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Sex Differences in Cardiovascular Risk Factors in a Rural Community from North Romania Region

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Abstract

The prevalence of coronary heart disease is higher in men but the prevalence of stroke and the annual number of cardiovascular deaths are higher in women. Despite these findings, the cardiovascular risk in the female population is still underestimated. The present study aimed to identify cardiovascular risk factors and correlations with atherosclerotic cardiovascular disease in 285 patients from a rural community in Romania, aged between 26-92 years, 187 (65,6%) females, 98 (34,4%) males, in order to establish gender differences. Traditional risk factors were assessed. We used descriptive statistic methods to calculate the average and standard deviation of the assessed parameters. Divided by gender, the cardiovascular risk factors presented important differences. Almost all cardiovascular risk factors were more importantly represented in the female group: type 2 diabetes mellitus (73.0%), chronic stress (70.0%), family history of cardiovascular disease (57.0%). Obesity was frequent in females but with no statistical difference. Of all the women, 57.9% had arterial hypertension compared to men (27.7%) the statistical significance being almost insignificant ($p = 0.052$). Women had 4.3 times greater odds of obesity, 14.2 fold increased odds for abdominal adiposity, 2.8 times greater odds of high waist-hip-ratio and more than three-fold greater odds of having metabolic syndrome ($p = 0.001$). Among men, BMI and waist circumference were significantly correlated with blood pressure, triglycerides, total, LDL-, and HDL-cholesterol and fasting glucose; in women, only blood pressure was positively associated with BMI and waist circumference. Further studies are needed to establish the correlation between gender and cardiovascular risk factors.

Keywords: cardiovascular disease, cardiovascular risk factors, coronary heart disease, stroke, metabolic syndrome.

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Introduction

The term “risk factor” appeared around the 1960s when many epidemiological data suggested a high correlation between some population characteristics and the prevalence of ischemic heart disease. The quantitative relationship between these risk factors and CHD risk has been elucidated by the Framingham Heart Study and other studies (Wilson PW et al 1998). Cardiovascular disease (CVD) is the primary cause of death in many developing countries. The most preventable form of CVD is coronary heart disease (CHD). American Health Association policy statement concluded that costs will rise to more than $1 trillion annually in the United States by the year 2030 and preventive measures are required (Weintraub, 2011).

The Framingham Heart Study is the origin of the term “risk factor”. Thomas Dawber was the director of the study between 1949 and 1966; his name being closely related to the future epidemiological research of risk factors (Dawber *et al.*, 1951). The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to CVD by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke. The researchers recruited 5,209 men and women aged between 30 and 62 years from the town of Framingham, Massachusetts, and began the first round of extensive physical examinations and lifestyle interviews that they would later analyze for common patterns related to CVD development (Dawber *et al.*, 1951).In a much broader sense, risk factors include patterns of lifestyle, certain bio-chemical and physiological characteristics and some individual modifiable factors (Mahmood *et al.*, 2014).

Cardiovascular disease is the primary cause of death in many developing countries. Early detection of risk factors is important to establish both primary and secondary preventive measures which may lead to decreased morbidity and mortality and reduced hospitalization costs. The majority of cardiovascular disease (CVD) is caused by risk factors that can be controlled, treated or modified, such as high blood pressure, cholesterol, overweight/obesity, tobacco use, lack of physical activity and diabetes. However, there are also some CVD risk factors that cannot be controlled (age, sex, genetic inheritance). The major and independent risk factors for CHD are cigarette smoking of any amount, elevated blood pressure, elevated serum total cholesterol and low-density lipoprotein cholesterol (LDL-C), low serum high-density lipoprotein cholesterol (HDL-C), diabetes mellitus, and advancing age (Grundy *et al.*, 1999).

A population-based study conducted more recently in 2004 in 52 countries, 5 continents (the INTERHEART study) led to the identification of nine risk factors involved in the onset of acute myocardial infarction: smoking, dyslipidemia,

hypertension, diabetes, obesity diet, physical inactivity, alcohol consumption, psychosocial factors (Anand, 2008). It is obvious that cardiovascular (CV) diseases represent the main cause of mortality worldwide with a prevalence that is continuously increasing. Prevention measures are needed urgently in order to detect the individuals that are at high risk for developing CV diseases. Thus, based on solid studies, various international societies have developed risk charts for the assessment of subjects' CV risk profile, the best known being SCORE risk chart (Systematic Coronary Risk Evaluation) applicable for European countries or the Framingham risk score for North America (Berger *et al.*, 2010).There should be underlined that risk factors have a high predictability for atherosclerosis and ischemic heart disease, the relationship is not strictly causal. They especially indicate a "predisposition" for disease (Elwood & Longley, 2010).

