UNIVERSITY OF MEDICINE AND PHARMACY

CRAIOVA

DOCTORAL THESIS ABSTRACT

The study of diabetes and cardiometabolic risk in Romanian population

PhD Supervisor:

Prof. Univ. Dr. MARIA MOȚA

PhD Student:

SANDU (ROȘU) MARIA-MAGDALENA

Craiova

2018

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Keywords: diabetes, cardiovascular risk, WHO-ISH charts, PREDATORR study, hypertension

Introduction

Over the past fifty years, along with social and lifestyle changes, chronic diseases, especially: obesity, type 2 diabetes mellitus (DM), dyslipidemia and coronary artery disease have become diseases that threaten human health, at this time one of the biggest health problems in the world.

Current statistics show that over two billion people are overweight or obese and over 400 million people have DM.

The transition from malnutrition to overeating indicates that developing populations have failed to sustain economic development and food security, causing cardiovascular diseases (CVD) and other chronic diseases. The adoption of a Western food style associated with reduced fruit and vegetable consumption has been associated with an epidemic of metabolic diseases, variability in blood pressure (BP) and glucose metabolism disorders.

Many publications have concluded that DM is an important risk factor for CVD, which is the leading cause of death in people with DM.

The risk assessment for CVD should take into account major risk factors such as smoking, hypertension, DM, dyslipidemia and predisposing risk factors: body weight gain, abdominal obesity, lack of physical activity, family history of CVD. Identifying risk factors for both DM and CVD is the first major step in developing a plan to reduce the risk of developing DM and/or CVD.

STAGE OF KNOWLEDGE (THEORETICAL PART)

1.1 EPIDEMIOLOGY OF GLUCIDIC METABOLISM DISORDERS (DIABETES, PREDIABETES)

DM is currently one of the greatest challenges of our century, given that in the past two decades the number of people with this disorder has doubled, reaching hundreds of millions of people worldwide today, without taking into account sex, age or social class [1]. The latest data published by the International Diabetes Federation (IDF) at the end of 2017 showed that over 425 million people aged 20-79 had DM worldwide, with a global prevalence of 8.8%, and it is estimated that by 2045 their number will reach 628.6 million (9.9%) [1,2]. 79% of people with DM live in low and middle income countries and it is estimated that the highest increases in DM

prevalence will be in regions where incomes will increase [1,2]. IDF estimates too that 212.4 million people (approximately 50% of all people with DM) are undiagnosed [1].

1.2 METHODS OF ASSESSING THE RISK OF DEVELOPING DIABETES

In this chapter, various risk assessment methods to develop DM have been described, such as the Diabetes Risk Score, FINnish Diabetes Risc SCore (FINDRISC), Type 2 Diabetes Risk Test, GERMAN DIABETES RISK SCORE.

1.3 EPIDEMIOLOGY OF CARDIOVASCULAR DISEASES

CVD is a group of heart and blood vessels diseases including: coronary and cerebrovascular disease, peripheral arterial disease (PAD), rheumatic heart disease, congenital disorders, deep vein thrombosis and pulmonary embolism [3]. CVD is still the leading cause of death worldwide [3,4], the total number of cardiovascular (CV) deaths has increased over the last decade by approximately 12.5% [4,5]; over 75% of CV deaths occur in low and middle income countries [3].

In 2015 more than 422 million CVD cases [4] and over 17.9 million people died due to this condition, equivalent to 31% of all deaths worldwide [3,4]; it is estimated that this number will increase to 23.3 million by 2030 [6,7].

1.4 CARDIOVASCULAR RISK FACTORS

Cardiovascular risk (CVR) factors are features that occur in healthy subjects and can statistically correlate with the likelihood of developing atherosclerotic CVD. However, these associations do not exclude the likelihood of CVD in non-risk individuals as well as the reverse: the absence of CVD in subjects with multiple risk factors. There have been described both the non-modifiable risk factors: age, gender, ethnicity, personal history of premature CVD, socio-economic status, genetic factors and modifiable risk factors: lack of physical activity, smoking, nutrition, serum lipids, hypertension, body weight, DM.

1.5 CARDIOVASCULAR RISK ASSESSMENT METHODS

The methods to estimate the CVR take into account a maximum number of probable determinants, so that the contribution of each of the risk factors can be found in different regions of the world [8-11]. These methods identify people at risk of CVD and

rank them in various risk categories to receive appropriate prevention and treatment measures to prevent/delay the onset of CVD or various CV events [12]. Framingham score, SCORE charts, Heart Risk Calculator, QRISK, World Health Organization and International Society of Hypertension (WHO/ISH) charts, ASSIGN score and Reynolds risk were described.

1.6ATHEROSCLEROSIS

Atherosclerosis is an inflammatory disorder that involves the formation of plaque structures (atheroma) in the arterial wall structure, especially large and medium arteries, of lipid-bearing plates, to which the inflammatory component, fibrosis and possibly calcification are added.

Atherosclerosis is a diffuse process that begins in the first decades of life, develops slowly with different periods of relative decay and exacerbation, asymptomatic until the vascular lumen is compromised. The risk of life-threatening DM patients is approximately ten times higher compared to those without DM, the main reason being that people with DM have more atherosclerosis [14].

The risk of coronary artery disease is two to four times higher for people with DM and it is stated that atheromatic plaques develop more rapidly and affect several vessels, the percentage of obstructed segments being directly proportional to the age of DM, the risk of myocardial infarction being very high. Individuals with DM without a history of myocardial infarction have the same risk as a person without DM who has suffered such an event [14,15]. It is described in the literature that the cardiovascular atherosclerotic disease appears 14.6 years earlier, it is more severe, it has a much more diffuse distribution than in individuals without DM, it is more distal, interesting the small arteries, with the cancellation of the protector role of women [15-18]. In individuals with DM, the atheromatic plaques are more bulky, are frequently calcified, have a higher necrotic nucleus, increase glycosylation advanced products, and increase the infiltration of macrophages and T lymphocytes [14].

PERSONAL CONTRIBUTION (PRACTICAL PART)

2.1 The importance of the theme

CVD is the main cause of morbidity and mortality worldwide, being a consequence of a wide variety of factors: genetic, epigenetic, socio-economic, environmental, individual. Romania is still one of the European countries with high CVR, as shown by the European Society of Cardiology guide from 2016 [19]. More than 62% of deaths in our country are caused by CVD, which makes it absolutely necessary to determine the prevalence of various risk factors to rapidly implement prevention strategies to slow the increase in cardiovascular mortality.

