

New national epidemiological survey for the assessment of trend in hypertension's prevalence, treatment and control among the adult population of Romania: SEPHAR III - design and methodology

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Abstract

In 2015, the need of having an estimation of the past and future trend of the main CV risk factors, led to the initiation of a new epidemiological survey - SEPHAR III. This paper aims to describe the objectives and methodology of SEPHAR III survey. Sampling was performed by a multi-stratified proportional procedure leading to the selection of a representative sample of 2000 adults (the minimum required sample for representativity is 1379 subjects). Stratification criteria were: territorial regions, locality type, gender and age groups (18-39 years, 40-59 years, 60-80 years). Subjects were randomly identified from General Directorate of Informatized Population's Records. The fieldwork was performed by 22 investigators teams in 84 study sites by means of a specially equipped medical caravan - SEPHAR BUS. Each enrolled subject was evaluated throughout 2 visits at 4 days interval by: 71-item study questionnaire, anthropometric measurements, blood pressure measurements, arterial stiffness and ABI measurements, carotid ultrasound examination, 12-lead ECG, standard echocardiography, non-invasive hemodynamic

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measurements and laboratory work-up. Between November 16th 2015 - April 25th 2016, 2124 subjects were enrolled, out of which only 1970 had complete data for analysis. General characteristics of the study sample were: mean age 48.45 ± 17.44 years, 52.5% females, 59% urban residents, satisfying the criteria for representativity of the Romanian adult population. SEPHAR III stands out as a complex survey that will provide crucial data for the assessment of past and future trend in hypertension's prevalence, treatment and control among the adult population of Romania. .

Keywords: hypertension, survey, epidemiology, cardiovascular, CV risk

Introduction

In a very high cardiovascular (CV) risk country like Romania, the data regarding the current prevalence of the main CV risk factors like hypertension (HT) and other lifestyle dependent risk factors and its past and future trend, represents the cornerstone of CV prevention strategies' development.

Up to now, representative data for the general population in Romania concerning the prevalence of HT and the main CV risk factors are available from 2005 when the SEPHAR project (Studiu Epidemiologic asupra Prevalenței Hipertensiunii Arteriale și a Riscului cardiovascular in Romania / Epidemiologic Study concerning the Prevalence of Arterial Hypertension and Cardiovascular Risk in Romania) was first initiated [1-6].

By extrapolating the results of this survey to the entire adult population, it has been concluded that in 2005 there were 8 million Romanian adult hypertensives (HT prevalence of 44.9%), in the majority of the cases being newly-diagnosed hypertensives - 22.9%[1-6].

In addition to the high prevalence of HT, SEPHAR I has shown a high prevalence of other CV risk factors like diabetes mellitus, dyslipidemia, obesity, with significantly higher values among hypertensives adults. Therefore, by assessing CV risk through the SCORE system, SEPHAR I's data reconfirmed that Romania is a country with a very high CV risk [1-7].

In 2012, the epidemiologic survey was repeated - SEPHAR II aiming for the first time to assess the evolution tendency of HT major CV risk factors' prevalence [1, 2, 8-10]. Its results revealed a declining tendency of HT prevalence (a 10.7% decrease) and an increasing tendency in the number of hypertensives undergoing treatment (a 52.2% increase) and of hypertensives with optimally controlled blood pressure values

(practically, a doubling in the number of cases with controlled blood pressure values), the general control of HT being 14.8% [1,2,8-10].

Besides these encouraging results, SEPHAR II survey also underlined concerning data about the increasing tendency in prevalence of other major CV risk factors, such as diabetes mellitus, dyslipidemia and obesity, compared to the results obtained in 2005 [1,2,8-10].

In this context, Romanian Society of Hypertension (RSH) has initiated from 2012 a series of educational programs for increasing general population's awareness on HT and the main lifestyle-dependent CV risk factors, throughout public campaigns and continuous medical educational programs for healthcare workers - both doctors and nurses that offer medical services to the hypertensive patients [1].

So far, having only two evaluations does not enable us to estimate a future trend of main CV risk factors' prevalence, treatment, and control in Romania, but only to have a glimpse of its tendency in the past 7 years.

In this context, in 2015 the need of having an estimation of the past and future trend of the main CV risk factors, and to evaluate the impact of the educational programs conducted by RSH between 2012-2015, led to the initiation of a new epidemiological survey - SEPHAR III.

