Vascular Health and Risk Management

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ORIGINAL RESEARCH

Coexistence of Standard Modifiable, Other Classical, and Novel and Classical Atherosclerotic Cardiovascular Disease Risk Factors in Middle Eastern Young Women

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Background: The coexistence of multiple standard modifiable risk factors (SMuRFs),classical and novel risk factors (RFs) for atherosclerotic cardiovascular disease (ASCVD) is common in the Middle East (ME). There is a paucity of data on the coexistence of these RFs in ME young women.

Aim: Comparing the prevalence and the statistical patterns of the SMuRFs, classical and novel RFs in target population.

Methods: In this case-control (1:2) study, consecutive young women aged 18–50 years were enrolled in 12 centers (July 2021 to October 2023). Prevalence and coexistence of 19 RFs were compared between cases with ASCVD and their controls. The RFs included SMuRFs (hypertension, type 2 diabetes, dyslipidemia, and cigarette smoking), other classical RF (obesity, family history of premature ASCVD, and physical inactivity), novel RFs and social determinants of health (health insurance, place of residence, depression, and level of education).

Results: The study included 627 subjects; 209 had ASCVD (median age 46 years, IQR 49–42 years) and 418 controls (median age 45 years, IQR 48–41 years). The presence of 1–2 RFs; (ASCVD: 63.2%, Control: 54.1%, p=0.037) and 3–4 RFs; (ASCVD: 27.8%, Control: 3.3%, $p < 0.001$) SMuRFs was more prevalent in women with ASCVD. Similarly, the presence of 4–5 RFs; (ASCVD: 40.7%, Control: 14.6%, p<0.001), and 6–7 (ASCVD: 10.5%, Control: 1%, $p < 0.001$). The classical RF were also significantly common in these women. The distribution of multiple novel RF was not statistically significant across both groups. Finally, regarding the socioeconomic RFs in women with ASCVDs, the presence of 1–2 RFs (ASCVD: 59.8%, Control: 76.1%, $p < 0.001$) was significantly less common while the presence of 3–4 RFs (ASCVD: 39.2%, Control: 21.8%, $p < 0.001$) was vastly more common.

Conclusion: An elevated rate of coexistence of classical RF in the case group, mainly socioeconomic and SMuRFs. By managing them primary and secondary ASCVDs prevention attained.

Keywords: atherosclerotic cardiovascular disease, multiple standard modifiable risk factors, classical cardiovascular disease, novel risk factors

Received: 10 March 2024
Accepted: 30 June 2024
Published: 8 July 2024

Introduction

Atherosclerosis is a chronic inflammatory disease involving multiple organs' arterial beds, leading to formation of plaques that tend to progress with time and culminate in plague rupture, which causes acute myocardial infarction and stroke.[1–4] Notably, atherosclerotic cardiovascular disease (ASCVD) stands as the leading cause of global mortality.[5–7] Various risk factors contribute to ASCVD, categorized as, classical risk factors, which include obesity, physical activity, family history of premature ASCVD, and standard modifiable risk factors (SMuRFs) that encompass hypertension, type 2 diabetes, elevated serum low-density lipoprotein cholesterol (LDL-C) Levels, and smoking.[7,8] Social determinants of health (SDH) include depression, urban living, low level of education, and lack of health insurance.[9,10] Additionally, women of childbearing age can be subjected to a new subset of novel risk factors for ASCVD, which include preterm delivery, hypertensive disease of pregnancy, gestational diabetes, polycystic ovarian disease (PCOS), premature menopause, radiation for breast cancer, persistent weight gain after pregnancy,[11–14] While ASCVD typically affects the elderly population,[15,16] nevertheless there is a rising recognition of the occurrence among young women, who constitute a unique demographic group despite their age, this cohort faces a distinct set of challenges in terms of diagnosis and management of AsCVD, which may differ from their elder counterparts.[17,18] Understanding the interplay and coexistence of these risk factors is crucial for providing effective healthcare to this demographic.[19] Several studies worldwide and more so in the Middle East, evaluated the ASCVD RFs in adult populations.[20–25] However, there is a scarcity of studies that addressed the coexistence of these RFs, especially in SMuRFs. In this analysis of the atherosclerotic novel and classical risk factors in Young Women in the Middle East (ANCORS-YW), we report the prevalence and coexistence of 19 RFs in a cohort of Middle-Eastern young women.