2.2 The study objectives

The present study has the following objectives:

Primary Goal:

- To estimate the prevalence of CVR categories in the Romanian adult population (with and without DM), using diagrams developed by WHO/ISH (Figure 1, Figure 2).

Secondary Goals:

- To analyse the CVR factors in the Romanian adult population
- To estimate the type 2 DM risk in the Romanian adult population using the Diabetes Risk Score.

2.3 Material and Methods

2.3.1 STUDY DESIGN

General data

- Design of the study: cross-sectional, epidemiological
- Period and location of the study

This study was part of the PREDATORR study (PREvalence of DiAbeTes mellitus, prediabetes, overweight, Obesity, dyslipidemia, hyperuricaemia and chronic kidney disease in Romania) and was conducted between December 2012 and February 2014 in our country coordinated by the Romanian Society of Diabetes, Nutrition and Metabolic Diseases and the Romanian Society of Nephrology – the study design and primary results were previously presented [20].

2.3.2 ETHICAL CONSIDERATIONS

This study was conducted according to the applicable International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) standards and the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants and was approved by the Romanian National Ethics Committee. All subjects received the necessary information about the study they were about to enroll and signed the informed consent [20].
In the PREDATORR study, the investigators were 101 general practitioners (GP), randomly assigned by software, from all eight historical regions of the country. From the patient's list of each GP, 27 subjects were randomly assigned [20].

2.3.3 THE INCLUDING CRITERIA of the PREDATORR study were [20]: age between 20 – 79 years, born and residing in Romania, living for the past ten years mainly in Romania, included on a GP's list, not pregnant, not lactating and signing informed consent.

2.3.4 THE EXCLUSION CRITERIA of the PREDATORR study were [20]:

• subjects less than 20 years of age and over 79 years of age
• subjects born outside Romania or who have lived most of the past ten years outside Romania
• subjects who refused or could not sign informed consent
• pregnant or breastfeeding women.

After setting the eligibility criteria, all subjects participated in an interview where demographic, anamnestic, clinical data, as well as specific laboratory tests were recorded.

2.3.5 DATA COLLECTION

a. Sociodemographic data: age, gender, geographical region, marital status, educational level.
Marital status was classified as: married, unmarried, divorced, widowed. As far as the educational level is concerned, the subjects had either a low educational level (no school/primary or secondary school) or high level of education (college, high school or university) [20]. Regarding the occupation of the subjects, they were: students, employees, farmers, retirees, social assistance, unemployed with or without social

assistance, subjects receiving social assistance and other categories.
b. Anthropometric/clinical data: height, current weight, maximum weight during life, hips circumference, waist circumference, right shoulder circumference, neck circumference, right waist circumference, fist circumference, body mass index (BMI), waist to hip ratio, BP measurement, pulse, palpation of the peripheral arterial pulse.
c. Personal history: regular menstruation, spontaneous abortions, premature birth, birth of children with malformations/dead children, macrosome fetus, complications during pregnancy.
d. DM complications (ischemic heart disease, cerebrovascular disease, PAD, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy), dyslipidemia, hyperuricemia, obesity, hypertension, myocardial infarction, angina pectoris, bypass (coronary, carotid, peripheral arteries), stroke, non-traumatic amputations, acute/chronic pancreatitis, viral B or C hepatitis, polycystic ovary syndrome, chronic kidney disease, cancer, other disorders.
e. Family history: DM, dyslipidemia, hyperuricemia, obesity, hypertension, ischemic heart disease, renal and endocrine diseases, cancer.
f. Smoking: subjects were considered smokers if they smoked more than one cigarette daily, daily or occasionally, or subjects who gave up smoking less than a year before. Non-smokers were considered subjects who never smoked or smokers who have quit smoking for more than a year.
g. Lifestyle data: physical activity, smoking, alcohol consumption, sleep, fruit/ vegetable/sweets consumption, number of meals, home-based medication.
h. Laboratory tests: fasting blood glucose, HbA1c, OGTT, insulinemia, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, non-HDL cholesterol, urea, serum creatinine, estimated glomerular filtration rate, pregnancy test, albuminuria on dipsticks, albumin/creatinine ratio.
Methods:
• Measurement of height - using a taliometer;
• Weight measurement - using an electronic scales;
• The body mass index was calculated as follows: BMI = weight in kilograms divided by the square of the height in meters
• Waist circumference (WC): Measurement was performed halfway between the coastal rebord and the iliac crest, with the centimeter placed horizontally.
Abdominal obesity was defined at abdominal circumference over 80 cm for women

and over 94 cm for men.

• Hip circumference: determined at the level of the big trohanter.

• BP determination was performed three times with the patient in sitting position, after 5 minutes of rest, with the cuff on both arms, at the heart level. We considered subjects with hypertension, subjects with SBP (systolic blood pressure) ≥ 140mmHg and/or DBP (diastolic blood pressure) ≥90mmHg, or antihypertensive treatment at home or personal history of hypertension. Hypertension was classified according to the ESH/ESC 2013 criteria [21].

In order to achieve the primary objective – to estimate the CVR in the Romanian adult population - we used the diagrams developed by WHO/ISH valid for the Europe B region (epidemiological sub-region where Romania is included), representing the 10 year risk for a major fatal or non-fatal CV event (myocardial infarction or stroke), depending on: age, gender, SBP, smoking status, total cholesterol (mmol/L) and diabetes status (Figure 1 and 2). There are 5 levels of CVR: <10%, 10-20%, 20-30%, 30-40%, >40%. We excluded subjects younger than 40 years old (age group 20 -39 years), as this is the minimum age at which CVR can be calculated with these diagrams. We also excluded subjects with a personal history of: ischemic vascular disease - myocardial infarction, cerebrovascular disease, coronary revascularization procedures and those with PAD, diagnosed based on self-reported diagnosis, clinical examination or medical records from GP's (electrocardiogram, arterial Doppler ultrasound, arteriography, etc.).

A subject with DM was defined as a person previously diagnosed with this condition who undergoes anti-diabetic medication, or as the new cases of DM that met WHO diagnostic criteria [20].

The fasting total-cholesterol level was determined; its value in mg/dl was divided to 38 to obtain the value in mmol/l, according to the criteria for estimating the CVR. Hypercholesterolaemia was defined as the total-cholesterol value ≥200mg/dL and/or current statin treatment, regardless of total cholesterol level.

