure, HBP- hypertension, SBP – systolic blood pressure, DBP- diastolic blood pressure, CVD - cardiovascular diseases, HbA1c - glycated hemoglobin form, DM – diabetes mellitus, eGFR CKDEPI - glomerular Filtration Rate Estimate by CKD-EPI Equation, Ao PWV- Aortic pulse wave velocity, ABI- ankle-brachial index, cIMT – carotid intimae-media thickness, LV – left ventricular, ISV - interventricular septum, PV- posterior LV wall thickness, LVMI – left ventricular mass Indexed to body surface area (g/m^2), LVH – left ventricular hypertrophy indexation body surface area, LA - left atrial, LA dilatation – volume LA indexation body surface area, FE – ejection fraction
[a] compared with NBP, [b] compared with HNBP, $p < 0.05$
95% CI – confidence interval

Arterial stiffness and ankle brachial index (ABI) measurements showed that aortic pulse wave velocity (Ao PWV) was significantly higher in HNBP and HBP while an ABI < 0.9 was more frequent in HBP group.

The evaluation of carotid arteries showed a higher intimae-media thickness (cIMT) in HNBP and HBP, with more frequent instable plaques in the HBP group.

Transthoracic echocardiography (TTE) measurements showed values of left ventricular mass indexed to body surface area (LVMI), interventricular septum (ISV) and posterior left ventricle wall thickness (PV), left atrial (LA) volume and LA dilatation, highest in HNBP and HBP groups than in NBP. The rates of delayed and impaired relaxation as signs of diastolic dysfunction, calculated by the study of E/A and E/e' ratio was 44% in HBP vs 41% in HNBP (NS) vs 31% in NBP ($p < 0.0001$), being significantly more frequent in HBP and HNBP groups. Left ventricular hypertrophy indexation body surface area (LVH) and the systolic dysfunction of LV (efection fraction - FE ≤ 50%) also increases in parallel, with the BP values being more frequent in the HBP group.

3. Association of risk factors with HNBP and HBP

The multivariable-adjusted ORs of HNBP and HBP associated with various risk factors are presented in Table 3.

Males are more likely than females to have HNBP and to develop HBP. Age (beginning from 55 years) and family history of CVD (including HBP) are significantly associated with HNBP and HBP. DM and dyslipidemia are risk factors for HNBP and significantly increased the risk of HBP. Overweight and obesity were risk factors for both HNBP and HBP. Depression as resulted by 13 items for evaluation of the state of depression was a risk factor for HBP, but in our study, it was not associated with HNBP. Compared to subjects with an elementary education status which predisposed them to HBP, those with a higher school education were less likely to have HNBP and HBP. Daily alcohol consumption (300 ml wine or 30 ml strong drinks) caused a modest but non-significant rise in the risk of HNBP and HBP. Cigarette smoking was not associated with HNBP and was also found to have a

Table 3. Adjusted OR (95% CI) of HNBP and HBP associated with various factors using a multinomial logistic model

Variables	HNBP adjusted OR (95% CI)	p	HBP adjusted OR (95% CI)	p
Males vs Females	1.4(1.1-1.8)	0.003	1.2(1.05-1.4)	0.01
Age groups 45-54 years	1.1(0.7-1.6)	0.5	1.2(0.9-1.6)	0.07
Age groups 55-64 years	1.8(1.1-2.6)	0.005	2.3(1.8-3.09)	0.0001
Age groups 65-74 years	1.9(1.2-3.1)	0.008	3.3(2.4-4.6)	0.0001
Age groups >75 years	3.1(1.9-5.2)	0.0001	2.9(1.9-4.2)	0.0001
Diabetes mellitus	1.4 (0.9-2.4)	0.1	2.2(1.6-3.04)	0.0001
Dyslipidemia	1.07(0.8-1.3)	0.3	1.1(0.9-1.3)	0.05
Overweight	1.2(0.8-1.7)	0.06	1.4(1.2-1.7)	0.0001
Obesity	1.3(0.9-1.8)	0.04	1.9(1.6-2.3)	0.0001
Depression	1.2 (0.8-1.9)	0.2	1.3(1-1.7)	0.04
Alcohol use	1.05 (0.7-1.2)	0.6	1.1(0.8-1.3)	0.75
Current Cigarette smokers	0.9(0.6-1.2)	0.5	0.6(0.5-0.8)	0.001
Family history of CVD (including HBP)	1.4 (1.01-1.9)	0.04	1.3 (1.05-1.6)	0.01
Elementary school	0.9(0.6-1.9)	0.9	1.5 (1.1-1.9)	0.001
High school	0.9(0.6-1.1)	0.4	0.6(0.5-0.8)	0.0001
Salt Intake	1.4(1.2-1.6)	0.0001	1.8(1.6-2.06)	0.0001