Materials and Methods

Inclusion Criteria

The ANCORS-YW study consecutively enrolled married women aged 18–50 years diagnosed with ASCVD, and who had at least one pregnancy. Each patient with ASCVD was age-matched (±5 years) with two women not known to have ASCVD. ASCVD included acute coronary syndrome (ACS) (ST-segment elevation MI, non-ST-segment elevation MI, and unstable angina), and coronary artery disease (CAD) diagnosed by coronary computed tomographic angiography. It also included stroke and transient ischemic attack (diagnosed by a neurologist based on standard clinical and imaging criteria), extracranial carotid artery disease (diagnosed by the presence of atherosclerosis of the common or internal carotid artery evident by arterial Doppler, computed tomographic, or invasive angiography), and peripheral arterial disease (PAD) of the lower extremities (lower extremity ischemic pain and/or atherosclerosis evident by arterial Doppler, computed tomographic, or invasive angiography).

Study Design and Settings

A case-control, multicenter study was conducted in the period between August 2021 and October 2023 in 12 hospitals.

Data Collection

Using a standard case report from included anthropometric and demographic profiles, novel and classical RFs, and social determinants of health (SDOH); place of residence, level of education, depression, and presence of health insurance were documented in the patients and controls.

Sample Size Calculation

With a significance level of 0.05, a power of 80%, and assuming a frequency of any one of the studied variables to be 10%, we have calculated the minimum sample size required to detect a clinically significant association (odds ratio = 2) between ASCVD and any of the studied predictors, maintaining a 1:2 case-to-control ratio. The computed sample size was 209 cases and 418 controls.

Definitions of Classical RFs Including SMuRFs

Hypertension (HTN) was defined as repeated resting blood pressure (BP) measurements > 140/90 mm Hg, a prior diagnosis by a treating physician, or use of BP medications. Type 2 diabetes was defined as the presence of classical symptoms of hyperglycemia and casual plasma glucose ≥ 200 mg/dl, fasting plasma glucose ≥ 126 mg/dl; serum level of glycated hemoglobin ≥ 6.5 a prior diagnosis by a physician for use of antidiabetic medications. Dyslipidemia was defined as an elevated serum level of low-density lipoprotein cholesterol LDL-C > 70 mg/dl in those with ASCVD or T2D, while LDL > 116 mg/dl in those with no ASCVD nor T2D or use of lipid-lowering agents. Low serum level of high-density lipoprotein cholesterol (HDL-C) was defined as serum levels < 50 mg/dl. Body mass index was calculated by the standard formula (weight (kg)/height (m2)). Diagnosis of metabolic syndrome was confirmed by the presence of at least three of the following criteria: HTN, obesity (BMI ≥ 30 kg/m2), known case of DM, serum level of HDL-C < 50 mg/dl, and serum level of triglycerides > 150 mg/dl.

Definitions of Novel RFs

Preterm delivery was defined as a live delivery before 37 weeks and after 20 weeks of gestation. Hypertensive disorders during pregnancy (HDP) was defined as gestational HTN taking place after 20 weeks of gestation. Chronic HTN was defined as a preexisting disease before the 20th week of gestation, pre-eclampsia was defined as hypertension after the 20th week of gestation and proteinuria, and eclampsia defined as seizures not attributable to other causes in the presence of preeclampsia. Gestational DM was diagnosed if one or more of the following criteria aremet: fasting plasma glucose ≥ 126 mg/dl, 2-h plasma glucose ≥ 200 mg/dl following oral glucose load, or random plasma glucose ≥ 200 mg/dl in the presence of diabetes symptoms.