A review which examined 55 trials that intended to reduce multiple risk factors suggested that intervention results in small reductions in risk factors (blood pressure, cholesterol, and smoking), but has little or no impact on the risk of CHD mortality or morbidity (Ebrahim *et al.*, 2011).But, early detection of risk factors is important to establish both primary and secondary preventive measures which may lead to decreased morbidity and mortality and reduced hospitalization costs. Cardiovascular disease (CVD) has been seen as a men's disease for decades, however it is more common in women than in men. It is generally assumed in medicine that the effects of the major risk factors (RF) on CVD outcomes are the same in both genders. Cardiovascular disease (CVD) represents the leading cause of mortality in both men and women (Mosca, Barret-Connor, & Wenger, 2011).

Even though the prevalence of coronary heart disease (CHD) is higher in men, the prevalence of stroke and the absolute annual number of CVD deaths are higher in women (Mosca, Barret-Connor, & Wenger, 2011). Despite these findings, both women and physicians tend to underestimate the cardiovascular risk in the female population (Jneid & Thacker, 2001; Mikhail, 2005). Moreover, in women, the frequently atypical manifestation of CHD and the underuse of diagnostic procedures result in delayed diagnosis of CHD (Jneid & Thacker, 2001; Hvelplund *et al.*, 2010). Recent evidence has emerged that recognizes new, potentially independent, CVD risk factors exclusive to women (Appelman *et al.*, 2015). Common disorders of pregnancy, such as gestational hypertension and diabetes, as well as some endocrine disorders in women of reproductive age and early menopause are associated with accelerated atherosclerosis and development of CVD. Female-specific risk factors might be identified enabling early detection of apparently healthy women with a high lifetime risk of CVD. With respect to female-specific RF only associations could be found between preeclampsia, gestational diabetes and menopause onset with the occurrence of CVD. These reviews show that CVD is the main cause of death in men and women; however the prevalence is higher in women (Tziomalos *et al.*, 2011). Determination of the CV risk profile should take into account that there are differences in the impact of

major CV risk factors leading to a worse outcome in women. Lifestyle interventions and primary prevention in women needs more consideration (Appelman, *et al.*, 2015).

While men and women have similar risk factors for cardiovascular diseases, many social behaviors in low and middle income countries differ by gender. For example, women who smoke have three times the risk of heart attacks and have their first heart attacks much earlier than men and non-smoking women (Bernabe-Ortiz *et al.*, 2012). Starting from these theoretical premises, the present study aimed to identify gender differences in cardio-vascular risk factors in a rural community from Romania, in order to establish some correlations with the risk of atherosclerotic cardiovascular disease.

Material and method

The main objective of this study was to evaluate the gender differences with specific cardiovascular risk factors in a rural community of the North Romanian Region and also the knowledge of pathological associations that would increase the cardiovascular and cardiometabolic risks in patients with cumulation of risk factors, differently in the two genders and, finally, establishing the influence of lifestyle on the incidence of risk factors in the studied population and their comorbidities. The results will be used to design prevention programs that have already proven to be absolutely necessary to promote a healthy lifestyle starting with teenagers, the influence (when possible) of risk factors in order to increase the life expectancy of the population and quality of life.

The objectives of the study were: 1. Creating a cross-sectional study in a rural population of Suceava county in order to determine the prevalence of cardiovascular risk factors and their different profile at the two genders; 2. Performing a study of the same rural population allowing complete characterization of the people with cardiovascular risk factors in terms of cardiovascular and cardiometabolic comorbidity profile and establish gender differences in the two inputs; 3. Evaluating the role of parameters related to lifestyle on the occurrence of some cardiovascular risk factors and comorbidities, analyzed separately in the two genders.

The studied population and data collection

The research was conducted in a rural community of Suceava county, being chosen as representative in terms of number of inhabitants, population stability, uniformity in educational, religious and ethnic features. An important element was the ongoing collaboration with local healthcare professionals and their willingness to actively participate in data collection.