Eligible subjects were divided into two categories: with or without diabetes.

For each category, CVR was calculated using the corresponding diagram.

Figure 1 – WHO/ISH charts for subjects with diabetes

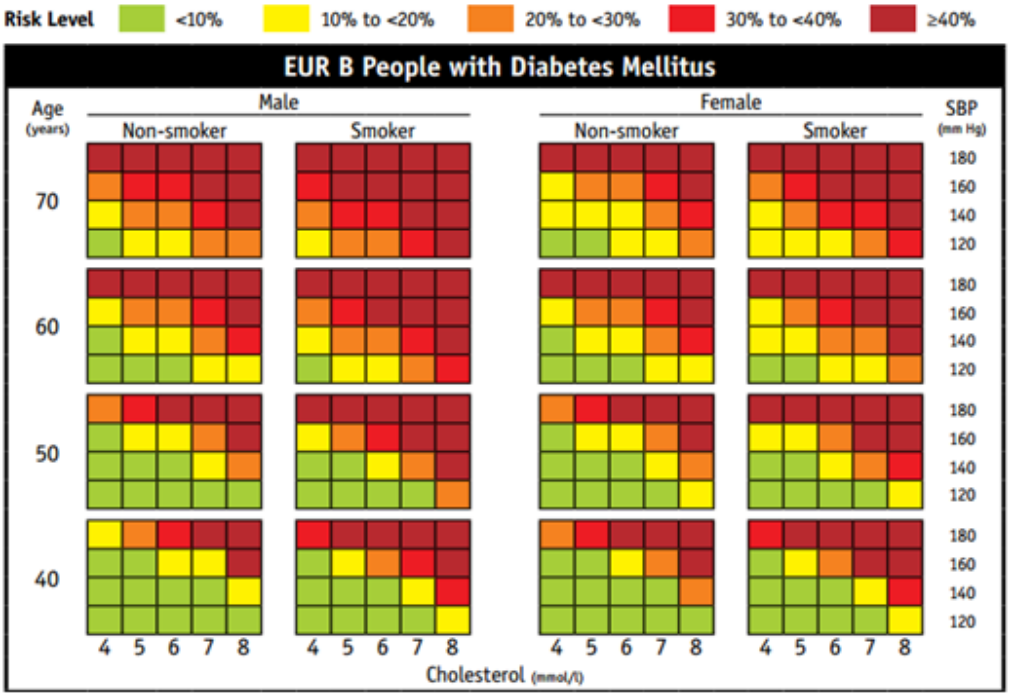
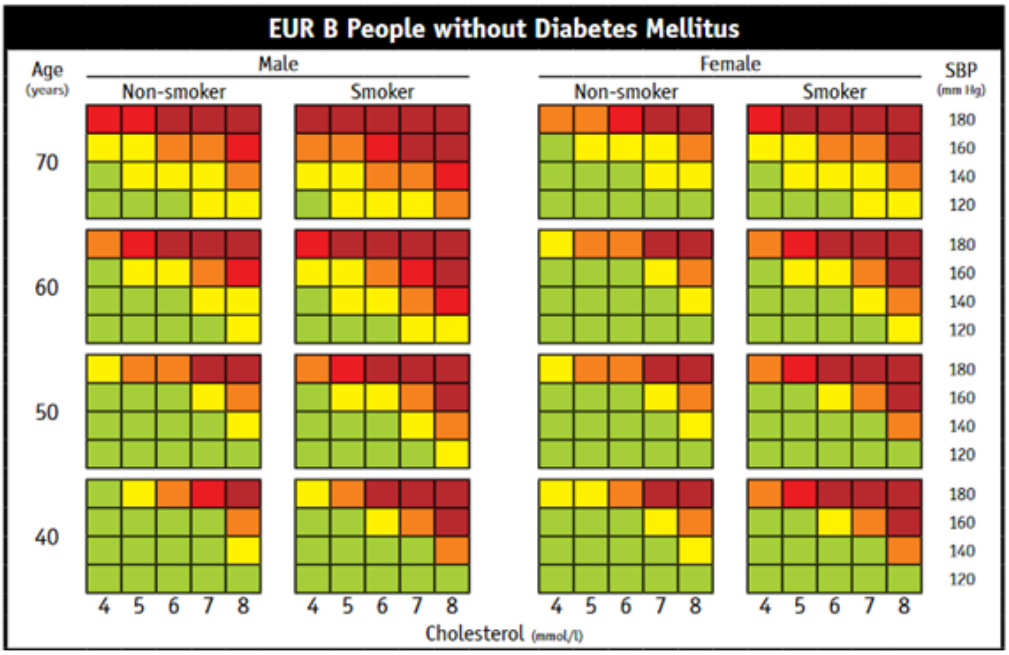


Figure 2 – WHO/ISH charts for subjects without diabetes



In order to achieve the secondary objective - the analysis of the CVR factors: the only unreacted CVR factor remained hypertension, as the other risk factors: DM, smoking, lipid profile or nutritional status were analyzed in other published studies [20,22,23] or currently being published.

Therefore, all subjects included in the PREDATORR study, whose design has been previously described, were studied for hypertension analysis.

As mentioned above, BP measurement was performed with the patient in sitting position, after 5 minutes of rest, with the cuff at both arms, at the heart level. Three measurements were performed at a time of at least one minute. Hypertensive subjects were defined as those with SBP ≥ 140mmHg or DBP ≥90mmHg during the study or if they were on antihypertensive treatment at home or subjects with a history of diagnosed hypertension [20].

Thus, subjects without hypertension were considered those with SBP <140mmHg or DBP <90mmHg - during the study or subjects without antihypertensive treatment at home or those with no personal history of hypertension.

Previously known hypertension was considered in subjects with personal history of hypertension and/or presence of antihypertensive treatment at home.

Hypertension actively detected during the study was considered when the subjects declared no personal history of hypertension, no antihypertensive treatment, but had elevated BP values (SBP ≥140mmHg and/or DBP ≥90mmHg) during the study visit.

Antihypertensive therapy has been classified according to the different classes of antihypertensive drug classes: angiotensin converting enzyme inhibitors, beta blockers, diuretics, angiotensin receptors blockers, calcium channel blockers, centrally active antihypertensive drugs.

