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Association between Components of Metabolic Syndrome and Rheumatic, Cardiovascular, Gastrointestinal, and Chronic Kidney Disease: A Cross-Sectional Study of Adults in Cyprus

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ABSTRACT

Background and Objective: Metabolic syndrome is a common metabolic disorder directly related to the increasing prevalence of obesity and linked to cardiovascular, gastrointestinal, rheumatic, and chronic kidney disease (CKD). This study aims to examine the association of three components of the metabolic syndrome (hypertension, type 2 diabetes, and obesity) with cardiovascular, gastrointestinal, rheumatic, and CKD, in the adult population of Cyprus.

Methods: Data were obtained from a cross-sectional study conducted in Cyprus from 2018 to 2019. Medical history was collected using a validated questionnaire.

Results: A total of 1140 men and women aged 18 and older participated in the study. The prevalence of cardiovascular, gastrointestinal, rheumatic, and CKD was 2.4%, 12.5%, 2.6%, and 1.0%, respectively. Univariate analysis showed that hypertension and central obesity were significant factors in the development of cardiovascular, gastrointestinal, and rheumatic diseases and CKD.

Conclusion and Implications for Translation: Healthcare practitioners should prioritize the identification and management of risk factors associated with these diseases at the clinical level, including the thorough monitoring of blood pressure as a significant predictor of cardiovascular, gastrointestinal, and rheumatic diseases. Individualized prevention and treatment strategies should be developed to address these specific risk factors in clinical practice.

Keywords: Cardiovascular Diseases, Chronic Kidney Diseases, Cyprus, Gastrointestinal Diseases, Metabolic Syndrome, Rheumatic Diseases

INTRODUCTION

Background of the Study

With the elimination of many of the past infectious diseases, non-communicable diseases have become the main cause of morbidity and mortality, not only in the developed world but also in less developed countries.[1] This is mainly attributed to the gradual shift of traditional lifestyle and the adoption of a Western lifestyle,[1] characterized by a diet high in fat and carbohydrates, and a

sedentary and physically inactive lifestyle, ultimately leading to overweight or obesity.[2]

The term "syndrome," originating from Greek and literally meaning "running together," refers to a collection of signs or symptoms that occur concurrently.[3] Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including centrally distributed obesity, reduced high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, hypertension, and hyperglycemia.[4] MetS is also known as syndrome X or insulin resistance syndrome.[5] Various organizations have published different definitions for its diagnosis, such as the World Health Organization (WHO) in 1999, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) of the USA in 2001, and the International Diabetes Federation (IDF) in 2005, each based on slightly different criteria.[6]

The prevalence estimates of MetS not only vary between different countries but also within the same country.[1] This variability occurs due to differences in the applied definition of MetS and is influenced by factors such as ethnicity and the age composition of the study population. In the United States, the age-adjusted prevalence was reported to be 23.9% according to the NCEP ATP III definition and 25.1% according to the WHO definition.[6] Regardless of the specific definition used, MetS is a commonly occurring condition,[7] and an improved understanding of MetS could have significant benefits for public health.[8]

It has been suggested that MetS is associated with cardiovascular disease (CVD), gastrointestinal diseases, rheumatic diseases, as well as chronic kidney disease (CKD).[9-12] For instance, MetS has been identified as an important risk factor for the incidence and mortality of CVD, with the National Health Service (NHS) in England indicating that hypertension, diabetes, and being overweight or obese are among the primary risk factors for developing CVD.[9] MetS is also linked to a three-fold increase in type II diabetes (DM2) and a two-fold increase in CVD,[13] making it a significant contributor to the modern-day epidemics of diabetes and CVD, thereby posing a major public health challenge worldwide.