The study was conducted in collaboration with a General Practitioner (GP) from Suceava County, in Patrauti who provided all necessary data on the basis of existing medical records. The exclusion criteria in this study were: previous personal history of cerebrovascular diseases (stroke, acute coronary syndrome), patients younger than 18 years old, patient refusal, the presence of psychiatric, cognitive or other disease that might alter the understanding of the study objectives or the ability to provide accurate information. Those who did not complete the interview were recorded as having refused to participate and were taken into account when calculating the refusal rate, but excluded from the final analysis. The study group consisted of 285 patients aged between 26 - 92 years. The rural community where the research was conducted has a population of 4,567 inhabitants, with relatively equal distribution on the two genders (2,262 males and 2,305 females). The distribution by age groups is as follows: between 18-65 years – 2,344 people (51.32%), of whom 1,203 males (26.34%) and 1,141 females (24.98%); over 65 years = 833 inhabitants (18.23%), 527 males (11.53%) , 306 females (6,7%).

The number of inhabitants in the records of the family doctor who conducted collaboration is 2659 people, of whom 1244 males (46.78%) and 1415 females (53.21%), with the following distribution by age: between 18-65 years = 1457 (54.79%) , 826 females (31.06%), 631 males (23.73%), between 65-90 years = 304 (11.43%) , 153females (5.75%), 151 males (5.67%) and over 90 years = 8 (0.30%), 6 females (0.22%), 2 males (0.08%). Population under 18 was not included in the study.

For each participant an individual file was completed(by GP) which included: age, gender, elements of lifestyle (smoking status, physical activity undertaken, drinking, type of diet), pathological personal history, anthropometric measures (weight, height , waist circumference, body mass index), systolic and diastolic blood pressure, and biochemical parameters (fasting plasma glucose, total cholesterol, HDL cholesterol, fasting serum triglycerides).

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (Statistical Package for the Social Sciences, Chicago, Illinois). Data were expressed as mean ± standard deviation (SD) or number of cases with percentage, for continuous and ordinal variables. T-test was used for comparing the continuous variables and chi-square test for categorical comparisons. For all data, a two-sided p value < 0.05 was considered statistically significant.

Results and discussion

Mean age of patients was 65.96 ± 11.93 years, with minimum age 26 and maximum age 92. In the study group, 187 (65.6%) were females while the men group was represented by 98 (34.4%) subjects. More than half of individuals had normal weight, 14% were overweight and 28% were obese. 14.7% of population had type 2 diabetes mellitus and 13% were former and active smokers. The presence of chronic stress was reported by 27% of patients while 21% had a positive family history of CVD. 85% of patients were hypertensive, most of them being classified into classes 1 and 2 of high blood pressure. More than 50% of subjects presented, suspected or documented coronary artery disease while 12% had a documented stroke (*Table 1*).

Table 1. The presence of cardiovascular risk factors in the study population and differences by gender

CV risk factor	Female	Male	p value
Type 2 diabetes mellitus (%, no)	73.8 (31)	26.2 (11)	0.150
Obesity (%)			
Normal weight	35.8	21.4	
Overweight	9.1	4.9	0.618
Obesity grade I	10.2	3.5	
Obesity grade II	8.1	3.9	
Obesity grade III	2.5	0.7	
Chronic stress (%, no)	70.9 (56)	29.1 (23)	0.154
Family history of CVD (%, no)	57.4 (35)	42.6 (26)	0.089
Arterial hypertension (%)			
Normal blood pressure	7.7	6.7	
Grade 1	24.6	13.7	0.052
Grade 2	24.9	12.6	
Grade 3	8.4	1.4	
Coronary artery disease (%, no)	63.5 (108)	36.5 (62)	0.220
Stroke (%, no)	70.6 (24)	29.4 (10)	0.328

Divided by gender, the cardiovascular risk factors presented important differences (*Table 1*). Almost all cardiovascular risk factors were more importantly represented in the female group: type 2 diabetes mellitus (73%), chronic stress (70%), family history of CVD (57%), suspected or documented coronary artery disease (63%) or stroke (70%). As well, the overweight and obesity predominance was higher in the female population but with no statistical difference. In women, 57.9% had arterial hypertension comparative to men where only 27.7% presented increased blood pressure, the statistical significance being almost insignificant ($p = 0.052$). Nonetheless, almost 98% of females were non-smokers, comparative to only 64% in men. 20% of men were former smokers and 15% were active smokers while only 2.1% of women smoked ($p < 0.001$) (*Figure 1*).