Polycystic ovary syndrome (PCOS) was defined by the presence of two clinical or biochemical hyperandrogenism features, ovulatory dysfunction, or polycystic ovaries. Premature menopause was defined as oligo-amenorrhea of more than 12 months associated with serial elevated gonadotropins on three occasions measured 4–6 weeks apart in women under the age of 40 years.

Depression was defined as prior diagnosis by a psychiatrist, or prescription of antidepressant medication.

Ethical Approval

The study received proper ethical oversight and Institutional Review Board approval from Price Hamza Hospital Institutional Review Board (IRB) committee number10165\ابحاث\ح م. The study complies with the declaration of Helsinki and each study participant has given consent to participate as well as consent to publish the data. The study is registered with ClinicalTrials.gov (NCT04975503).

Statistical Analysis

Frequencies and percentages were used to describe categorical variables. Means and standard deviations were used to describe normally distributed continuous variables, while median and interquartile ranges (IQR) were used to describe not normally distributed continuous variable. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess normality of continuous variables. Not normally distributed continuous variables were compared using the Mann–Whitney test, while Student's *t*-test was used to compare normally distributed continuous variables. The chi-square test was used for to compare between categorical variables. Data analysis was carried out using Stata version 17 software (StataCorp. 2021). A two-sided p-value of less than 0.05 was considered statistically significant.

Results

A total of 627 women were included in this study, with a mean age of 44.2 years. Table 1 depicts the demographic and clinical profiles of the whole cohort. The mean BMI was 29.54 kg/m2. Most of the study participants were obese (43.4%) or overweight (33.5%). The most prevalent comorbidity was hypertension (37%). Regarding abnormalities in lipid profile, 31.9% of the females had elevated LDL and 19.8% of low HDL. The most common medication group was lipid lowering medications (39.1%) followed by beta-blockers (38.44%) and antiplatelets (36.0%).

Table 1 Demographics and Clinical Characteristic Among Middle Eastern Young Women

	Number	Percentage
Mean Age (years)	44.15	–
Age groups		
21–30	13	2.07
31–40	114	18.18
41–50	500	79.74
Mean BMI (kg/m^2)	29.54	–
BMI category		
Underweight	8	1.28
Normal	135	21.53
Obese	274	43.70
Overweight	210	33.49
Smoking		
Smoker	183	29.19
Non-smoker	444	70.81
Ex-smoker	25	3.98
Second-hand smoking	124	19.78
Physical inactivity	469	74.80
Educational level		
Secondary school or less	387	61.72
Bachelor's degree and higher	240	38.27
Urban Residence	463	73.84
Lack of Health insurance	387	61.72
Comorbidities and risk factors		-
ASCVD	209	33.33
HTN	232	37.00
DM	132	21.05
Heart failure	28	4.47
Sleep apnea	8	1.28
HDP	15	2.39
GDM	78	12.44
Preterm delivery	125	19.94
Persistent weight gain after pregnancy	120	19.14
Premature menopause	62	9.89

(*Continued*)

Table 1 (Continued).

	Number	Percentage
PCOS	42	6.70
Breast cancer	5	0.80
Autoimmune disease	31	4.94
Depression	54	8.61
Family history or premature ASCVD	199	31.74
Lipid profile		
Total cholesterol (mg/dl)	205.5	-
Elevated total cholesterol (>240 mg/dl)	65	10.37
Triglyceride (mg/dl)	190.3	-
Elevated triglyceride (>150 mg/dl)	128	20.41
LDL (mg/dl)	127.23	-
Elevated LDL (>70 mg/dl) with ASCVD/DM, >116 mg/dl with no DM/ASCVD)	200	31.90
HDL (mg/dl)	46.34	-
Low HDL (<45mg/dl)	124	19.78
Medication groups		
Antiplatelets agents	226	36.04
Lipid-lowering agents	245	39.07
Beta-blockers	241	38.44
RAAS inhibitors	169	26.95
OACs	18	2.87
Diuretic	63	10.05
OHA	82	13.08
Insulin	21	3.35
Hormone replacement therapy	11	1.75
Other	128	20.41