Furthermore, a review study discussed the association between the individual components of MetS, specifically obesity and abdominal obesity, and gastrointestinal diseases.[10] The study concluded that obesity, especially visceral obesity, which is the core of MetS, is involved in several gastrointestinal diseases. In addition, individuals with autoimmune rheumatic diseases, such as systemic lupus erythematosus and rheumatoid arthritis, have an increased prevalence of MetS.[11] Insulin resistance and hyperinsulinemia, which are among the most significant metabolic factors, contribute to the association of MetS with CKD.[12] However, there is limited research examining the individual components of MetS in relation to all the aforementioned health conditions or diseases.[14]

According to a cross-sectional study conducted in Cyprus between 2018 and 2019, the most prevalent chronic diseases in Cyprus were diseases of the circulatory system (25%), followed by those of the endocrine system (17%) and the digestive-excretory system (13%).[15] At the same time, data related to metabolic syndrome in Cyprus are limited. One study suggested that the overall prevalence of MetS was 22.2%, using the National Cholesterol Education Program Adult Treatment Panel III criteria. The study found that the prevalence of MetS increases with age, is higher in men than in women (26.5 vs. 18.3%, respectively), and is higher in rural than in urban areas (26.0 vs. 20.6%, respectively).[16]

Objectives of the Study

The aim of this study is to investigate the potential association between three components of the MetS (using the IDF definition): Hypertension, elevated fasting plasma glucose or Type II diabetes, and central obesity (defined as body mass index [BMI] >30 kg/m^2) with the following conditions: (i) CVD, (ii) gastrointestinal diseases, (iii) rheumatic diseases, and (iv) CKD. The findings of this study have the potential to contribute to the development of targeted health education and intervention programs in Cyprus aimed at addressing these diseases.

METHODS

This research was a cross-sectional study conducted from May 2018 to June 2019 and recruited women and men over 18 years old who were living in the five government-controlled municipalities of the Republic of Cyprus (Nicosia, Limassol, Larnaca, Paphos, and Ammochostos). Individuals living in nursing homes or those who were institutionalized were excluded from the study. Using a stratified approach, the final sample had similar characteristics, including region, age, and gender, to the general population of Cyprus (all $p > 0.05$). More details about the study's methodology are presented elsewhere.[15]

Study Variables

A standardized questionnaire was used to collect data from participants and included sections on sociodemographic characteristics, medical history, and lifestyle characteristics. A pilot study was conducted on approximately 10% of the total sample to validate the questionnaire, leading to necessary modifications based on the results. The questionnaire was self-reported, except for the medical history section, which was gathered through a face-to-face interview.

The medical history section included 47 chronic diseases across all human systems (i.e., cardiovascular, digestive/excretory, endocrine, immune, nervous, renal/urinary, reproductive, respiratory, skeletal/muscular systems, and neoplasms). Diseases were coded according to the International Classification of Diseases, 10th Revision, and information was collected using the question "Have you ever been diagnosed by a physician with any of the following chronic diseases? Choose all that apply." Cardiovascular diseases include at least one of the following: Angina (I20.9), atrial fibrillation (I48.91), heart failure (I50), and coronary heart disease (I25.1). Similarly, gastrointestinal diseases included at least one of the following: Gastric reflux (K21), irritating bowel syndrome (K58), Crohn's disease (K50), inflammatory bowel disease/chronic enteritis/ulcerative colitis (K50–K52), and colon cancer (C18.9). Rheumatic diseases included lupus (M32.9) and rheumatoid arthritis (MO6.9). Finally, CKD (N18.9) was also considered.

Sociodemographic characteristics included the age of the participant in years, gender (male/female), and educational status. Educational status was classified into three categories commonly used in Cyprus, namely (i) primary education (participants who completed only primary education - <7 years of schooling); (ii) secondary education (participants who completed middle or high school - 7–12 years of schooling); and (iii) higher education (participants who have a university degree - >12 years of schooling).[17,18] Weight was reported in kilograms and height in meters. BMI was calculated as weight divided by height squared. According to the WHO classification, obesity was defined as BMI >29.9 kg/m^2, overweight as BMI 25–29.9 kg/m^2, normal as BMI 18.5–24.9 kg/m^2, and underweight as BMI <18.5 kg/m^2.