HNBP - high normal blood pressure, HBP- hypertension, CVD – cardiovascular diseases,
$p < 0.05$, 95% CI – confidence interval

significantly negative association with HBP. Finally, salt intake is significantly associated with HNBP and HBP, regardless of age or sex.

After adjusting for age, gender, and family history of CVD/HBP, individuals with overweight/obesity and those with a high salt intake showed an increased risk for HNBP: OR 1.62, CI 1.32-1.98, p< 0.001, respectively OR 2.12, CI 1.67-2.68, p< 0.001. Clustering of these 2 factors was associated with a 3.52 higher OR (CI 2.78-4.76, p< 0.001) of HNBP compared with absence of the association.

4. Study groups related comorbidities and the risk of CVD

Related comorbidities among NBP, HNBP and HBP subjects are presented in Table 4.

Although the majority of the HBP subjects identified in the SEPHAR III survey (78%) had at least one comorbidity, in the group of HNBP subjects there were 50% and only 30% of those with NBP. The rates of CHD, HF, PAD, TIA and stroke were significantly highest in HNBP and HBP patients compared with NBP, whereas the rates of AF and RF were correlated with the HBP status. Nevertheless, the use of statins and antiplatelet treatment was not frequent (from 3 to 5%) with no significantly differences between the groups.

CV risk estimation using SCORE risk estimation was possible for 1303 (66.1 %) subjects: 312 (36.06 %) in NBP, 102 (47.2 %) in HNBP and 889 (100%) in HBP subjects. Table 5 shows the characteristics of study groups associated with calculated Score risk.

In each category of Score Risk, the number of HBP subjects is significantly greater than in NBP and HNBP subjects. Compared with the total number of subjects in each category of Score Risk, there are no differences in percentage of subjects with low to moderate risk between NBP and HNBP group, but are more with very high risk in HNBP than in NBP group; p=0.003, 95% CI: 2.1-12.8. Also, if we compare the percentage of subjects with high or very high risk in the group of HNBP vs NBP, there are more in HNBP group: 18.05 % (39 from 216) vs 10.6 % (92 from 865); p=0.002, 95% CI: 2.3-13.4

DISCUSSION

This study focused on a lot of adults aged between 18 and 80 years, representative of the Romanian population. The prevalence of HNBP was 11% (13.8% in males and 8.4% in females) and the prevalence of HBP was 45.1 % (48.4% in males and 42.2% in females) in all participants, which together means ~ 56% of population. By extrapolating the results from the SEPHAR III survey to the entire adult population of Romania, we can estimate that in 2016, there were approximately 7.4 million Romanian HBP patients and 1.8–1.9 million Romanian HNBP adult subjects. The latest represents a cohort associated with an increased risk of incident HBP at a rate of 8–20% over 4 years and also associated with increased risk of CVD[4-7,12].

The prevalence of HNBP in our study was only 11%, which is significantly less than the 31% observed in American adults and 32.8% observed in Netherlan-