To achieve the third objective: to estimate the risk for type 2 DM for the Romanian adult population, we used the Diabetes Risk Score algorithm, a DM risk prediction tool, available online at https://riskscore.diabetes.org .uk / start [24].

It takes into account seven non-invasive features such as age, sex, ethnicity, family history of DM - to 1st degree relatives (parent, sister/brother, children), waist circumference, BMI, personal history of hypertension.

The Diabetes Risk Score questionnaire contains 7 questions, each question having multiple responses; for each answer a certain score is obtained, at the end of the questionnaire the total points are calculated, according to which the risk can be

classified in one of the 4 categories [25]: low risk (0-6 points), slightly increased risk - 15 points), moderate risk (16-24 points), high risk (25-47 points).
To achieve this goal, we excluded all subjects previously diagnosed with DM, and in the rest of the subjects we calculated the risk of type 2 DM, subjects being divided into different risk categories by scoring.

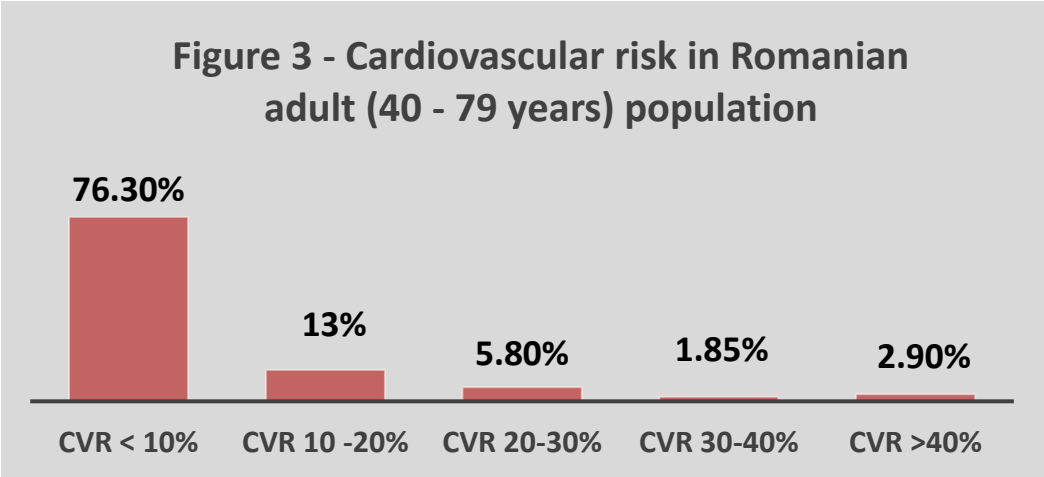
2.4 STATISTICAL DATA ANALYSIS

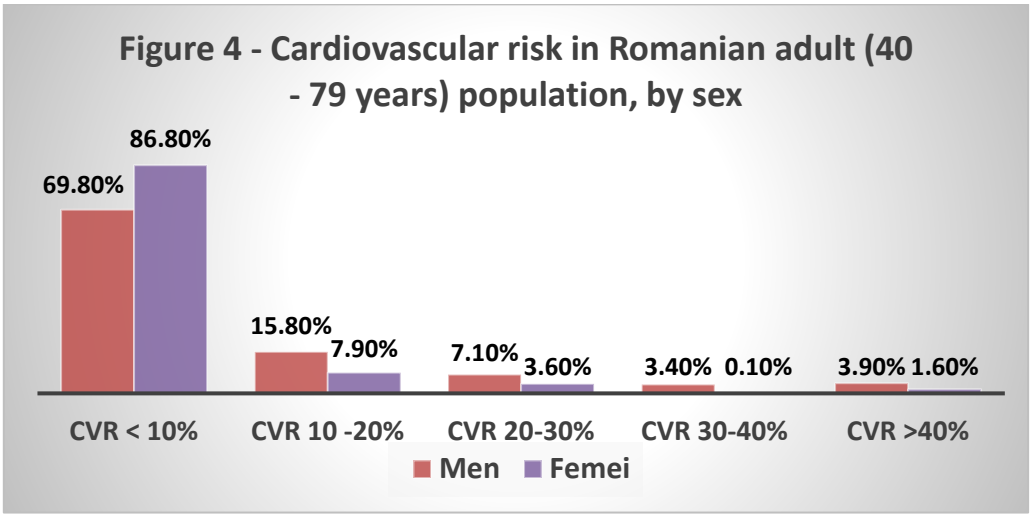
The data collected by the 101 GP'S were entered into a database, coded and subsequently analyzed using the IBM SPSS Statistics 19.00 software (IBM Corporation, Armonk, NY, United States of America) the level of statistical significance was given by $p \leq 0.05$. All data were analyzed by age group and gender. The chi-square test was used to compare the percentages, and Student's test to compare the mean values.
Other statistical tests used were: Spearman correlations, Pearson correlations, logistic regression, ROC curve, data weighting was based on results of the latest 2011 census, 95% confidence interval calculation.

2.5 RESULTS

I. Primary objective
A. To estimate the CVR in the Romanian adult population (with and without DM), using diagrams developed by WHO/ISH.
Following the exclusion criteria, there were 1631 eligible subjects: 45.1% men and 54.9% women.
Among CVD risk factors, prevalence of hypercholesterolemia was the highest, followed by hypertension, smoking and diabetes. The prevalence of hypercholesterolemia was 69.1% (95% CI 66.3% - 71.9%), with no statistically significant gender differences. The prevalence of DM in the study group was 14.9% (95% IC 10.3% - 19.5%), higher in males: 17.4% (95% CI 12.5% - 22.3%), than in females: 12.8% (95% CI 8.6% - 17.1%), statistically significant difference between the two sexes ($p = 0.006$). The prevalence of smoking in the studied group was: 40.91% (95% IC 37.1% - 44.7%), with the percentage of male smokers 56.1% (95% CI 52.2% - 59.9%) being almost double that of female smokers: 28.3% (95% CI 24.8% - 31.8%).
The CVR calculated using the WHO/ISH diagrams showed that 2.9% (95% IC 2.8% - 3.1%) of the Romanian population aged 40-79 years has a higher than 40% risk of

experiencing a major fatal or non-fatal CV event over the next ten years while 1.85% (95% CI 1.8% - 1.9%) has a risk of 30-40% (Figure 3). The 10 year risk of CV event increased with age, being higher in men than in women (Figure 4).