Other lifestyle characteristics considered were smoking status and exercise/sedentary activity. The current smokers were defined as those who smoked regularly at the time of the study. In addition, we used definitions from the Centers for Disease Control and Prevention and Behavioral Risk Factor Surveillance System, defining sedentary activity as no physical activity or irregular physical activity reported (i.e., fewer than 3 times/week and/or <20 min/session).[19] Exercise was categorized as "no" for individuals who did not engage in any kind of exercise and "yes" for those who reported any form of exercise.

The definition of MetS by the IDF was used. According to the definition,[20] MetS is characterized by the presence of central obesity (defined as increased waist circumference over ethnically specific values) plus any two of the following four factors: (i) Elevated triglycerides (≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality), (ii) low high-density lipoprotein cholesterol (<40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality), (iii) high blood pressure (BP) (systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension), and (iv) elevated fasting plasma glucose (FPG ≥100 mg/dL (5.6 mmol/L), or previously diagnosed Type 2 Diabetes). According to the definition, if FPG is >5.6 mmol/L (>100 mg/dL), the oral glucose tolerance test is strongly recommended, but this is not necessary to define the presence of MetS.

Statistical Analysis

The Shapiro–Wilk normality test was used to examine the normality of the continuous variables. Continuous variables with normal distribution are presented as mean ± standard deviation. Categorical variables are presented as frequency (percentage). Unadjusted logistic regression models were used to check if a covariate was associated with a specific group of diseases and the Wald chi-square test is reported. Subsequently, four multiple logistic regression models were utilized to investigate whether there was an association between the three components of MetS considered (hypertension, DM2, and central obesity) and each group of diseases, after adjusting for possible confounders, namely age, gender, educational status, smoking, exercise, and sedentary activity. All statistical procedures used were conducted using SAS version 9.4 and all tests were two-tailed, performed at an alpha level of significance equal to 0.05.

Potential participants were informed about the study's aim and their right to withdraw from the study at any time. They were assured that their participation would remain anonymous. In addition, participants were fully briefed on all procedures involved in the study before they provided their consent to participate.

RESULTS

Sociodemographic Characteristics

A total of 1119 participants were included in the study. More than half (56.2%) were females, about 65.1% had completed higher education, and the mean age was 40.6 ± 16.7 years old.

Main Variable (Dependent or Outcome) Results

We observed that approximately 64% of the study participants reported having a sedentary lifestyle, and 35.5% were current smokers. The mean BMI of the participants was 25.0 ± 4.6 kg/m^2, with approximately 12% classified as obese (BMI >30 kg/m^2). Furthermore, when considering the components of MetS, we found that 11.8% of the participants had central obesity, 12.6% had hypertension, and 2.1% had type 2 diabetes [Table 1].

Table 1: Sociodemographic, lifestyle, and anthropometric characteristics of the study sample.

Characteristics	Overall (*n*=1119)
Sociodemographic characteristics	
Gender, *n*[a] (%)	
Female	629 (56.2)
Male	490 (43.8)
Mean age±SD (years)	40.6±16.7
Educational status, *n*[b] (%)	
Primary education	59 (5.3)
Secondary education	330 (29.6)
Higher education	725 (65.1)
Lifestyle characteristics	
Sedentary activity, *n*[a] (%)	
Irregular physical activity	720 (64.3)
No physical activity	399 (35.7)
Smoking, *n*[c] (%)	
Current smoker	395 (35.5)
Non-smoker	717 (64.5)
Exercise, n[d] (%)	
Physically active	578 (52.0)
Physically inactive	533 (48.0)
Anthropometric characteristics	
Mean BMI±SD (kg/m^2)	25.0±4.6
Obese, N[a] (%)	132 (11.8)
Metabolic syndrome	
Central obesity, *n*[a] (%)	
Yes	132 (11.8)
No	987 (88.2)
Hypertension, *n*[a] (%)	
Yes	141 (12.6)
No	978 (87.4)
Type 2 diabetes, *n*[a] (%)	
Yes	24 (2.1)
No	1095 (97.9)

SD: Standard deviation, BMI: Body mass index. *n*[a]=1,119; *n*[b]=1,114; *n*[c]=1,112; *n*[d]=1,111

Table 2: Health-related conditions or diseases overall, and by gender.