This paper aims to describe the objectives and methodology of SEPHAR III survey.

SEPHAR III Research objectives

- I. Assessment of hypertension and other major cardiovascular risk factors prevalence in the adult population in Romania in 2016

- II. Assessment of the past trend in the prevalence and control of hypertension and major CV risk factors in the adult population in Romania during 2005-2016, and estimation of theirs the future in the next 5 years.
- III. Assessment of total cardiovascular risk in the adult population in Romania
- IV. Assessment of salt consumption in the adult population in Romania which could represent the basis for a law project regarding the decrease dietary-salt intake
- V. Development of a predictive epidemiologic model for the cardiovascular disease mortality evolution in Romania which could represent the basis for a law project for primary prevention of cardiovascular disease in Romania
- VI. Estimation of sleep apnea syndrome prevalence in the adult population in Romania
- VII. Assessment of depression in the adult population in Romania and its impact on cardiovascular morbidity
- VIII. Assessment of cognitive dysfunction in the adult population in Romania

Material and methods

SEPHAR III survey was conducted by Romanian Society of Hypertension and "Life without hypertension" Foundation under the auspice of Romanian Ministry of Health.

The SEPHAR III survey team, designated by RSH and coordinated by Professor Maria Dorobantu, was responsible for the design and implementation of this project. The majority of the team has participated as well in the design and implementation of the first two epidemiologic surveys - SEPHAR I (2005) and SEPHAR II (2012).

The study protocol and its implementation procedures were supervised by the project reviewers and approved by the Local Ethics Committee. Project reviewers were designated by National Institute of Public Health, by the 2nd Mathematics Department of the Faculty for Applied Science from University of Bucharest, by the Biochemistry Department of University of Medicine and Pharmacy Targu-Mures.

Research population

For a research population of 16,269,839 Romanian adult population [11] of which 40.41% are estimated to be hypertensive based on SEPHAR II results [8], with a maximum error of $\pm 2.18\%$ at a confidence level of 95%, the minimum required sample size is 1379 subjects individuals.

Sampling procedure

Sampling was performed by a multi-stratified procedure, leading to the selection of a representative sample of 2000 adults. Subject selection followed the principle of equality of chances of being enrolled in the study, regardless of the size of the place of residency.

Stratification criteria for sample selection were:

Regional territories

Romania has a total area that has been divided in the following 7 regions plus Bucharest, based on the recommendations of the National Institute of Statistics:

- North-Eastern Region: Bacau, Botosani, Iasi, Neamt, Suceava and Vaslui
- South-Eastern Region : Braila, Buzau, Constanta, Galati, Tulcea and Vrancea
- Southern Region: Arges, Calarasi, Dambovita, Giurgiu, Ialomita, Prahova and Teleorman
- South-Western Region: Dolj, Gorj, Mehedinti, Olt and Valcea
- North-Western Region : Bihor, Bistrita-Nasaud, Cluj, Maramures, Satu-Mare and Salaj
- Central Region : Alba, Brasov, Covasna, Harghita, Mures and Sibiu
- Bucharest: Bucharest Municipality and Ilfov county

Type of residence:

- Rural - 46%
- Urban - 54% (locality with over 200,000 inhabitants; locality with 50,001-200,000 inhabitants and localities with a maximum of 50,000 inhabitants)

Gender:

- Male - 48.6%
- Female - 51.4%

Age groups:

- 18-39 years of age - 38.1%

- 40-59 years of age – 34.3%
- 60-80 years of age – 27.6%

Identification of the subjects:

The first step was to identify from the database of the General Directorate of Informatized Population's Records, where streets are displayed in alphabetical order, the addresses corresponding to the subjects with a certain socio-demographic characteristic (age and gender).

The required numbers of addresses was calculated as double the number of selected subjects from each region, and for Bucharest as triple the number of selected subjects (Table 1).

The actual selection of subjects is achieved by choosing from a list the person who is registered at the corresponding PAS number, which is calculated by the formula: $PAS = N/n$, where N is the number of people living in the corresponding locality, and n is the number of people selected for the study sample from the corresponding locality. The START-POINT is calculated with the following formula: $START-POINT = PAS/2$ in order to choose from the lists the number that designate the first selected subject, from which the selection process begins.

Table 1. SEPHAR III sample size and number of selected addresses by regions.