The distribution of classical (traditional), novel, and socioeconomic risk factors among the whole group of young women is demonstrated in Table 2. Among traditional risk factors, the presence of HTN (ASCVD: 56.46%, Control: 27.27%, $p < 0.001$), DM (ASCVD: 39.71%, Control: 11.72%, $p < 0.001$), smoking (ASCVD: 39.23%, Control: 24.16%, $p < 0.001$), elevated LDL levels (ASCVD: 54.55%, Control: 20.57%, $p < 0.001$), family history or premature ASCVD (ASCVD: 48.33%, Control: 23.44%, $p < 0.001$) were significantly more common in females with ASCVD. For novel risk factors, the prevalence of hypertensive disease of pregnancy (ASCVD: 30.62%, Control: 22.73%, $p = 0.32$), gestational DM (ASCVD: 16.75%, Control: 10.29%, $p = 0.021$), and pre-term delivery (ASCVD: 26.32%, Control: 16.75%, $p = 0.005$) was significantly more in ASVCD females. Regarding SDOH risk factors, low level of education (ASCVD: 74.64%, Control: 55.26%, $p<0.001$), and health insurance (ASCVD: 71.29%, Control: 56.94%, $p < 0.001$) were significantly more prevalent among females with ASCVD.

Table 2 The Distribution of Classical (Traditional), Novel, and Socioeconomic RF Among the Study Group with ASCVD and Their Controls

RF	ASCVD women (n=209)	Control Women (n=418)	Total (n=627)	P-value
7 Traditional (Classical) RF				
HTN	118 (56.5%)	114 (27.3%)	232 (37%)	<0.001
DM	83 (39.7%)	49 (11.7%)	132 (21.1%)	<0.001
Smoking	82 (39.2%)	101 (24.2%)	183 (29.2%)	<0.001
LDL >70 with ASCVD/DM, >116 with no DM/ASCVD	114 (54.6%)	86 (20.6%)	200 (31.9%)	<0.001
BMI≥30	95 (45.5%)	174 (41.6%)	269 (42.9%)	0.361
Family history or premature ASCVD	101 (48.3%)	98 (23.4%)	199 (31.7%)	<0.001
Physical inactivity	162 (77.5%)	307 (73.4%)	469 (74.8%)	0.269
8 Novel RF				
HDP	64 (30.6%)	95 (22.7%)	159 (25.4%)	0.032
GDM	35 (16.8%)	43 (10.3%)	78 (12.4%)	0.021
Preterm delivery	55 (26.3%)	70 (16.8%)	125 (19.9%)	0.005
Persistent weight gain after pregnancy	31 (14.8%)	89 (21.3%)	120 (19.1%)	0.053
Premature menopause	20 (9.6%)	42 (10.1%)	62 (9.9%)	0.850
PCOS	14 (6.7%)	28 (6.7%)	42 (6.7%)	1.000
Radiation breast cancer	1 (0.5%)	4 (1.0%)	5 (0.8%)	0.525
Autoimmune disease	14 (6.7%)	17 (4.1%)	31 (4.9%)	0.152
4 Socioeconomic RF				
Low level of education	156 (74.7%)	231 (55.3%)	387 (61.7%)	<0.001
Urban Residence	148 (70.8%)	315 (75.4%)	463 (73.8%)	0.222
Depression	18 (8.6%)	36 (8.6%)	54 (8.6%)	1.000
Lack of health insurance	149 (71.3%)	238 (56.9%)	387 (61.7%)	<0.001