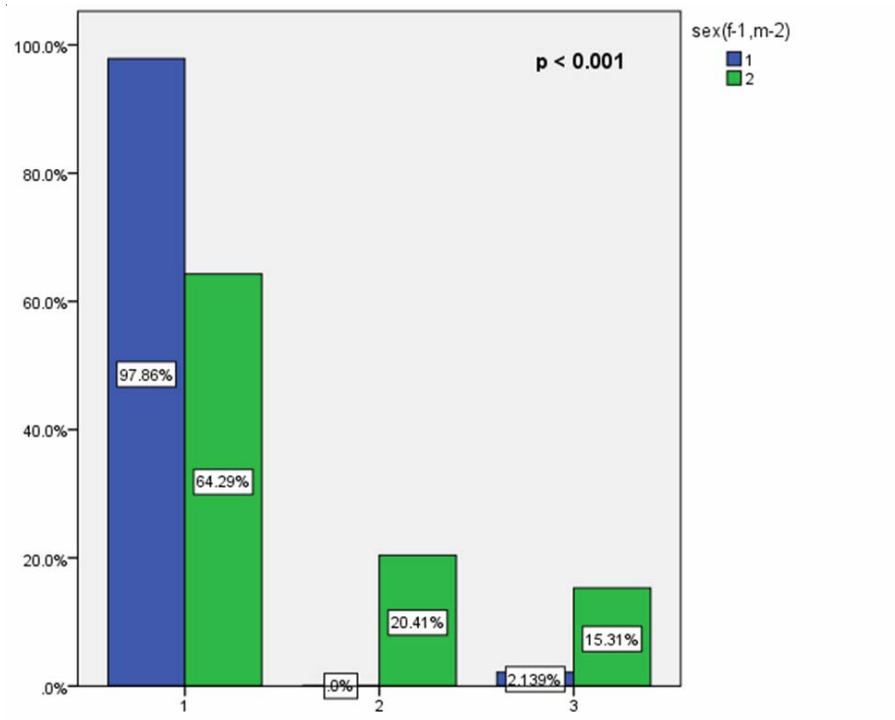

Figure 1. Smoking differences by gender (1 represents non-smokers; 2 – former smokers; 3 – active smokers)

Regarding biochemical markers, the study group was dyslipidemic, both mean total cholesterol and triglyceride levels being over the superior values (208 mg/dl, respectively 156 mg/dl). However, HDL and LDL cholesterol were in normal ranges, while uric acid was high (5.83 mg/dl), maximum value being 9 mg/dl. In diabetic patients, the glycosylated hemoglobin, HbA1C had high values (average 8.04%) suggesting a bad control of diabetes in this specific region. Mean results can be found in *Table 2*.

By analyzing biochemical markers by gender, women were significantly older than men in the study population ($p = 0.013$). Total cholesterol, triglycerides and LDL cholesterol were rather similar between the two groups. However, HDL cholesterol was significantly decreased in the male group (49.52 ± 14.56 vs. 55.61 ± 16.86, $p = 0.010$). Even though the uric acid had higher values in men (6.83 ± 1.83 vs. 4.83 ± 1.94), the statistical significance was not reached ($p = 0.09$) probably due to thevariation of values. The glycosylated hemoglobin, HbA1C presented close values after dividing by gender. All biochemical results divided by gender can be also found in *Table 2*.

Table 2. Biochemical values in the study population by gender

Parameter	Total (n = 285)	Minimum	Maximum	Female (n = 187)	Male (n = 98)	p value
Age (years)	65.96 ± 11.93	26	92	67.22 ± 11.61	63.55 ± 12.22	0.013
Total cholesterol (mg/dl)	208.62 ± 42.17	112	339	209.42 ± 39.85	207.43 ± 46.46	0.731
Triglycerides (mg/dl)	156.54 ± 99.27	39	895	152.21 ± 88.64	164.67 ± 116.71	0.316
HDL cholesterol (mg/dl)	53.50 ± 16.32	23	146	55.61 ± 16.86	49.52 ± 14.56	0.010
LDL cholesterol (mg/dl)	123.01 ± 36.48	29	232	124.38 ± 35.85	120.46 ± 37.76	0.469
Uric acid (mg/dl)	5.83 ± 2.08	3	9	4.83 ± 1.94	6.83 ± 1.83	0.097
Glycosylated hemoglobin (HbA1C) (%)	8.04 ± 2.56	4	15	8.29 ± 3.03	7.56 ± 1.33	0.399

The age-adjusted prevalence of obesity (BMI e" 30) was 13% and 35%, among men and women (p = 0.0003), respectively. The prevalence of abdominal obesity was 11% and 58% (p < 0.0001), and high WHR (men: >0.9, women: >0.85) was 51% and 73% (p = 0.002) for men and women respectively. Women had 4.3 times greater odds of obesity (95% CI: 1.9-10.1), 14.2 - fold increased odds for abdominal adiposity (95% CI: 5.8-34.6), and 2.8 times greater odds of high waist-hip-ratio (95% CI: 1.4-5.7), compared to men.

