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Original Article

Role of sex and gender-related variables in development of metabolic syndrome: A prospective cohort study

Pouria Alipour [a,b,1], Zahra Azizi [a,1], Valeria Raparelli [c,d,e], Colleen M. Norris [e,f], Alexandra Kautzky-Willer [g], Karolina Kublickiene [h], Maria Trinidad Herrero [i], Khaled El Emam [j,k,l], Peter Vollenweider [m], Martin Preisig [n], Carole Clair [o,2], Louise Pilote [a,p,2,*]

[a] Centre for Outcomes Research and Evaluation, McGill University Health Centre Research Institute, Montreal, QC, Canada
[b] Faculty of Medicine, McGill University, Montreal, Canada
[c] Department of Translational Medicine, University of Ferrara, Ferrara, Italy
[d] University Center for Studies on Gender Medicine, University of Ferrara, Ferrara, Italy
[e] Faculties of Nursing, Medicine and School of Public Health, University of Alberta, Edmonton, Alberta, Canada
[f] Heart and Stroke Strategic Clinical Networks-Alberta Health Services, Alberta, Canada
[g] Department of Internal Medicine III, Division of Endocrinology and Metabolism, Gender Medicine Unit, Medical University of Vienna, Vienna, Austria
[h] Department of Clinical intervention, Science and Technology (CLINTEC), Section for Renal Medicine, Karolinska Institute and Karolinska University hospital, Stockholm, Sweden
[i] Clinical & Experimental Neuroscience (NiCE-IMIB-IUIE), School of Medicine. University of Murcia, Murcia, Spain
[j] Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
[k] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario. Canada
[l] Replica Analytics Ltd, Ottawa, Ontario, Canada
[m] Department of Medicine, Internal Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[n] Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[o] Center for Primary Care and Public Health, University of Lausanne, Lausanne, Switzerland
[p] Divisions of Clinical Epidemiology and General Internal Medicine, McGill University Health Centre Research Institute, Montreal, QC, Canada

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ABSTRACT

Introduction: The burden of metabolic syndrome (MetS) and its components has been increasing mainly amongst male individuals. Nevertheless, clinical outcomes related to MetS (i.e., cardiovascular diseases), are worse among female individuals. Whether these sex differences in the components and sequalae of MetS are influenced by gender (i.e., psycho-socio-cultural factors)) is a matter of debate. Therefore, the purpose of this study was to determine the association between gender-related factors and the development of MetS, and to assess if the magnitude of the associations vary by sex.

Method: Data from the Colaus/PsyColaus study, a prospective population-based cohort of 6,734 middle-aged participants in Lausanne (Switzerland) (2003–2006) were used. The primary endpoint was the development of MetS as defined by the Adult Treatment Panel III of the National Cholesterol Education Program. Multivariable models were estimated using logistic regression to assess the association between gender-related factors and the development of MetS. Two-way interactions between sex, age and gender-related factors were also tested.

Results: Among 5,195 participants without MetS (mean age=51.3 ± 10.6, 56.1 % females), 27.9 % developed MetS during a mean follow-up of 10.9 years. Female sex (OR:0.48, 95 %CI:0.41–0.55) was associated with decreased risk of developing MetS. Conversely, older age, educational attainment less than university, and low income were associated with an increased risk of developing MetS. Statistically significant interaction between sex and strata of age, education, income, smoking, and employment were identified showing that the reduced risk of MetS in female individuals was attenuated in the lowest education, income, and advanced age strata. However, females who smoke and reported being employed demonstrated a decreased risk of MetS compared to

* Corresponding author.
E-mail address: Louise.pilote@mcgill.ca (L. Pilote).
[1] First co-authors.
[2] Co-senior authors.

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males. Conversely smoking and unemployment were significant risk factors for MetS development among male adults.

Conclusions: Gender-related factors such as income level and educational attainment play a greater role in the development of MetS in female than individuals. These factors represent novel modifiable targets for implementation of sex- and gender-specific strategies to achieve health equity for all people.