Table 4. Main comorbidities among study participants

VARIABLES	Total N, (%)	NBP N, (%)	HNBP N, (%)	p[a] (95%CI)	HBP N, (%)	p[a,b] (95%CI)
Total	1970	865 (43.9)	216 (11)	<0.0001 (27.03-37.7)	889 (45.1)	NS[a] <0.0001[b] (28.2-38.9)
CAD	507 (25.7)	164 (19)	58 (27)	0.009 (1.9-14.8)	285 (32.1)	<0.0001[a] (9.04-17.1) NS[b]
AF	118 (6)	35 (4)	11 (5)	NS	72 (8.1)	0.0003[a] (1.8-6.3) NS[b]
HF	193 (9.8)	35 (4)	22 (10)	0.0004 (2.3-10.9)	136 (15.3)	<0.0001[a] (8.6-14.01)[a] 0.04[b] (0.08-9.4)[b]
PAD	86 (4.3)	9 (1)	6 (3)	0.02 (0.2-5.3)	71 (8)	<0.0001[a] (5.2-9)[a] 0.009[b] (1.4-7.5)[b]
TIA and stroke	60 (3.04)	9 (1)	6 (3)	0.02 (0.2-5.3)	45 (5.1)	<0.0001[a] (2.5-5.8) NS[b]
Renal failure	70 (3.5)	17 (2)	5 (2)	NS	48 (5.4)	0.0002[a] (1.6-5.2) 0.03[b] (0.2-5.4)
Statin treatment	90 (4.6)	43 (5)	11 (5)	NS	36 (4)	NS[a,b]
Antiplatelet treatment	73 (3.7)	26 (3)	11 (5)	NS	36 (4)	NS[a,b]

NBP - optimal and normal blood pressure, HNBP - high normal blood pressure, HBP- hypertension, CAD – coronary artery disease, AF – atrial fibrillation, HF – heart failure, PAD -peripheral arterial disease, TIA – transient ischemic attack, N & % - numbers and percentage
[a] compared with NBP, [b] compared with NHBP, p < 0.05, 95% CI – confidence interval

ds[12,13]. Prevalence of HNBP was also less in Turkey, around 14.5% but is thought to be 36% in one 2011 meta-analysis, with a total sample of 250,741 individuals[14,15]. The prevalence of HNBP in our sample is also considerably less compared to previously reported prevalence data in another European country, such as the 39.8% in Hungary[16]. In a report from the original cohorts of Brisighella Heart Study (Italy) and ENAH study (Croatia), HNBP prevalence was 25%, which is double than in our study[17]. However, our results are

Table 5. Characteristics of study groups associated with calculated Score risk

VARIABLES	Total – n (%)	NBP – n (%)	HNBP -n (%)	p[a] (95%CI)	HBP -n (%)	p[a,b] (95%CI)
Total – N	1970	865 (43.9)	216 (11)	<0.0001 (27.03-37.7)	889 (45.1)	NS[a] <0.0001[b] (28.2-38.9)
Score Risk evaluation -N	1303 (66.1)	312 (36.06)	102 (47.2)	<0.002 (3.8-18.4)	889 (100)	0.0001[a,b] (60.6-67)[a] (46.1-59.3)[b]
Low to moderate Score < 5%, N	914 (46.3)	220 (25.4)	63 (29.1)	NS	631 (70.9)	<0.0001[a,b] (41.2-49.5)[a] (34.7-48.1)[b]
High Score 5-9%, N	37 (1.8)	9 (1.04)	3 (1.3)	NS	25 (2.8)	0.007[a] (0.4-3.1) NS
Very High Score > 10%, N	352 (17.8)	83 (9.6)	36 (16.6)	0.003 (2.1-12.8)	233 (26.2)	<0.0001[a] (13.09-20.1) 0.003[b] (3.4-14.8)

Legend: NBP - optimal and normal blood pressure, HNBP - high normal blood pressure, HBP- hypertension, NA – not applicable, N & % - numbers and percentage of row, n – numbers of column
[a] compared with NBP, [b] compared with HNBP, p < 0.05
95% CI – confidence interval

on the lower end of reported data for the prevalence of HNBP in other European regions (reported range of 30–40%)[18]. It's well known that studies that excluded individuals with HBP generally reported a higher prevalence of HNBP than those that included patients with HBP from the same countries, but this can't explicate the surprisingly lower prevalence of HBP in our sample[4]. The estimates of BP values in our study are somewhat different, involving the use of a special fully equipped medical caravan – the SEPHAR Bus, whereas other studies were based on selected population or only from one region of a country. By having a unique design (it allowed covering all 82 sites across the Romania in a small period of time), a complete evaluation of all participants was possible, including rigorous BP measurements, minimizing the variation of BP and offering an estimation of a real trend in BP characteristics[10,11]. In addition, the prevalence of 45.1% HBP is on the higher end between European Countries, in contrast with findings from recent epidemiological studies in Western Europe and could explain distribution analysis ascertained that the majority of participants have HBP[19,20].