The CVR was higher in men with obesity and overweight compared to women.
Also, in smokers, the risk was significantly higher than in non-smokers. We observed that 32.8% of smokers had a CVR ≥ 10%, while 18% of non-smokers had a CVR ≥ 10%.

Regarding the educational level, we observed that in both genders the percentage of subjects with CVR > 40% was higher in those with a low educational level.

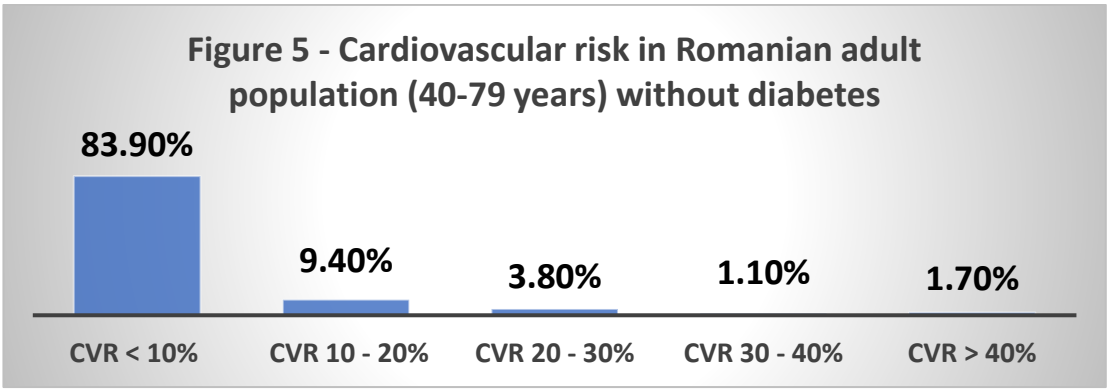
In terms of occupation, both women and men with social assistance had the highest CVR. The lowest risk was observed among all students, unmarried women, women working in agriculture and unemployed men and women with unemployment benefits.

B. Estimating the CVR in the Romanian adult population without DM

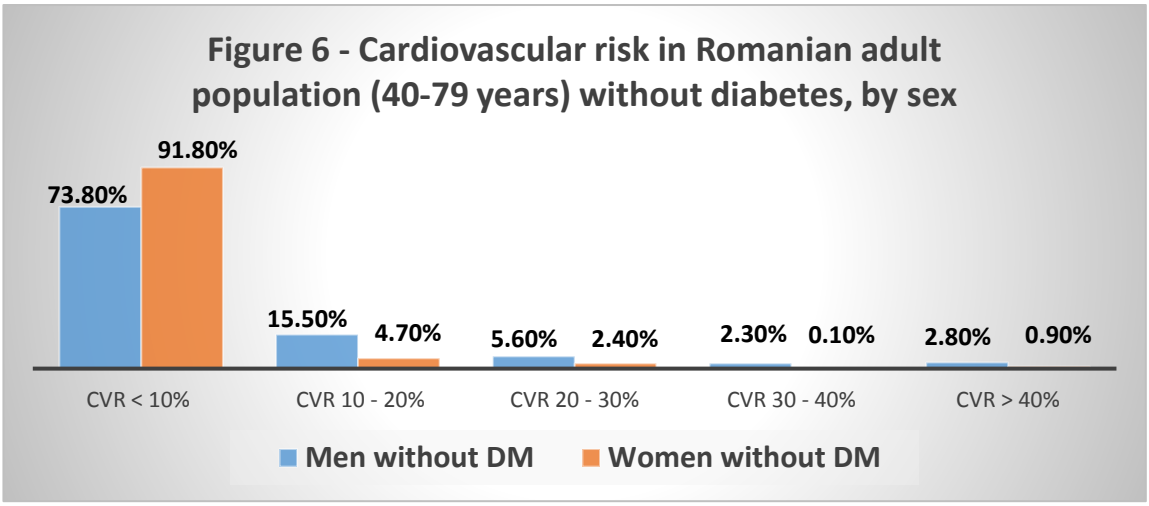
The objective of this sub-study was to estimate the CVR in the Romanian adult population without DM, using diagrams developed by WHO/ISH.

Following the exclusion criteria (those mentioned in the baseline study plus subjects with DM), there were 1388 eligible subjects aged 40-79 years without personal history of CVD and without DM. Of these, 43.8% (n = 608) were men and 56.1% (n = 780) were women.

The CVR calculated using the WHO/ISH diagrams showed that 83.9% (95% IC 82% - 85.9%) of the subjects has a lower than 10% risk of developing a major fatal or non-fatal cardiovascular event over the next ten years while 1.1% (95% IC 0.5% - 1.6%) and 1.7% (95% CI 1% - 2.4%) has a high CVR to develop a major CV event (Figure 5).



The CVR increased with age, the highest risk was registered in the 70-79 years age group and was significantly higher in males (Figure 6).