1. Introduction

Metabolic syndrome (MetS), defined as clustering of abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure, is strongly associated with cardiovascular related mortality and morbidity around the world [1,2]. According to the World Health Organization (WHO) definition, the population attributable risks of MetS for the development of cardiovascular disease (CVD) and mortality are 17 % and 7 %, respectively [2,3]. In addition, individuals with MetS are at an increased risk of other diseases including prothrombotic and proinflammatory states, non-alcoholic fatty liver disease, and reproductive disorders [1,3,4]. Modernization, and industrialization, which contribute to the reduction of daily activity levels (i.e., sedentary lifestyle) and poor diet (i.e., over-eating) are some of the most studied contributors to the global rise in the prevalence of MetS [5,6]. Beyond biological sex, the question is to whether social determinants of health (SDOH) influence these changing trends remains to be determined.

Various factors are implicated in the development and control of the components of MetS [7–9] and while a majority of studies have investigated the physiological processes implicated in the development of MetS [7–9], few studies have investigated the interplay between biological sex and sociocultural gender. Whereas sex refers to an individual's biological/genetic makeup, gender encompasses the psycho-socio-cultural aspects of one's roles, relationships, identity, and institutions, including SDOH, and may be associated with the development of MetS [10]. Furthermore, the interactions between gender and other social factors may vary between males and females, reflecting the unique contributions of the culture/country where a person lives [10–13].

From a sex-specific perspective, the incidence of MetS is higher in males, but females with MetS are at higher risk for CVD [3,14,15]. Amongst the MetS components, females are more likely to experience abdominal obesity and dyslipidemia, while males are reported to be at higher risk of diabetes mellitus and hypertension [16].

In contrast to sex-related factors, the role of gender-related factors such as income level and educational attainment play in the development of MetS, has been less explored and needs to be better elucidated [17,18]. In fact, gender-related factors may partially explain the difference that exists amongst sexes in development of MetS and CVD sequalae. By understanding their underlying role in the development and progression of MetS, preventative approaches might be designed and applied to decrease the likelihood of developing MetS and consequently CVD. Therefore, the purpose of this study was to investigate the role of gender-related variables in development of MetS amongst male and female adults in a prospective cohort study.

2. Methods

The CoLaus (Cohorte Lausannoise)/PsyColaus study is a population-based cohort including subjects, aged 35 to 75 years living in Lausanne, Switzerland, with the goal of investigating the biological, genetic, and environmental determinants of cardiovascular risk factors [19]. A detailed description of the study has been previously published [19]. Briefly, the study includes a sample of 6733 middle-aged, mainly Caucasian participants randomly selected and recruited between 2003 and 2006, from Lausanne, a town of 117,161 inhabitants (79,420 Swiss nationality) in Switzerland. Inclusion criteria were written informed consent and age 35–75 years. Baseline data were collected at the outpatient clinic in the center Hospitalier Universitaire Vaudois (CHUV). Five years follow up data collection occurred in 2009, 2014, and 2018. For the purposes of this study, baseline (2003–2006), and follow-up data (2009–2012) and (2014–2017) from the CoLaus registry were used to conduct a secondary analysis investigating the impact of sex and gender-related factors in the development of MetS. This cohort was selected because of the extensive availability of gender-related factors.

2.1. Endpoints

The primary endpoint was the development of MetS as defined by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) [20,21], European [22], and the Canadian diabetes guidelines [23] [presence of ≥3 of the following risk factors: 1) waist circumference ≥102 cm for males and ≥88 cm for females; 2) elevated triglycerides (≥1.7 mmol/L); 3) reduced HDL-C (<1.0 mmol/L for males and <1.3 mmol/L for females); 4) elevated blood pressure (systolic ≥130 and/or diastolic ≥85 mmHg) or use of antihypertensive drugs, and 5) elevated fasting plasma glucose (≥5.6 mmol/L) or medical treatment of hyperglycaemia] in either the first or second follow-up visits (first follow-up: 5.6 (4.5–8.8) years, second follow-up: 10.9 (0.8–15.1) years). Participants with three or more risk factors were considered to have MetS. Individuals with MetS at baseline were excluded from analysis [20,23] (Fig. 1).

2.2. Gender-related variables

The GOING-FWD consortium, focused on the study of sex, sociocultural gender, and chronic non-communicable diseases (https://www.mcgill.ca/going-fwd4gender/), proposed a systematic multistep approach to measure gender in retrospective studies. This approach was utilized to identify gender-related variables and outcomes as well as for data analysis [24]. Gender-related factors were classified based on the Women's Health Research Network's gender framework [25] (i.e. gender identity, gender roles, gender relations and institutionalized gender) and included employment status, occupation category, living with children, marital/partnered status, educational level attainment, personal income, presence of anxiety and/or depression, antidepressant medication use, and behavioural factors including alcohol consumption and smoking. To obtain the occupational category at baseline and follow-up periods, participants were asked "Which is your current occupation" (10 possible answers). The response was then categorized into high (entrepreneurs, professionals, managers), middle (self-employed, middle managers, skilled clerks), and low (service-oriented clerks, farmers, manual workers) [26].