	Overall (*n*=1119)	Gender		*p*-value
		Female (*n*=629)	Male (*n*=490)	
Cardiovascular events				
Yes	27 (2.4)	12 (44.4)	15 (55.6)	0.21
No	1092 (97.6)	617 (56.5)	475 (43.5)	
Gastrointestinal diseases				
Yes	140 (12.5)	95 (67.9)	45 (32.1)	**<0.001**
No	979 (87.5)	534 (54.55)	445 (45.45)	
Rheumatic diseases				
Yes	29 (2.6)	21 (72.4)	8 (27.6)	0.07
No	1090 (97.4)	608 (55.8)	482 (44.2)	
CKD				
Yes	11 (1)	7 (63.6)	4 (36.4)	0.76
No	1108 (99)	622 (56.1)	486 (43.9)	

CKD: Chronic kidney disease. Bold values indicate statistically significant association (p<0.05).

The prevalence of cardiovascular events, gastrointestinal diseases, rheumatic diseases, and CKD was found to be 2.4%, 12.5%, 2.6%, and 1.0% respectively. We observed a statistically significant association between gender and the occurrence of gastrointestinal diseases. Among females, 67.9% had gastrointestinal diseases, while the corresponding percentage among males was 32.1% (p < 00.01) [Table 2].

In univariate analyses, hypertension (p < 0.01), age (p < 0.01), education status (p < 0.01), and exercise (p = 0.03) were statistically significant predictors of cardiovascular events. Similarly, hypertension, age, and gender (all p < 0.01) were statistically significant predictors of gastrointestinal diseases, while hypertension, age, and education status (all p < 0.01, and exercise (p = 0.02) were associated with rheumatic diseases. Furthermore, hypertension, DM2, age, education status (all p < 0.01), and central obesity (p = 0.02) were associated with CKD.

In the multivariate analysis, adjusting for age, gender, educational status, sedentary activity, exercise, and smoking, only age remained a statistically significant predictor of cardiovascular events (odds ratio [OR] = 1.06, 95% confidence interval [CI]: 1.03–1.09). Similarly, age (OR = 1.04, 95% CI: 1.02–1.05) and gender (OR = 0.50, 95% CI: 0.33–0.75) were statistically significant predictors of gastrointestinal diseases. As for rheumatic diseases, age (OR = 1.06, 95% CI: 1.03–1.09) and gender (OR = 0.34, 95% CI: 0.13–0.84) were found to be statistically significant predictors. However, none of the variables considered in the multivariate analysis showed a significant association with CKD [Table 3].

DISCUSSION

To the best of our knowledge, this population-based study is the first of its kind in the Cypriot population and provides information regarding the association between components of MetS, namely hypertension, DM2, and central obesity, with the following conditions or diseases: (i) Cardiovascular events, (ii) gastrointestinal diseases, (iii) rheumatic diseases, and (iv) CKD. The results showed a statistically significant association between hypertension with cardiovascular events,

Table 3: Multiple logistic regression of the predictors on cardiovascular events, gastrointestinal diseases, rheumatic diseases, and chronic kidney disease.