REGION	SAMPLE POPULATION	SELECTED ADDRESSES
NORTH-EASTERN	327	654
SOUTH-EASTERN	253	506
SOUTH	313	626
SOUTH-WESTERN	206	412
WESTERN	182	364
NOTH-WESTERN	258	516
CENTRAL	235	470
BUCHAREST	226	678
TOTAL	2000	4226

Table 2. Stadard errors of the estimate.

Estimated percentage value	Standard error (n=2000)
10%	±1,31%
30%	±2.01%
50%	±2,19%
70%	±2.01%
90%	±1,31%

Standard error of the estimate

Errors of an estimate for a certain parameter results as a consequence of performing the study based on a representative sample and not on the entire population. The size of the standard error of the estimate depends on the sample size and on the estimated parameter value (Table 2).

Calculation of the sample size and sampling was achieved by dr. Oana Tautu, biostatistician at CLAR RESEARCH company.

Description of Project Implementation

All selected subjects received a letter by post office at least one month before the beginning of the study in the respective region, thus being notified about the project, its goals, the sampling procedure, date of the first study visit and a pre-stamped envelope through which they will inform the coordinating team about their availability to take part or not in the study.

SEPHAR III Team and Fieldwork

The fieldwork team was made of cardiologists as primary investigators and residents in cardiology and nurses as sub investigators, and a series of nurses designated by the laboratory coordinator, responsible for blood and urine samples collection and their transport to the central laboratory. Each team working with selected subjects had 6 members:

- 1 coordinating investigator
- 4 sub-investigators - 2 senior residents in cardiology (fourth of fifth year residents) and 2 -

nurses (designated by ARE-HTA: Romanian Association for Education in Hypertension)

- 1 nurse designated by the central laboratory

A total of 22 working teams travelled to each of the 84 study sites (42 cities and 42 communes through the entire country) by a **special medical caravan - SEPHAR BUS** fully equipped with medical and laboratory equipment required for the clinical, paraclinical and laboratory testing, each team spending 8 consecutive days in the field.

Before the beginning of the field activity, all the field team members received proper training by a specially designated training team, regarding:

- the working principles of the interviewer
- how to use the electronic case-report form and how to enter the data in the database
- how to complete a specific questionnaire
- how to perform all the investigations required by the study protocol

Nurses designated by the central laboratory participating in the study also received specific training concerning the collection and transportation of biological samples by the central laboratory.

Like previous SEPHAR surveys, SEPHAR III encompasses two visits at 4 days interval, and its organizational stages are depicted in Figure 1.

During the first visit, the investigator and sub investigators briefly explained the goals of the project to the selected subjects.

After the signing of the informed consent to participate in the study, each enrolled subjects was evaluated by: study questionnaire, anthropometric parameters measurements, sitting and standing blood pressure measurements, arterial stiffness measurements, ankle-brachial index measurement and carotid B mod Doppler ultrasound examination.

At the end of the first visit, each enrolled subjects will be scheduled for the second visit and instructed how to prepare for fasting blood sampling and how to collect a morning urine sample.

In the second study visit, after the collection of blood and urine samples by nurses designated by the central laboratory, each enrolled subjects underwent: sitting blood pressure measurements, 12-lead ECG recording, noninvasive hemodynamic measurement and standard echocardiography.

Data collection

Study Questionnaire

The study questionnaire consisted of 71-items:

- 11 items regarding socio-demographic data,
- 12 items regarding medical history (including past medical history and family history) and risk factors (smoking, leisure time, physical activity, et.al),