The coexistence of multiple risk factors in the study group is demonstrated in Table 3. The present study found that the presence of 1–2 (ASCVD: 63.2%, Control: 54.1%, p=0.037) and 3–4 (ASCVD: 27.8%, Control: 3.3%, $p < 0.001$) SMuRRFs was more prevalent in females with ASCVD. On contrast, the presence of 0 SMuRRFs was more prevalent in females without ASCVD (ASCVD: 9.1, Control: 42.6%, $p < 0.001$). In females with ASCVDs, the presence of 4–5 (ASCVD: 40.7%, Control: 14.6%, p<0.001), and 6–7 (ASCVD: 10.5%, Control: 1%, $p < 0.001$) classical risk factors were significantly more common, while the presence of 0 (ASCVD: 0%, Control: 5.02%, p=0.002) and 1–3 (ASCVD: 48.8%, Control: 79.4%, $p < 0.001$) classical risk factors were significantly less common. The distribution of multiple novel risk factors was not statistically significant across both groups.

Finally, regarding the socioeconomic risk factors in women with ASCVDs, the presence of 1–2 risk factors (ASCVD: 59.8%, Control: 76.1%, $p < 0.001$) was significantly less common, while the presence of 3–4 risk factors (ASCVD: 39.2%, Control: 21.8%, $p < 0.001$) was significantly more common.

A detailed breakdown of risk factor patterns in Middle Eastern young women with ASCVD and controls is demonstrated in Supplementary Table 1.

Table 3 Coexistence of Multiple RF in Middle Eastern Young Women with ASCVD and Their Controls

Risk Factors	Young Women with ASCVD (N=209)	Young Women with no ASCVD (N=418)	p-value
SMuRFs			
0 RF	19 (9.1%)	178 (42.6%)	<0.001
1–2 RFs	132 (63.2%)	226 (54.1%)	0.037
3–4 RFs	58 (27.8%)	14 (3.3%)	<0.001
All Classical RFs			
0 RF	0 (0%)	21 (5.02%)	0.002
1–3 RFs	102 (48.8%)	332 (79.4%)	<0.001
4–5 RFs	85 (40.7%)	61 (14.6%)	<0.001
6–7 RFs	22 (10.5%)	4 (1.0%)	<0.001
Novel RFs			
0 RF	73 (34.9%)	165 (39.5%)	0.302
1–2 RFs	115 (55.0%)	225 (53.8%)	0.842
3–5 RFs	20 (9.6%)	28 (6.7%)	0.260
6–8 RFs	1 (0.5%)	0	0.682
Socioeconomic RFs			
0 RF	2 (1.0%)	0 (0%)	0.189
1–2 RFs	125 (59.8%)	318 (76.1%)	<0.001
3–4 RFs	82 (39.2%)	91 (21.8%)	<0.001

Discussion

The study's findings provide crucial insights into the simultaneous presence of risk factors (RFs) and their correlation with ASCVD within this demographic. The research indicates that the co-occurrence of SMuRFs, socioeconomic RFs, and all classical RFs was notably higher in the ASCVD group compared to those without ASCVD. These findings align with prior studies, including one conducted in South Korea in 2019,[26] which also demonstrated a significant association between RFs and ASCVD. Similarly, a recent study published in 2023 found that a family history of smoking and obesity was linked to future cardiovascular disease.[27] By emphasizing the elevated prevalence of these risk factors, our study sheds light on the complex interplay between health-related behaviors, social determinants, and ASCVD risk among young women in the Middle Eastern region. This comprehension can guide targeted interventions aimed at mitigating the burden of ASCVD. This aligns with established evidence indicating the multifactorial nature of ASCVD etiology and underscores the importance of adopting a comprehensive approach to cardiovascular risk assessment and management. Furthermore, our study contributes to addressing existing gaps in the literature by specifically focusing on ASCVD risk factors in a population that has been historically underrepresented in cardiovascular research.