HNBP individuals appear to have a greater prevalence of traditional CVD risk factors, compared to those with NBP. In this study, waist circumference, BMI, TC, LDL and HDL cholesterol, TG, FBG, HbA1c, uric acid, serum creatinine, e GFR CKD - EPI and albumine/creatinine ratio were significantly highest in HNBP subjects than in NBP. There is no significant difference for these values between HNBP and HBP subjects and the results are generally concordant with the other studies[5,12-21].

The multiple logistic regression analysis showed that male sex, age > 55 years, overweight, obesity, and salt intake, were significantly associated with both HNBP and HBP. In addition, dyslipidemia, DM, depression state and a low level of education were significantly associated with HBP. However, a high education level was shown to be a protective factor, suggesting, as in other studies, that those with a higher education were better informed about hypertension and subsequently had a healthier lifestyle[21]. In our study, alcohol use was not a predictor of HNBP or HBP, and we also found that smoking appeared to be a protection factor for HBP [OR 0.60, CI 0.48-0.75, p= 0.001] (Table 3). Pooled analysis of ten smoking studies investigated the association between smoking and HNBP, and eight studies reported drinking status in 16,557 individuals with HNBP. All of these showed conflicting results, whereas some analyses suggested that individuals who smoke may lower BP compared with non-smoking individuals[15,22,23]. The relationship between smoking and development of HBP is still unclear and controversial, but it was noted that a lower BP in smokers than non-smokers might be ascribed to the effect of smoking reducing weight[24]. Like in other studies, an index BMI, which defined overweight [OR 1.18, CI 0.82-1.70, p=0.06] and obesity [OR 1.33, CI 0.98-1.81, p=0.04], was a strong modifiable predictor of HNBP and HBP[4,5,15,16] (Table 3).

SEPHAR III, based on the Kawasaki formula, estimates the salt intake for first time in a representative cohort for the general adult population of Romania[10,11]. As expected, salt intake is significantly associated with HNBP and HBP regardless of age or sex, being significantly higher than in NBP (Table 3). There is no significant difference for these values between HNBP and HBP subjects and similar to other Central/East European Countries, daily salt intake in Romania is almost double beyond the recommended intake by current guidelines[3].

Arterial stiffness measurements estimated by Ao PWV were significantly higher in HNBP and HBP, while an ABI <0.9 was more frequent in the HBP group. Our results confirm previous findings that claim that arterial functions are impaired even at the prehypertensive stage[25,26]. As in other studies, the evaluation of carotid arteries showed a higher cIMT in HNBP and HBP, with more frequents instable plaques in HBP group[27,28].

TTE measurements showed values of LVMI, ISV, PV, LA volume and LA dilatation, being highest in HNBP and HBP groups than in NBP. The MONICA/KORA Augsburg trial was a study of individuals with HNBP with a follow-up of ten years, which found a significantly greater age-related increase in LV wall thickness (11.9 vs 4.7%, p<0.001) and LV mass (15.7 vs 8.6%, p=0.006) and an increased incidence of LV concentric remodelling (hazard ratio (HR) 10.7; 95% CI 2.82–40.4) and LVH (HR 5.3; 95% CI 1.58–17.9), compared with individuals with NBP[29]. The rates of delayed relaxation were more frequent in HBP and HNBP groups, whereas LVH and the systolic dysfunction were more frequent in HBP subjects. Few studies have shown an association between the diastolic dysfunction and HNBP status, but in our study, the rates of delayed relaxation, LA volume augmentation and LA dilatation like markers of diastolic dysfunction, appears to be significantly more frequent in HNBP than

in NBP individuals, with no differences between HNBP and HBP. Our data confirm the continuous relationship between increasing degree of BP and deterioration of diastolic dysfunction, showing that changes in diastolic function are already present in prehypertensive stages[30-33].