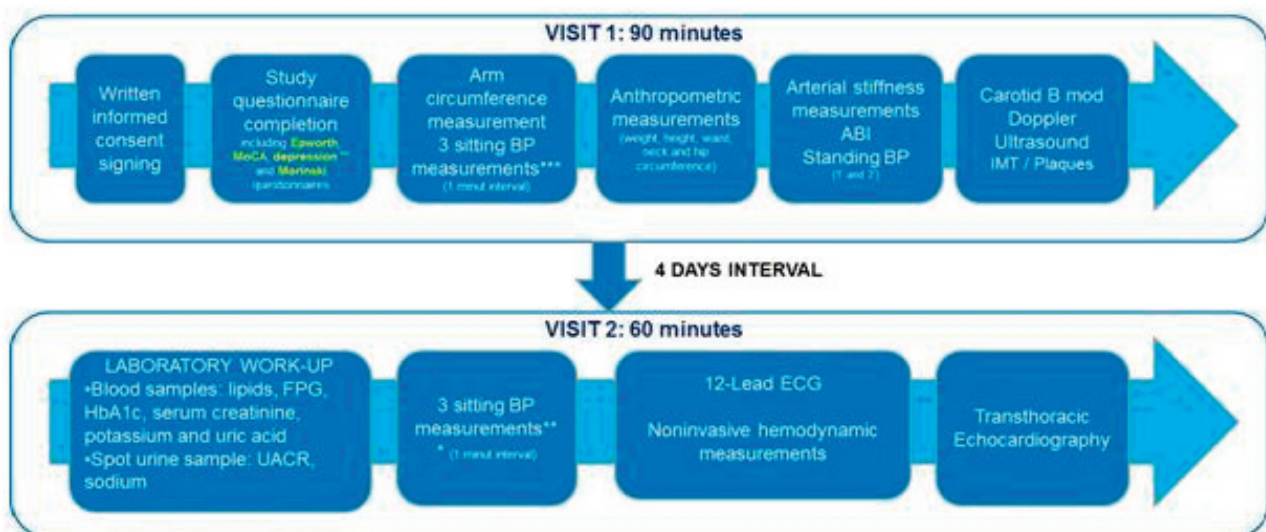


Figure 1. SEPHAR III' study visits flow chart.

- 3 items addressing socioeconomic barriers in accessing medical services,
- 3 items assessing dietary habits (salt, fats and alcohol intake),
- 11 items about the knowledge of methods of CVD prevention and complications due to poor control of risk factors, the source of knowledge about health and disease as well as usage of preventive methods,
- 2 items regarding medication,
- 4 items of Morisky Medication Adherence Scale (MMAS) [12],
- 9-items of Epworth Sleepiness Scale,
- 1 item for Montreal Cognitive Assessment (MoCA) test score [13],
- 13 items for evaluation the depression state (recommended by the current ESC Guidelines for CV prevention) [14]
- 3 items specially addressed to females (females medical history, usage of birth-control pills).

Electronic Case-Report Forms and data base

SEPHAR III is the first Romanian epidemiologic survey that has an electronic case-report form (eCRF) and data base specially design in accordance with the study protocol. The data was directly recorded into the data base through the completion of the eCRF during each study visit step-by-step after each investigation.

Blood pressure measurements

Blood pressure (BP) measurements were taken using an automatic oscillometric blood pressure measuring device certified by AAMI (Association for the Advancement of Medical Instrumentation), European Society of Hypertension (ESH) and British Hypertension Society (BHS), model OMRON M6 AC with an adjustable cuff for arms circumferences between 24-42cm. The use of other devices was forbidden. Before performing BP measurements, arm circumference was measured (using a tailor's tape measure with a maximum deviation of 0.5 cm, at the widest level of the arm) in order to check if the cuff size is adequate (if arm's circumference was more than 42 cm, a cuff for obese subjects was used).

Blood pressure was measured at both arms and after that, two additional measurements was performed at the arm with the highest BP value on the first measurement, at 1 minute interval. At the second visit, all

the three BP measurements were performed at the arm selected at the first visit.

BP measuring conditions respected the current recommendations of the European Society of Hypertension [15].

Anthropometric measurements

The anthropometric measurements were made using the following devices:

- Weight - using an approved electronic scale (model Omron BF511), with a maximum deviation of 0.1 kg, with the subject wearing light cloths (without outer garments and without shoes)
- Height - using a portable measuring device with a maximum deviation of 0.5 cm,
- Waist circumference, hip circumference, arm and neck circumference - using a tailor's measuring tool, with a maximum deviation of 0.5 cm.

Arterial stiffness and ankle-brachial index

(ABI) measurements

Arterial stiffness and ABI measurements were performed by an oscillometric device (model Arteriograph TensioMed) with the patients in supine position, on the dominant arm and leg, after at least 10 minutes rest. The subjects must restrain from smoking, drinking coffee and eating at least 3 hours before the measurement. Measured parameters were: aortic pulse wave velocity (PWV_{ao}), aortic augmentation index (AIX_{ao}), aortic SBP, aortic PP, revers time (RT), diastolic reflexion area (DRA), systolic area index (SAI), Diastolic area index (DAI), ejection duration (ED), brachial SBP/DBP/PP and brachial AIX, and ABI.