Women had more than three-fold greater odds of having metabolic syndrome (p = 0.001) compared to male counterparts, including abdominal obesity, low HDL-cholesterol, and high fasting blood glucose components. In contrast, female participants had 50% lower odds of having hypertension, compared to men (95% CI: 0.3-1.0).

Among men, BMI and waist circumference were significantly correlated with blood pressure, triglycerides, total, LDL-, and HDL-cholesterol (BMI only), and fasting glucose; in contrast, only blood pressure was positively associated with BMI and waist circumference in women.

In existing literature it is stipulated that the classic risk factors for CVD are the same in women and men, but there are gender differences in the prevalence of risk factors. Mosca, Barret-Connor and Wenger (2011) mentions that although women and men overall have nearly equal percentages of hypertension (1 in 3 adults), data from the National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of high blood pressure is greater in women >65 years of age.The highest rate of hypertension is among black women, 44%, and is increasing. The death rate caused by hypertension in 2007 was 37.0 per 100 000 for black women compared with 14.3 per 100 000 for white women (Mosca, Barret-Connor, & Wenger, 2011).

Diabetes mellitus is more prevalent among women than men e”20 years of age (8.3% versus 7.2%). Type II diabetes mellitus imparts a greater risk of CHD in women than men and is not explained by differences in risk factors, but rather by the more favorable survival rate of women (than men) without diabetes mellitus. On the basis of the NHANES data, the age-adjusted prevalence of the metabolic syndrome is highest among Mexican-American women (40.6%), which is H”22% higher than in Mexican-American men. The prevalence of total cholesterol e”240 mg/dL in 2008 for those e”20 years of age was 16.2% among women and 13.5% among men.2 In contrast, the percent of women with high-density lipoprotein cholesterol <40 mg/dL was 9.7% compared with 29.5% among men (Mosca, Barret-Connor, & Wenger, 2011).

Comparative with existing literature we found that lifestyle risk factors also vary by gender, race, and ethnicity. For example, Mosca, Barret-Connor, & Wenger (2011) reported that cigarette smoking has decreased overall in the United States, but remains more common among men than women (23.1% versus 18.1%). Non-Hispanic white women have a higher rate of smoking (20.7%) than black women (18.8%) and Hispanic women (9.4%). Two thirds of Americans are overweight or obese (72% of men and 64% of women) as defined by body mass index. Among women, non-Hispanic blacks and Mexican-Americans are more likely to be obese than non-Hispanic whites (50% versus 45% versus 33%, respectively). From 1999 to 2008, the increase in the prevalence of obesity was greater among men than women. Full adherence to three heart-healthy lifestyle behaviors (smoking abstinence, physical activity, and fruit and vegetable intake) was nearly 50% higher among women than men without CHD in a 2000 sample of the US population. These data suggest that population-wide approaches are needed to reduce the burden of CVD in both genders.

Bernabe-Ortiz and colab. (2012) in The Peru Migrant Study refers to a Brazilian study which demonstrated that high cholesterol and hypertension were more prevalent among women compared to men. In Peru, three studies have shown that metabolic syndrome, abdominal obesity, and low high density lipoprotein-cholesterol (HDL) are higher in women than men while there seems to be no differences in hypertension, hypertriglyceridemia or high fasting glucose. Appelman *et al*., (2015) is one of those who examined the available literature regarding the prevalence and effects of the traditional major RFs for CVD in men and women. This included large prospective cohort studies, cross-sectional studies and registries. Furthermore, a literature search was performed to examine the impact of female-specific RFs on the traditional RFs and the occurrence of CVD. He found that the effects of elevated blood pressure, overweight and obesity, and elevated cholesterol on CVD outcomes are largely similar between women and men; however prolonged smoking is significantly more hazardous for women than for men. This review shows that CVD is the main cause of death in men and women; however the prevalence is higher in women. Determination of the CV risk profile

should take into account that there are differences in impact of major CV risk factors leading to a worse outcome in women. As a consequence, lifestyle interventions and awareness in women needs more consideration.