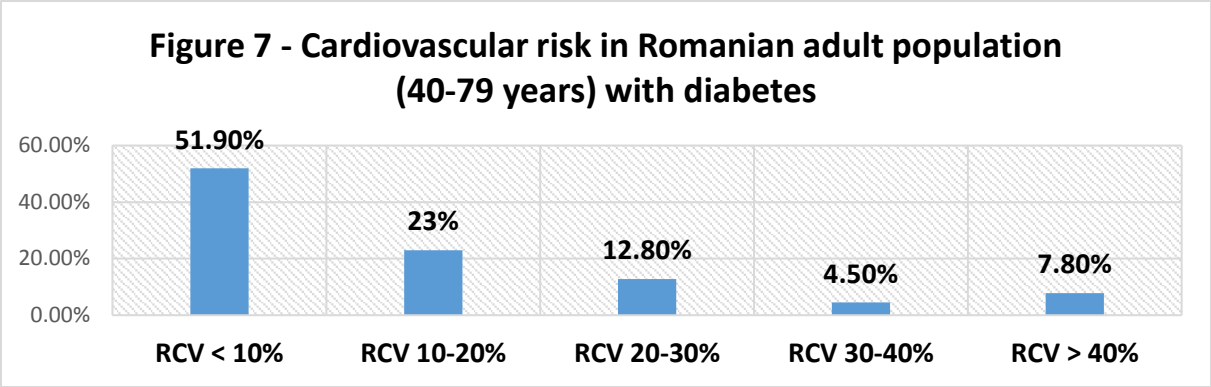


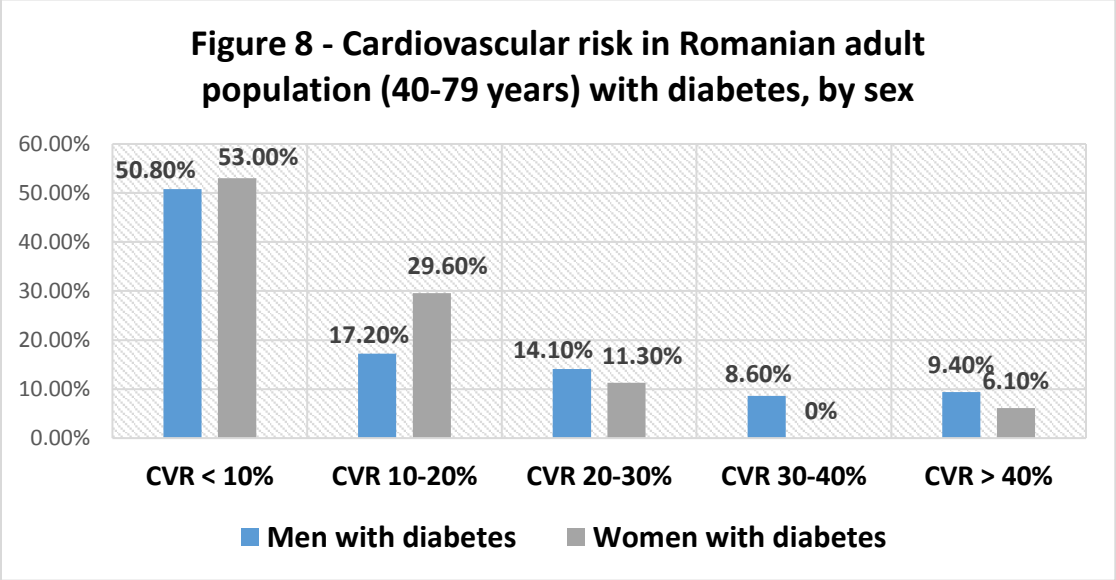
C. Estimating the CVR in the Romanian adult population with DM

The objective of this sub-study was to evaluate the CVR in the Romanian adult population with DM using the WHO/ISH charts.

This time, in addition to the initial exclusion criteria, we added subjects without DM, so there were 243 subjects between 40 and 79 years, with previous DM or DM detected during the PREDATORR study. Of these, 52.6% (n = 128) were men and 47.4% (n = 115) were women.

The CVR calculated using the diagrams developed by the WHO/ISH showed that half of the subjects: 51.9% (95% CI 45.4% - 58.3%) had a small risk, below 10%, to develop a major CV event over the next ten years. On the other hand, 4.5% (95% CI 1.9% - 7.2%) and 7.8% (4.4% - 11.3%) of subjects with DM had a high CVR (30-40% %) (Figure 7). It was also observed that in this case too, the CVR increases with age, the highest risk being in the 70-79 years age group, and it was also observed that it was higher in male subjects compared with women (Figure 8).





The risk was higher in smokers than in non-smokers.

II. Secondary Goal:

1. ANALYSIS OF CARDIOVASCULAR RISK FACTORS

The analysis of most risk factors has been published or is being published in other studies, the only risk factor that remained unannounced was hypertension.

2727 subjects aged between 20 and 79 were included in this sub-study, of which 47.40% (n = 1294) were males and 52.60% (n = 1433) women. It can be seen that most subjects were in the 60-79 age group, had a high educational level and were married (Table 1). The charateristics of the study participants are shown in Table 1.

Table 1 – Characteristics of the study population, stratified by sex and age group

Age groups	Men (%, no)	Women (%, no)	p (M vs W)
20 – 39 years 40 – 59 years 60 – 79 years Total (men + women)	15.46% (200) 36.47% (472) 48.06% (622) 47.40% (1294)	14.51% (208) 38.17% (547) 47.31% (678) 52.60% (1433)	
Total	2727 (100%)		
Marital status			
Widowed			
20 – 39 years	0% (0)	0.50% (1)	
40 – 59 years	0.80% (4)	7.90% (43)	
60 – 79 years	9.60% (60)	34.70% (235)	
Divorced			
20 – 39 years	3.00% (6)	2.90% (6)	
40 – 59 years	5.30% (25)	9.10% (50)	
60 – 79 years	4.80% (30)	6.80% (46)	
Unmarried			
20 – 39 years	37.50% (75)	25.50% (53)	
40 – 59 years	3.00% (14)	4.90% (27)	
60 – 79 years	1.10% (7)	2.80% (19)	
Married			
20 – 39 years	58.50% (117)	70.20% (146)	
40 – 59 years	90.70% (428)	77.90% (426)	
60 – 79 years	84.20% (524)	55.30% (375)	
Educational level			
Low			
20 – 39 years	4.00% (8)	5.30% (11)	
40 – 59 years	4.30% (20)	8.30% (45)	
60 – 79 years	17.30% (107)	32.40% (219)	
High			
20 – 39 years	96.00% (191)	94.70% (196)	
40 – 59 years	95.70% (449)	91.70% (500)	
60 – 79 years	82.70% (513)	67.60% (456)	
BMI (kg/m^2)	(Mean ± SD)	(Mean ± SD)	
20 – 39 years	26.73 ± 4.73	25.05 ± 6.22	
40 – 59 years	29.05 ± 4.81	28.84 ± 6.08	
60 – 79 years	28.31 ± 4.62	29.56 ± 5.30	
Obesity (BMI > $30kg/m^2$)	% (nr)	% (nr)	
20 – 39 years	20.00% (40)	20.60% (43)	p=0.902
40 – 59 years	37.00% (175)	40.40% (221)	p=0.303
60 – 79 years	30.70% (191)	42.90% (291)	**p<0.001**
Waist circumference (cm)	(Mean ± SD)	(Mean ± SD)	
20 – 39 years	94.92 ± 15.66	83.11 ± 15.21	
40 – 59 years	104.01 ± 12.52	94.04 ± 14.69	
60 – 79 years	103.59 ± 12.40	97.81 ± 13.65	
Abdominal obesity (WC >80cm - women, WC >94cm - men)	% (no)	% (no)	
20 – 39 years	47.00% (94)	52.40% (109)	p=0.324
40 – 59 years	82.40% (389)	83.90% (459)	p=0.612