	Cardiovascular events			Gastrointestinal diseases			Rheumatic diseases			Chronic kidney disease		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Hypertension												
Yes	1.99	0.81, 4.90	0.135	1.38	0.82-2.33	0.231	2.21	0.89, 5.50	0.088	3.78	0.84, 17.04	0.083
DM2												
Yes	0.55	0.07, 4.63	0.579	0.49	0.14-1.77	0.277	0.61	0.07, 5.02	0.642	4.57	0.88, 23.62	0.070
Central obesity												
Yes	0.76	0.24, 2.39	0.637	1.04	0.59-1.82	0.905	0.56	0.16, 1.98	0.365	2.40	0.56, 10.32	0.239
Age	**1.06**	**1.03, 1.09**	**<0.001**	**1.04**	**1.02–1.05**	**<0.001**	**1.06**	**1.03, 1.09**	**<0.001**	1.01	0.96, 1.07	0.635
Gender												
Female	*Ref*			*Ref*			*Ref*			*Ref*		
Male	1.08	0.46, 2.54	0.860	**0.50**	**0.33–0.75**	**<0.001**	**0.34**	**0.13, 0.84**	**0.020**	0.27	0.06, 1.30	0.103
Educational Status												
Primary education	*Ref*			*Ref*			*Ref*			*Ref*		
Secondary education	0.69	0.26, 1.81	0.555	0.87	0.57–1.33	0.780	0.93	0.38, 2.31	0.791	1.71	0.32, 9.25	0.534
Higher education	0.83	0.25, 2.74	0.996	0.65	0.29–1.47	0.372	0.68	0.19, 2.48	0.570	7.13	0.95, 53.69	0.051
Sedentary Activity												
No physical activity	*Ref*			*Ref*			*Ref*			*Ref*		
Irregular physical activity	0.89	0.39, 2.00	0.776	1.26	0.85–1.88	0.254	0.61	0.28, 1.34	0.220	0.67	0.18, 2.46	0.544
Smoking												
Non-smoker	*Ref*			*Ref*			*Ref*			*Ref*		
Current smoker	0.59	0.23, 1.48	0.259	1.42	0.97–2.07	0.075	0.52	0.21, 1.30	0.164	0.99	0.22, 4.41	0.987
Exercise												
Physically inactive	*Ref*			*Ref*			*Ref*			*Ref*		
Physically active	1.73	1.73, 4.00	0.201	1.07	0.72–1.59	0.725	1.35	0.59, 3.12	0.479	3.51	0.81, 15.23	0.093

DM2: Type 2 diabetes, C.O: Central obesity, O.R: Odds ratio, CI: Confidence interval. Bold values indicate statistically significant association ($p<0.05$)

gastrointestinal diseases, and rheumatic diseases. In addition, the study suggested an association between hypertension, DM2, and CKD.

Hypertension, age, education status, and exercise were associated with cardiovascular events in our study in univariate analysis. These findings are consistent with the suggestions made by the NHS of the UK, which states that CVD is linked to hypertension, DM2, being overweight or obese, smoking, inactivity, higher age, and gender.[21] We observed that individuals with hypertension had higher odds of experiencing heart problems. This observation aligns with the findings of the Interheart study, which reported that hypertension is associated with an increased risk of myocardial infarction.[17] Furthermore, in our study, we found that individuals who completed only primary education had a higher probability of having heart problems compared to those who completed higher education. This finding is consistent with other studies suggesting that individuals with lower education levels in low-income and middle-income countries face a higher risk of major cardiovascular events compared to those with higher levels of education.[18] Low education can directly hinder an individual's ability to access effective care in various ways. It can lead to a lack of awareness regarding the importance of seeking timely care, reduced access to information on where and how to obtain care, and difficulties in overcoming existing barriers through formal channels and social networks.[18] In addition, individuals with lower socioeconomic status may face

challenges in affording necessary healthcare or reside in neighborhoods with limited access to healthcare facilities, particularly in countries without universal health coverage. Moreover, our analysis revealed that exercise has a protective effect against cardiovascular events. This finding is supported by a review study that highlighted how increasing physical activity levels over time are associated with a reduced risk of coronary heart disease and CVD mortality.[22]

Furthermore, our study revealed that individuals with hypertension have increased odds of reporting gastrointestinal diseases in univariate analysis. This finding is consistent with another study suggesting that genetically predicted higher systolic BP may have a causal effect on the risk of inflammatory bowel disease, including both ulcerative colitis and Crohn's disease.[23] Interestingly, in our study, we found that females appear to have a protective effect against gastrointestinal diseases, with the odds of developing gastrointestinal diseases being 43% lower in females compared to males. This contrasts with the results of another study that indicated a higher prevalence of conditions such as functional dyspepsia and irritable bowel syndrome in women.[24] That study further suggested that among patients with irritable bowel syndrome, women are more likely to experience severe symptoms and coexisting anxiety or depression.[24] It is important to note that our study did not examine the specific connection between biological disturbances (such as persistent mucosal inflammation after acute gastroenteritis), environmental factors (such as abuse), psychological stressors, and their influence on altering gastrointestinal tract motility and/or sensation, leading to symptoms.