2.3. Statistical analyses

Categorical variables are reported as frequencies and percentages. Continuous variables are reported as means ±standard deviations for normally distributed data and medians (IQR) for skewed data. Baseline characteristics for all participants were stratified (by in MetS and sex categories) and compared using *t*-test and chi-square for continuous and discrete variables, respectively. Non-parametric equivalent tests were used in non-normal distributions. Summaries of all variables were explored and plotted to assess missingness. After assessing the pattern of missingness (missing at random or non-random), a multiple imputation

by chained equations (MICE) method, in which missing data are imputed based on the distribution of other variables in the dataset, was utilized for analysis of the data.

Bivariate and multivariable models were estimated using logistic regression to assess the association between gender-related factors and development of MetS over the follow-up period. All models included sex and other covariates based on their clinical relevance and bivariate analyses. Two different bivariate and multivariable models were employed for predicting MetS in the cohort. The first model type was used to report the main effect of sex in addition to gender-related variables as independent variables. The second type included repeated sets of models including two-way interactions between each gender-related variable and sex. Sensitivity analyses were performed in age-stratified groups ($\geq$ 50 and $<$ 50 years old) to explore the effect of menopausal status based on the median menopausal age in other studies [27]. All analyses were performed using R software (V4.0.3) with two-sided statistical significance set at an alpha = 0.05.

3. Results

MetS categorization was established for all participants. Individuals with MetS at baseline (1511 (22.4 %)) or with missing data (27 (0.42 %)) required to compute MetS at baseline were excluded from study (Fig. 1). Of the 5195 remaining participants (mean age=51.3 years ±10.6, 56.1 % females), 18.3 % and 14.4 % developed MetS at the first and second follow-up visits respectively. The detailed components of MetS are summarized in Table 2 and Fig. 2. Amongst the MetS components, having elevated blood pressure was the most prevalent component of MetS (Fig. 2) and its prevalence increased over time. In contrast, the prevalence of high blood sugar and triglyceride levels decreased by the second follow-up. Male individuals had a greater number of components contributing to MetS at baseline and at all follow-up periods compared with females. Of the 3495 cohort participants, 967 (males: 524 (35.2 %), females: 452 (22.5 %)), had developed MetS as measured at either the first or second follow-up data collection period. In this cohort, gender-related factors differed between sexes (Table 1). Females were more likely to be part-time workers, had attained a lower level of formal education, and reported a lower income level.

Participants who developed MetS were less likely to report being employed at baseline (69 % vs 76.1 %, $P<0.001$), more likely to work in a low occupation (29.5 % vs 20.0 %, $P<0.001$), and to report attaining less formal education (17.1 % vs 25.6 %, $P = 0.001$) than participants without MetS. Moreover, they did not live with children, consumed more alcohol per week, and had a greater prevalence of antidepressant use (Table 3).

The results of the multivariable analysis demonstrated that female sex (OR:0.48 95 %CI: 0.41–0.56) was associated with a decreased probability of developing MetS. Conversely, older age (OR: 1.74, 95 % CI: 1.40–2.18), lower education attainment level (OR: 1.91, 95 %CI: 1.51–2.41), lower income (OR: 1.24, 95 %CI: 0.99–1.56), were independently associated with a greater risk of the development of MetS in the adjusted model (Appendix 2, Figs. 3,4). The 2-way interaction terms between age, education, income, smoking, and employment with sex remained significant with a greater effect size among females (Appendix 3). In the sex-stratified model, older age was associated with higher likelihood of MetS for both sexes; however, the magnitude of effect was greater in females older than 60 years of age. Gender-related variables including being married (OR: 1.38, 95 %CI: 1.01–1.90), lower education