60 – 79 years	81.30% (506)	90.40% (613)	**p<0.001**
SBP (mmHg)	(Mean ± SD)	(Mean ± SD)	
20 – 39 years	125.88 ± 12.54	115.92 ± 13.55	**p<0.001**
40 – 59 years	136.05 ± 16.59	131.93 ± 23.65	**p=0.001**
60 – 79 years	145.30 ± 20.52	139.81 ± 20.44	**p<0.001**
p – between age groups	**p<0.001**	**p<0.001**	
DBP (mmHg)			
20 – 39 years	75.38 ± 10.03	72.77 ± 9.66	p=0.007
40 – 59 years	82.12 ± 11.53	79.51 ± 10.34	**p<0.001**
60 – 79 years	81.30 ± 12.66	79.75 ± 13.33	p=0.027
p – between age groups	**p<0.001**	**p<0.001**	

When we analyzed the BP values measured during the PREDATORR study, we noticed that the mean SBP increased significantly statistically with age for both sexes ($p < 0.001$) and male subjects had higher values of both SBP and DBP; the highest SBP values were recorded in male subjects aged over 60 years.

Previously known hypertension (personal history of hypertension and/or antihypertensive treatment at home) was found in 10.7% for subjects aged 20 to 39, 43.1% for those aged 40 to 59, and in three quarters (75.1%) of subjects aged between 60 and 79 years. In terms of gender distribution, it was observed that in subjects aged 20 to 59 years, previously known hypertension was more common in males, whereas in the 60-79 age group, hypertension was more common in the women. A high proportion of subjects with hypertension did not have BP values in targets, as follows: 27.2% of subjects aged 20-39 years, 41.3% of those aged 40-59 and 48.7% of those in the 60-79 age group had BP values > 140/90 mmHg. The percentage men with previously known hypertension and BP values >140/90 mmHg was higher compared to women with known hypertension - therapeutically uncontrolled in 20-39 years age groups (28.5% vs. 25.0%) and 60-79 years age group (51.1% vs. 46.6%), with the opposite situation being present in medium-age hypertensive subjects (40-59 years).

Most subjects diagnosed with hypertension during this study were aged between 40 and 59 years: 11.1% (12.9% - males and 9.5% females), followed by those over 60 years: 9.7% (13.6% men and twice as fewer women as 6.0%), the smallest subjects with undiagnosed hypertension were young subjects aged 20-39: 5.8% (8.0% - males and 3.8% women). It can be seen that the frequency of new cases of hypertension actively detected during the study was higher in male subjects at all age groups. Most of the hypertensive subjects diagnosed during the study had SBP values between 140 and 159 mmHg (grade 1 hypertension).

Table 2 describes the prevalence of hypertension in the Romanian adult population (data were weighted according to the latest census in 2011).

The total prevalence of hypertension was 47.38%, the number of hypertensive subjects aged between 20 and 79 years was estimated at 7153920. The percentage of hypertensive men: 48.62% (n = 3560964) was higher than that of women with this condition: 46.23% (n = 3592956). As expected, the prevalence of hypertension increases with age (Table 2).

Table 2 – The prevalence of hypertension in Romanian adult population (weighted data)

Age groups	**Men (%, no)**		**Women (%, no)**		**Total**	
20 – 39 years	**21%**	**614645**	**11.5%**	**322481**	**16.35%**	**937126**
40 – 59 years	**56.3%**	**1562612**	**52.2%**	**1474617**	**54.23%**	**3037229**
60 – 79 years	**85.3%**	**1383707**	**83.77%**	**1795858**	**84.43%**	**3179565**
Total	**48.62%**	**3560964**	**46.23%**	**3592956**	**47.38%**	**7153920**

In terms of the influence of other factors, hypertension was more frequently ($p < 0.001$) in subjects with overweight (odds ratio = 2.03; 95% CI 1.59% - 2.59%) and obesity (odds ratio = 4.25; 95%CI 3.27% - 5.51%) compared to normoponderal subjects. Also, hypertension was significant statistically ($p < 0.001$) correlated with glucidic metabolism disorders, its prevalence being almost three times greater in subjects with DM compared to those with normal glucose tolerance (odds ratio in subjects with known DM = 2.76 95%CI: 1.97% - 3.86% and odds ratio in subjects with unknown DM 2.93 95%CI: 1.59% - 5.39%). Hypertension was more common in subjects with ischemic heart disease ($p < 0.001$), in smokers ($p = 0.392$) and those with low educational level.

The logistic regression analysis showed that hypertensive men were less controlled than hypertensive women ($p < 0.001$); also a weak control of BP values was registered with the aging ($p = 0.018$), in subjects with overweight and obesity ($p = 0.004$), in those with DM detected during the study, in former and current smokers and those with a low educational level (table 8).

Regarding antihypertensive treatment, 18.7% of subjects with known hypertension did not receive drug therapy, 27.7% were receiving antihypertensive

treatment in monotherapy, 34.7% were under double antihypertensive drugs and most of them (37.6%) were receiving three or more antihypertensive drugs.

The most common antihypertensive drugs used in monotherapy were beta blockers (37.68%), angiotensin-converting enzyme inhibitors (29.78%), diuretics (18.54%), angiotensin receptor blockers (7.90%) and calcium channels blockers (6.07%).

When dual therapy was chosen for the treatment of hypertensive patients, the most commonly used combinations were: diuretic + angiotensin-converting enzyme inhibitor (36.89%), angiotensin-converting enzyme inhibitor + beta blocker (17.71%), diuretic + beta-blocker (13.83%), angiotensin receptor blocker + diuretic (8.73%), beta blocker + angiotensin receptor blocker (7.52%), diuretic + calcium channels blocker (3.88%) and beta-blocker + calcium channels blocker (2.66%).

Overall, the most commonly used classes of antihypertensive medication were: diuretics (60.23%), beta blockers (54.92%), angiotensin-converting enzyme inhibitors (54.50%), calcium channels blockers (24.51%), angiotensin receptor blocker (19.03%) and centrally active antihypertensive drugs (2.52%).

2. SECONDARY OBJECTIVE – TO ESTIMATE THE RISK FOR TYPE 2 DIABETES USING THE DIABETES RISK SCORE ALGORITHM

In order to accomplish this sub-study, out of the 2728 subjects included in the PREDATORR study were excluded subjects with a personal history of DM, as well as those who did not have all the necessary complete data.