In relation to rheumatic diseases, our results found a statistically significant association between education status and this group of diseases in univariate analysis. This finding is partially supported by another study, which suggested that higher educational attainment is associated with lower relative odds of rheumatoid arthritis (with 63% lower odds for every additional 4.2 years of education).[25] The same study also noted that education, as a proxy for socioeconomic deprivation, may be associated with other important environmental risk factors that increase the risk of rheumatoid arthritis.[25] In addition, our study revealed a higher probability of having rheumatic diseases in individuals with hypertension compared to those without hypertension. This finding aligns with another study that reported mean BP as the most consistent predictive factor for rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis.[26] Regarding exercise, our analysis indicated a protective effect against gastrointestinal diseases. Specifically, mild-to-moderate intensity exercises are associated with a protective role against colon cancer, diverticular disease, cholelithiasis, and constipation. However, acute strenuous exercise may induce symptoms such as heartburn, nausea, vomiting, abdominal pain, diarrhea, and even gastrointestinal bleeding.[27]

Even though the number of participants with CKD was small in our study, we observed that individuals with only primary education had a higher probability of having CKD compared to those with higher education in univariate analysis. This finding is consistent with other studies indicating that CKD is more prevalent among individuals with low socioeconomic status, which includes factors such as education, occupation, and income.[28] In addition, our study found a higher probability of CKD in individuals with DM2 and hypertension. These results align with the common understanding that DM2 is frequently associated with CKD and end-stage renal disease.[29] Furthermore, CKD has been linked to diabetes and hypertension in developed countries.[30]

Strengths and limitations of the study

It is important to acknowledge the limitations of our study. First, we employed a cross-sectional design, which means that we could only examine associations between outcomes and predictors, not establish causal relationships. Furthermore, we did not apply survey weighting, and institutionalized individuals were excluded from the sample, which might have led to an underestimation of the prevalence of the diseases under investigation. Despite these limitations, our study possesses several strengths. It is a large population-based study that employed a representative sample of both men and women across all age groups (18+) and geographical areas of Cyprus. In addition, detailed data were collected from participants, including information on multiple diseases and risk factors, utilizing a validated questionnaire.

CONCLUSION AND IMPLICATIONS FOR TRANSLATION

Hypertension appears to play an important role in heart conditions, gastrointestinal diseases, rheumatic diseases, and CKD. It also seems that DM2 and central obesity are associated with CKD and that age and gender are relevant factors in the conditions considered. Furthermore, hypertension, type 2 diabetes, and obesity can potentially be prevented or managed to some extent. By addressing these modifiable risk factors, we can reduce the incidence of these conditions, thereby decreasing morbidity and mortality rates and improving overall health. Countries should develop public health awareness and intervention programs to educate and inform people about healthy lifestyles, which will help better cope with these conditions.

Key Messages

1) Hypertension Blood Pressure (BP) appears to play an important role in heart conditions, gastrointestinal diseases, rheumatic diseases, and chronic kidney disease (CKD). 2) Type II diabetes (DM2) and central obesity are associated

with CKD and that age and gender are also relevant factors associated with the conditions considered. 3) Countries should develop public health awareness and intervention programs to educate and inform people regarding healthy lifestyles, in general, which will help better cope with these conditions.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest: The authors declare no competing interests. **Financial disclosure:** Nothing to declare. **Funding/Support:** There was no funding for this study. **Ethics approval:** The study was approved by the Cyprus National Bioethics Committee (CNBC) (ΕΕΒΚ ΕΠ 2018.01.123), dated 18 July 2018. **Declaration of patient consent:** Patient's consent is not required as there are no patients in this study. **Use of artificial intelligence (AI)-assisted technology for manuscript preparation**: The author confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI. **Disclaimer:** None.

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