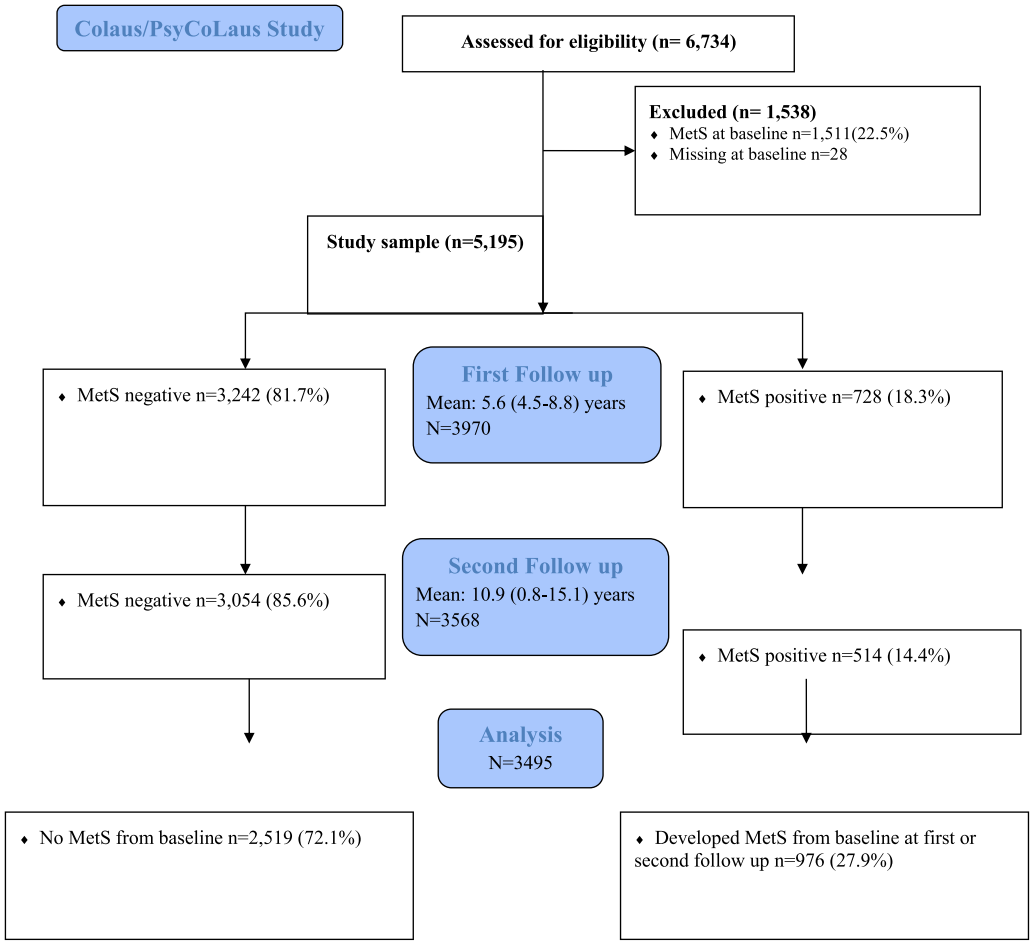

Fig. 1. Flow Diagram.