Carotid Doppler B mode ultrasound evaluation and standard echocardiography

Imagistic evaluation of the carotid arteries and heart was performed by General Electric Vivid Q portable echocardiograph.

The evaluation of carotid arteries performed with a linear probe (7,5 și 10 MHz) consisted in the measurement of intima-media thickness (IMT) on the distal wall of the each common carotid artery at approximately 1cm prior to the carotid bulb and evaluation of carotid plaques defined as thickening of the wall protruding into the lumen at least 50% compared

to adjacent segments or ≥ 1.5 mm thick in absolute value.

Transthoracic echocardiography was performed with the patient in left lateral position, ECG guided, with image acquisition on 3 cardiac cycles. Echocardiographic parameters were: interventricular septum and posterior LV wall thickness, LV mass, LV ejection fraction, left atrium size and volume and E/A ration and evaluation of LV wall movements.

Noninvasive hemodynamic measurement

Noninvasive hemodynamic measurements was performed by Transthoracic bio-impedance using HOT-MANN system. The measured hemodynamic

parameters were: cardiac index (CI), heart rate (HR), stroke index (SI), mean arterial pressure (MAP), SBP, DBP, left systolic work index (LSWI), systemic stroke vascular resistance, volemia, inotropism, cronotropism and vasoreactivity.

12-lead ECG recordings

The 12-lead ECG recordings were performed by GE MAC 600 device, with patient in supine position, with standard electrode placement. Evaluated ECG parameters were: rhythm (sinus rhythm, atrial fibrillation, other), hear rate, pR interval duration, qRS complex duration, the presence of atrio-ventricular and/ or intra-ventricular conduction disturbances, pathologic

Table 3. SEPHAR III's laboratory work-up.

Test	Methodology/reagents/manufacturer	Analyzer	Analytical characteristics of the method applied					
			Bias		Within-run imprecision		Between-run imprecision	
			N	P	N	P	N	P
Serum creatinine	Jaffe method/picrate acid in alkaline milieu/Roche	Cobas 6000	-1,82	-6,09	1,08	1,49	2,3	1,61
Serum uric acid	Enzymatic/uricase, peroxidase/Roche	Cobas 6000	0	-2	0,9	0,7	2,2	2,2
Serum potasium	Ise /indirect ion-selectiv electrode/Roche	Cobas 6000	0,7	0,7	0,5	0,5	0,75	0,92
Serum triglycerides	Enzymatic/glycerol kinase and glycerol phosfatase/ Roche	Cobas 6000	-4,17	-3,81	1,12	0,69	2,1	2,3
Serum total cholesterol	Enzymatic/cholesterol esterase and cholesterol oxidase/Roche	Cobas 6000	-0,36	0,36	0,65	1,18	1,79	1,84
Serum HDL-cholesterol	Enzymatic/peg-cholesterol oxidase/Roche	Cobas 6000	-3,11	-4,14	1,23	0,9	2,05	3,16
Serum LDL-cholesterol	Spectrofotometriy							
Plasma glucose	Enzymatica/ hexokinase and glucose-6-phosphate dehydrogenase/Roche	Cobas 6000	-0,68	-2,89	1,16	0,99	1,68	1,5
Glycated hemoglobine (HbA1c)	Tinia, IFCC standardised and DCC/NGSP traceable/Roche	Cobas 6000	-3,74	-8,14	1,5	1,1	1,34	2,06
Albuminuria	Immunoturbidimetry/Roche	Cobas 6000	0,93	-2,3	2,5	2,19	2,5	1,1
Urinary sodium	Indirect / Ion selective electrodes							

changes of ST/T, pathologic Q waves, the evaluation of LVH by Cornell product and Romhilt-Estes.

Blood and urine samples collection

Blood samples were drawn by the nurse designated by the central laboratory after checking proper fasting time - 8-14 hours prior.

The nurse used a preassembled blood draw kit containing: one 21 ½ G needle; Vacutainer system; one 3.5 mL vacuum test tube with gel separator, for biochemistry tests (red cap); one 3 mL vacuum test tube with EDTA anticoagulant (lavender cap) for glycated hemoglobin; one 3 mL vacuum test tube with glycolysis inhibitor sodium fluoride (grey cap) for glycemia; one pair latex gloves; disposable cotton pads saturated with an antimicrobial solution to clean the puncture area; a tourniquet; one analysis request form; self-adhesive tags.