Despite its contributions, our study has several limitations that warrant consideration. Firstly, there is the potential for selection bias since participants were recruited from tertiary care centers, which may not be fully representative of the entire Middle Eastern population of young women with ASCVD, thus limiting the generalizability of our findings. Additionally, as is the case with all registries, the presence of difficulty to remember past medical history or lifestyle

factors. Moreover, while our study primarily focused on classical and socioeconomic risk factors, we did not extensively investigate other potentially relevant factors such as dietary habits, environmental exposures, and genetic predispositions, which could have provided a more comprehensive understanding of ASCVD risk in studied population. Finally, the lack of significant differences in the coexistence of novel risk factors (eg, preterm delivery and breast cancer) between the ASCVD and control groups may suggest that these factors may not exert as significant an influence on ASCVD development in young women, at least within the scope of this study.

Our study's findings offer critical perspectives into the nuanced landscape of risk factors for atherosclerotic cardiovascular disease (ASCVD) among young women in the Middle Eastern region. By delineating the varying contributions of different risk factors to ASCVD risk in this population, our research underscores the imperative for further investigation into the role of novel risk factors in ASCVD pathogenesis. Moreover, our findings prompt a reassessment of current preventive strategies, emphasizing the necessity for targeted interventions that prioritize modifiable risk factors and promote holistic cardiovascular health among young women in the Middle East. Catalyzing these transformative changes, our study holds the potential to propel significant advancements in cardiovascular care, foster interdisciplinary collaborations, and ultimately contribute to the realization of healthier, more equitable societies. Importantly, our study's implications extend beyond research domains into clinical practice, public health policy, and societal well-being. By highlighting the prevalence of coexisting classical and socioeconomic risk factors, particularly emphasizing the significance of SMuRFs, our findings underscore the multifaceted nature of ASCVD in this demographic, emphasizing the importance of addressing both traditional cardiovascular risk factors and socioeconomic determinants in preventive and management strategies.

Conclusion

Huge challenges in preventing ASCVD in ME patient including Jordan, therefore tackling this burden is of utmost importance. Our study has demonstrated that in ME young women with ASCVD, had a high rate of coexistence of classical risk factors (SMuRFs in particular) and socioeconomic RFs. Insights into clustering patterns of risk factors are important for both the physician and the patient as it may guide management and prioritize the primary and secondary prevention strategies. Larger studies are needed to consolidate this data and evaluate the presence of non-traditional risk factors in this vulnerable population.

Data Sharing Statement

In accordance with the data-sharing guidelines outlined by Dove Medical Press, we express our dedication to disseminating individual, de-identified participant data originating from our registry. The specific dataset earmarked for sharing encapsulates the information employed throughout this study. Access to the data will be facilitated exclusively through the corresponding author, reachable at wessam.alsaud@gmail.com. Initiating on July 1, 2024, we anticipate that the data will be accessible for a period of six months.

Acknowledgments

The authors would like to thank the following members of the study investigators team who enrolled patients for the study Aladdin Ababneh, Asil Jallad, Basel Y. Abushammala, Ahmad Aldabbas, Ahmad Alshraideh, Ahmad Al Fakhouri, Ahmad Tawalbeh, Amr Ababneh, Amr Said, Asmaa Saad Basha, Aya Hassan, Baraa Khadrawi, Bayan Omari, Caroline Sabanekh, Deema Bani YouniS, Dina Rasheed, Farah Najdawi, Farah Qasem, Joud Shehadeh, Hadeel Al Emam, Hadeel Asfour, Hammam Abuaisheh, Hamzeh Ikari, Hebah AlShabatat, Layan Ababneh, Layan Attili, Lina Amairi, Leen Sawalha, Maha Abu Ajamieh, Maher Younis, Mahmoud Dardas, Mohammad Eshbair, Mahmoud Qushteh, Mohammad Bani Bakr, Mohammad Bahhour, Mohammad Jum'ah, Mohammed Khaled, Mohannad Abdelhadi, Majeda Jallad, Raghad Abuhalimeh, Rasheed Ibdah Saad A Mahmoud, Safa Amro, Said Al-Najjar, Sara Durgham, Tahani Hayek, Taimaa Fkhaideh, Tala Abdallat, Tareq Abdallah, Tariq Alrawajih, Zaid Ababneh.

Disclosure

The authors report no conflicts of interest in this work.

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