Conclusions

Our study revealed that divided by gender, the cardiovascular risk factors presented important differences in our group meaning that almost all cardiovascular risk factors were more importantly represented in the female group apart from smoking. Women had more than three-fold greater odds of having metabolic syndrome ($p = 0.001$) compared to male counterparts, including abdominal obesity, low HDL-cholesterol, and high fasting blood glucose components. In contrast, female participants had 50% lower odds of having hypertension, compared to men (95%CI: 0.3-1.0). The present study has clear practical implications in terms of the initiation of the targeted measures for primary prevention into the studied population. Data obtained from the survey on the prevalence of risk factors could be extrapolated to other population and can be used in the future for cardiovascular and cardiometabolic risk assessment and early initiation of preventive measures.

References

Anand, S., Islam, S., Rosengren, A., Franzosi, M.G., Steyn, K., Yusufali, A., Keltai, M., Diaz, R., Rangarajan, S., & Yusuf, S. (2008). Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *European Heart Journal*, *29*(7), 932-940.

Appelman, Y., van Rijn, B.B., Ten Haaf, M.E., Boersma, E., & Peters, S.A. (2015). Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis, 241*(1), 211-218.

Berger, J.S., Jordan, C.O., Lloyd-Jones, D., & Blumenthal, R.S. (2010) Screening for cardiovascular risk in asymptomatic patients. *Journal of the American College of Cardiology*, *55*(12), 1169-1177.

Bernabe-Ortiz, A., Pastorius Benziger, C., Gilman, R.H., Smeeth, L., Miranda. J.J. (2012). Sex Differences in Risk Factors for Cardiovascular Disease: The Peru Migrant Study. *PLoS ONE 7*(4), e35127.

Dawber, R.T, Meadors, G.F., & Moore, Jr. F.E. (1951). Epidemiological Approaches to Heart Disease: The Framingham Study. *American Journal of Public Health and the Nation's Health*, *41*(3), 279–286.

Ebrahim, S., Taylor, F., Ward, K., Beswick, A., Burke, M., & Davey Smith, G. (2011). Multiple risk factor interventions for primary prevention of coronary heart disease. Cochrane Database Syst Rev.; CD001561.

Elwood, P.C., Longley, M. (2010). My Health - Whose Responsibility - a jury decides. *Journal of Epidemiology and Community Health*, *64*, 761-764.

Grundy, S.M., Pasternak, R., Greenland, P., Smith Jr. S., & Fuster, V. (1999). Assessment of Cardiovascular Risk by Use of Multiple-Risk-Factor Assessment Equations, A Statement for Healthcare Professionals From the American Heart Association and the American College of Cardiology. *Circulation, 100*, 1481-1492.

Hvelplund, A., Galatius, S., Madsen, M., *et al.* (2010). Women with acute coronary syndrome are less invasively examined and subsequently less treated than men. *European Heart Journal*, *31*, 684-690.

Jneid, H., & Thacker, H.L. (2001). Coronary artery disease in women: different, often under treated. *Cleveland Clinic Journal of Medicine. 68,* 441-448.

Mahmood, S.S., Levy, D., Vasan, R.S., & Wang, T.J. (2014). The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. *Lancet*, *383*(9921), 999-1008.

Mikhail, G.W. (2005). Coronary heart disease in women is underdiagnosed, undertreated, and under-researched. *BMJ*, *331*, 467-468.

Mosca, L., Barret-Connor, E., & Wenger, N.K. (2011). Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation*. *124*, 2145-2154.

Tziomalos, K., Giampatzis, V., Baltatzi, M., *et al.* (2014). Sex-Specific Differences in Cardiovascular Risk Factors and Blood Pressure Control in Hypertensive Patients. *The Journal of Clinical Hypertension, 16*(4), 309-312.

Weintraub, W.S., Daniels, S.R., Burke, L.E. *et al*. (2011). Value of Primordial and Primary Prevention for Cardiovascular Disease: A Policy Statement From the American Heart Association. *Circulation, 124*(8), 967-990.

Wilson, P.W., D'Agostino, R.B., Levy, D., Belanger, A.M., Silbershatz, H., Kannel, W.B. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation, 97*, 1837-1847.