Thus, 2031 subjects aged 20 to 79 years were analyzed, of which 54.40% (n = 1105) were women with mean age 54.58 ± 14.10 years and 45.59% (n = 926) men with mean age 54.33 ± 14.38 years.

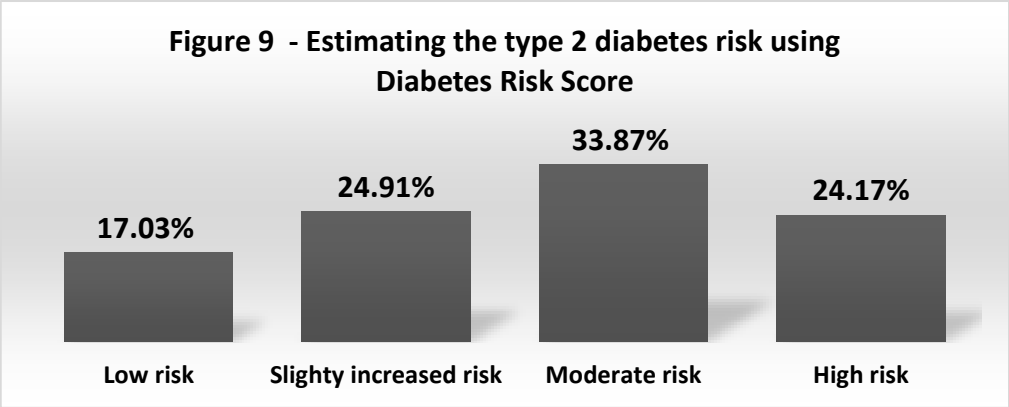
The characteristics of the group analyzed in this sub-study are shown in Table 3.

Table 3 - Characteristics of the analyzed group to estimate the risk of developing type 2 DM

Age group	Men (%, no)		Women (%, no)		Total	
20-49 years (0p)	334	16.44%	372	18.31%	706	34.76%
50-59 years (5p)	182	8.96%	255	12.55%	437	21.51%
60-69 years (9p)	277	13.63%	329	16.19%	606	29.83%

>70 years (13p)	133	6.54%	149	7.33%	282	13.88%
Total	926	45.59%	1105	54.40%	2031	100%
First relatives with DM	No	%	No	%	No	%
Yes (5p)	172	18.57%	216	19.54%	388	19.10%
No (0p)	754	81.42%	889	80.45%	1643	80.89%
Waist circumference	No	%	No	%	No	%
< 90 cm (0p)	151	16.30%	453	40.99%	604	29.73%
90-99.9 cm (4p)	249	26.88%	289	26.15%	538	26.48%
100-109.9 cm (6p)	318	34.34%	221	20.00%	539	26.53%
≥ 110 cm (9p)	208	22.46%	142	12.85%	350	17.23%
BMI	Nr	%	Nr	%	Nr	%
BMI <25kg/m^2 (0p)	232	25.05%	361	32.66%	593	29.19%
BMI 25-29.9 kg/m^2 (3p)	431	46.54%	347	31.40%	778	38.30%
BMI 30-34.9 kg/m^2 (5p)	202	21.81%	270	24.43%	472	23.23%
BMI >35 kg/m^2 (8p)	61	6.58%	127	11.49%	188	9.25%
Personal history of hypertension	Nr	%	nr	%	Nr	%
Yes (5p)	561	60.58%	632	57.19%	1193	58.73%
No (0p)	365	39.41%	473	42.80%	838	41.26%

The risk of developing type 2 DM over the next 10 years in subjects included in this study was as follows: 17.03% of subjects - low risk, 24.91% of subjects - slightly increased risk, 33.87% of moderate risk and 24.17% of subjects - high risk.



11.23% of men included in this sub-study had a low risk, 26.56% - slightly increased risk, 35.96% - moderate risk and over a quarter, 26.24% - high risk.

The risk of developing type 2 DM in female subjects included in this sub-study was: 21.90% - low risk, 23.52% - slightly increased risk, 32.12% moderate risk and 22.44% high risk.

The risk of developing type 2 DM was higher in male subjects, less in the 70-79 age group, where the gender difference was insignificant statistically ($p = 0.623$). The risk of developing type 2 DM increased significantly statistically ($p < 0.0001$) with age in both sexes.

CONCLUSIONS:

This study includes the evaluation of cardio-metabolic risk as well as the risk factors for the Romanian adult population aged between 20 and 79 years who were enrolled in the national epidemiological study PREDATORR.

This study led to the following conclusions, which may be applicable in clinical practice to prevent and delay the onset of cardiovascular disease, diabetes mellitus as well as risk factors:

- Romania is a country with a high cardiovascular risk, according to the European Cardiology Guideline from 2016 (19): 1.85% of the adult population was in the 30-40% CVR category and 2.90% in the > 40% CVR category
- In subjects with diabetes, 4.50% were in the 30-40% CVR category and 7.80% in the >40% CVR category
- 47.38% of the Romanian adult population has hypertension; the prevalence of hypertension in male subjects was 48.62% and in females 46.23% (weighted data)

- 18.7% of subjects with hypertension did not receive antihypertensive treatment, 27.7% of subjects were treated with a single antihypertensive agent, 34.7% - dual antihypertensive therapy and 37.6% - had three or more antihypertensive drugs
- The most commonly used classes of antihypertensive medication were: diuretics (60.23%), beta blockers (54.92%), angiotensin converting enzyme inhibitors (54.50%), calcium channels blockers (24.51%), angiotensin receptor blockers (19.03%) and centrally active antihypertensive drugs (2.52%)
- 17.03% of subjects had a low risk of developing type 2 diabetes, whereas over three quarters of the subjects included in the PREDATORR study were in the categories at increased risk of developing type 2 DM in the next 10 years: 24.91% of the subjects had a slightly increased risk, 33.87% moderate risk and 24.17% high risk
- The risk of developing type 2 diabetes was higher in male subjects, less in the 70-79 age group, where the difference between the two sexes was insignificant.

SPECIAL CONTRIBUTION

This paper is the only study that assesses the cardiovascular risk in the Romanian adult population using the charts developed by the World Health Organization and the International Society of Hypertension.

This thesis also includes the only study in Romania that evaluates the risk of developing type 2 diabetes with the Diabetes Risk Score questionnaire or other questionnaires.

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