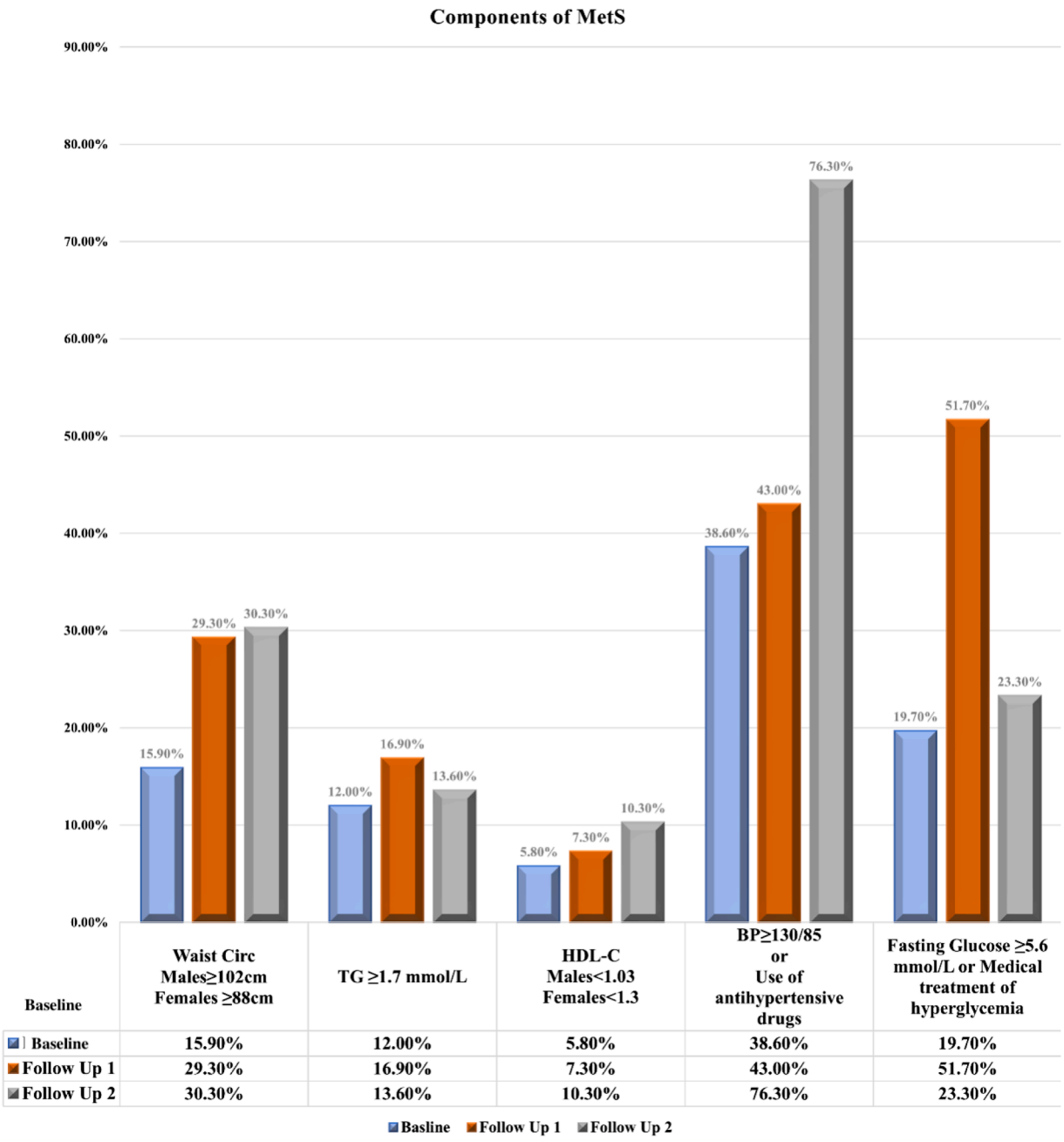

Fig. 2. Components of MetS at baseline, and follow ups.

attainment level (OR: 2.34, 95 %CI: 1.64–3.39), lower income (OR: 1.47, 95 %CI: 1.03–2.1), and smoking (OR: 0.72, 95 %CI: 0.56–0.92) were statistically significant predictors of developing MetS in females, while reporting a lower formal education was the only significant predictor of developing MetS amongst males (OR:1.56, 95 %CI: 1.13, 2.15) (Appendix 2, Figs. 3,4).

We found significant interactions between sex and strata of age, education, income, smoking and employment regarding the risk of MetS (Appendix 2, Figs. 3–6). Indeed, the protective effect of being a female was diminished in females who reported the lowest level of formal education, lowest income level, and were in an advanced age stratum. Conversely, females who smoke or are employed were less likely to develop MetS. Notably among male participants smoking and unemployment were stronger risk factors than among female individuals.

A sensitivity analysis was performed to compare participants in age group ≥ 50 years to those <50 years (Appendix 1). Female sex was a protective factor for developing MetS in both age groups (<50 years' group OR:0.38, 95 %CI: 0.3, 0.47; ≥ 50 years OR:0.56, 95 %CI: 0.46, 0.69). Interaction between sex and gender-related factors were seen more frequently in the lower age category. Another sensitivity analysis was performed using yearly household income which had fewer missing data compared to the original income variable. The results were like the original models.

4. Discussion

This study reports how gender-related factors influence the development, and progression of MetS in a large population-based cohort in Lausanne, Switzerland. The gender-related factors that predicted the development of MetS differed substantially between males and females. Specifically, lower level of formal education, lower income, and low occupation category were associated with the development of MetS in

Table 1
Baseline characteristics ($N = 5195$).