Similar to others studies, hypertension related comorbidities are significantly higher in HBP and HNBP groups than in NBP individuals: 78% HBP participants identified in the SEPHAR III survey had at least one comorbidity, 50% in the group of HNBP and 30% between those with NBP[34-36]. The rates of CHD, HF, PAD, TIA and stroke were significantly higher in HNBP and HBP patients compared with NBP, whereas the rates of AF and RF were not significantly associated with NHBP but with HBP status. A total of 507 participants (25.7% of the total population) had CHD; 19% in NBP, 27% in HNBP and 32.1% in HBP. This is extremely high for a population representative of the adult population aged 18-< 80 years, but in Romania although there are important limitations regarding the data-collection system, there is a clear tendency of increasing mortality due to ischemic heart disease. According to different international statistics, Romania holds fourth place in the world in terms of mortality due to ischemic heart disease and stroke in men and third place in women[7,37].

In addition, a marker of subclinical disease, like Albumine/Creatinine ratio, is significantly higher in HNBP than in NBP individuals: 31.5 ± 288.3 vs 8.3 ± 26.4 mg/mmol, p=0.02. There is no significant difference in these values between HNBP and HBP subjects (31.5 ± 288.3 vs 29.8 ± 211.2 mg/mmol) but it is evident that increases in Albumine/Creatinine ratio, parallel BP and antedate development of HBP[38]. Interestingly, and as suggested by 2018 ESC Hypertension Guidelines, in HNBP and HBP groups, we found an increase in serum uric acid to levels lower than those typically associated with gout but significantly higher than NBP individuals[3] (Table 3).

The present study showed that 47.2 % of adults with HNBP had at least one of the following CVD risk factors (dyslipidemia, DM, overweight/obesity) and 18.05% were at high or very high cardiovascular risk, as estimated by the SCORE system. If we compare the percentage of subjects with high or very high risk in the group of HNBP vs NBP, there are more in HNBP group: 18.05 % vs 10.6 %; p=0.002, 95% CI: 2.3-13.4 (Table 5). Since HNBP is a phase in the progression to HBP, this might imply that almost half of individuals with HNBP, and especially those at high and very high cardiovascular risk (almost 1 for 5), are at risk of hypertension and other CVDs[4-7]. By extrapolating the results from the SEPHAR III survey to the entire adult population of Romania, we can estimate that from 1.8–1.9 million Romanian individuals having HNBP in 2016, there are now at least 250000–300000 more HBP subjects to be added out of the estimated 7.4 million adult Romanian population at the time of survey[11,39].

LIMITATIONS AND STRENGTHS OF SEPHAR III SURVEY

SEPHAR III methodology enables a complete estimation of BP trends and a complete target organ damage evaluation[10,11]. The strengths of the study include the large sample size associated with the principle of equality of chances of being enrolled in the study, regardless of the size of the place of residency and direct measurement of BP, rather than self-reported values. Use of the automated model OMRON M6 with an adjustable cuff for arm circumferences from 24 to 42 cm, respecting the current guideline recommendations of the ESH/ESC provided a reliable measurement of BP and was beneficial in eliminating biases related to the traditional manual BP measurement[2,3]. The response rate in SEPHAR III survey was good (72.58%) but even that, the results of this cross-sectional study may not entirely reflect the health status of the general population in Romania, since the study population represented a convenience sample of those who signed written consent to participate: 2124 respectively, with 1970 study participants with eligible data from the total number of 4226 randomly selected addresses from 84 study sites all around the country.

CONCLUSIONS

Individuals with HNBP represent ~11% of the population and had a higher proportion of cardiovascular risk factors when compared with normotensives. This might imply that they are at risk of HBP and others CVD. HNBP and HBP combined afflicts ~56% of Romanian adults (18–80 years). Possible explanations of this trend may be the following: unhealthy lifestyle and diet, including increased salt intake and the increase rate of obesity and DM. It's of paramount importance to inform and educate the general public and health care providers not only about HBP but also to be aware of HNBP subjects at risk for cardiovascular diseases and of steps that should be taken to treat modifiable risk factors in these people.

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