After confirmed the subject's personal data, the nurse took samples of venous blood with the subject in sitting position with a maximum duration of stasis of 30 seconds, marked all the test tubes with stickers containing the subject's individual study code, transferred urine from the recipient it was collected in by the subject to the vacuum transport tube also marked with the subject's individual study code and prepared the material for transportation by a special car directly to the central laboratory or its subsidiary. The list of blood and urine test performed is presented in Table 3.

Statistical analysis

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 analyze 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, ANOVA or Kruskal-Wallis test for differences between means of 3 independent groups. Chi-square test was used to analyze differences between categorical data.

Data was weighted for region, locality type, age groups and gender.

Results

Study Flow

SEPHAR III survey was conducted in two steps: the first between November 16th - November 23rd in Bucharest-Ilfov Region and the second between February 15th - April 25th 2016.

From the total number of 2124 subjects who gave written consent to participate in the study 154 were excluded as they were lost to follow up (LFU). Therefore only 1970 subjects had eligible data for the analysis (complete questionnaires + both study visits).

General characteristics of the study group

The actual participants in the study were those who signed a written consent for all elements of the study, i.e. the questionnaire, blood pressure and anthropometric measurements and laboratory work-up.

Among the participants, there were 1034 females (52.5%) and 936 males (47.5%); 669 (34%) were aged 18-39 years, 670 (34%) were aged 40-59 years and 631 (32%) were aged 60-80 years. The mean age in the examined sample was 48.45 ± 17.44 years (48.52 ± 17.51 years in females and 48.39 ± 17.38 years in males).

The sample structure by age, gender, area of residence and territorial regions is almost identical to the structure of Romanian Adult Population from the last population census available at the time of the survey conduction and meets the minimum criteria of representativity according to the stratified sampling procedure.

The socio-demographic characteristics of the study group are shown in Table 4.

Discussion

Similar to the previous SEPHAR surveys, SEPHAR III's conduction complied with the ethical and legal rigors imposed by both Romanian law, good clinical practice rules and by local ethics committee.

Although similar in many aspects of the methodology with the previous two SEPHAR surveys that will allow a proper trend analysis, SEPHAR III' survey stands out by several design novelties. First, benefiting from a specially dedicated electronic platform, SEPHAR III will allow for the first time the investigators to perform annual follow-up of the same subjects, a desiderate

Table 4. General characteristics of SEPHAR III' study sample.

SAMPLING CRITERIA	MINIMUM REPRESENTATIVE SAMPLE	SEPHAR III STUDY SAMPLE
Total number of subjects	1379	1970
Distribution by regions		
• NE	226 (16,39%)	207 (10.5%)
• SE	175 (12,69%)	257 (13.0%)
• S	215 (15,59%)	321 (16.3%)
• SW	142 (10,29%)	219 (11.1%)
• W	125 (9,06%)	197 (10.0%)
• NW	178 (12,91%)	286 (14.5%)
• CENTER	162 (11,75%)	254 (12.9%)
• BUCHAREST-ILFOV	156 (11,32%)	229 (11.6%)
Distribution by genders:		
• Feminine	709 (51.4%)	1034 (52,5%)
• Masculine	670 (48.6%)	936 (47.5%)
• F:M	1,06	1,10
Distribution by area of residence		
• Rural	634 (46%)	808 (41%)
• Urban	745 (54%)	1162 (59%)
Distribution by age categories		
• 18-39 years	525 (38,1%)	669 (34.0%)
• 40-59 years	473 (34.3%)	670 (34.0%)
• 60-80 years	381 (27.6%)	631 (32.0%)

that could not be achieved by the previous SEPHAR surveyes. Second, using the special medical caravan - SEPHAR BUS has facilitated the fieldwork of the investigatirs and allowed to perform for the first time a complete evaluation of target organ damage in a large number of subjects in a relative short time interval. Also, SEPHAR III will reveal the data regarding crucial aspects that impacts HT prevalence and controll in our country such as salt intake and therapeutic adherence.

Conclusion

SEPHAR III stands out as a complex survey that will provide crucial data for the assessment of trend in hypertension's prevalence, treatment and control among the adult population of Romania.

SEPHAR III design and methodology can be successfully implemented in other high CV risk countries

form the East European Region, offering thus grounds for preventive strategies addressing the special needs of this region.

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Conflict of interest

None declared.

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