	Overall	Males	Females	P
Sex	$N = 5195$	$N = 2281$	$N = 2914$	
	–	43.9	56.1	–
Age (years)	$N = 5195$	$N = 2281$	$N = 2914$	<0.001
	51.3 ± 10.6	50.5 ± 10.5	51.8 ± 10.5	
Caucasian	$N = 5195$	$N = 2281$	$N = 2914$	0.88
	4744 (91.3)	2081 (91.2)	2663(91.4)	
BMI (Kg/m2)	$N = 5194$	$N = 2281$	$N = 2914$	<0.001
	24.5 ± 3.7	25.3 ± 3.2	23.9 ± 3.9	
History of Stroke	$N = 5192$	$N = 2281$	$N = 2911$	0.9
	42(0.8)	19(0.8)	23(0.8)	
History of CAD	$N = 5194$	$N = 2281$	$N = 2913$	<0.001
	63(1.2)	46(2.0)	17(0.6)	
History of CVD	$N = 5193$	$N = 2280$	$N = 2913$	0.01
	245(4.7)	126(5.5)	119(4.1)	
History of MI	$N = 5193$	$N = 2280$	$N = 2913$	<0.001
	53(1.0)	40(1.8)	13(0.4)	
Employment Status	$N = 5190$	$N = 2279$	$N = 2911$	<0.001
Employed	3698(71.3)	1835 (80.5)	1863(64.0)	
Working hours	$N = 3698$	$N = 1835$	$N = 1863$	<0.001
Part time	308(8.3)	90(4.9)	218(11.7)	
Full time	3390(91.7)	1745 (95.1)	1645(88.3)	
Occupation category	$N = 3847$	$N = 1887$	$N = 1960$	<0.001
Low	983(25.6)	563(29.8)	420(21.4)	
Middle	2204(57.3)	865(45.8)	1339(68.3)	
High	660(17.2)	459(24.3)	201(10.3)	
Marital Status	$N = 5190$	$N = 2279$	$N = 2911$	<0.001
Never Married	910(17.5)	372(16.3)	538(18.5)	
Divorced/Widowed	1245(24)	385(16.9)	860(29.5)	
Married	3035(58.5)	1522 (66.8)	1513(52.0)	
Education Level	$N = 5186$	$N = 2277$	$N = 2909$	<0.001
Mandatory	986(19)	356(15.6)	630(21.7)	
Apprenticeship	1785(34.4)	803(35.3)	982(33.8)	
High School	1291(24.9)	524(23.0)	767(26.4)	
University	1124(21.7)	594(26.1)	530(18.2)	
Income	$N = 3000$	$N = 1299$	$N = 1701$	<0.001
Low	755(25.2)	225(17.3)	530(31.2)	
Middle	1322(44.1)	562(43.3)	760(44.7)	
High	923(30.8)	512(39.4)	411(24.2)	
Domestic status	$N = 3619$	$N = 1510$	$N = 2109$	<0.001
Living Alone	1133(31.3)	307(20.3)	826(39.2)	
Single parent	212(5.9)	48(3.2)	164(7.8)	
Couple	1251(34.6)	574(38)	677(32.1)	
Couple with children	1023(28.3)	581(38.5)	442(21.0)	
Smoking	$N = 5191$	$N = 2279$	$N = 2912$	<0.001
Never	2177(41.9)	809(35.5)	1368(47.0)	
Former	1595(30.7)	789(34.6)	806(27.7)	
Smoker	1419(27.3)	681(29.9)	738(25.3)	
Alcohol intake	$N = 5195$	$N = 2281$	$N = 2914$	<0.001
Units per week	6.5 ± 8.5	9.6 ± 10.4	3.9 ± 5.5	
Antidepressant use	$N = 5195$	$N = 2281$	$N = 2914$	<0.001
	395(7.6)	114(5.0)	281(9.6)	
Major Depressive Disorder	$N = 4056$	$N = 1762$	$N = 2294$	<0.001
	1673(41.2)	543(30.8)	1130(49.3)	
Generalized Anxiety Disorder	$N = 4033$	$N = 1749$	$N = 2284$	0.04
	95(2.4)	31(1.8)	64(2.8)	

BMI: Body Mass Index, CAD: Coronary Artery Disease, CVD: Cardiovascular Disease, MI: Myocardial infarction.
Occupation Categories: "High" (entrepreneurs, professionals, higher managers), "Middle" (self-employed, lower managers, skilled clerks), and "Low" (unskilled clerks, farmers, skilled manual workers, unskilled manual workers) levels.
Income Categories: Low= <4999 chf, Middle (5000 chf – 9499 chf), High (>9500 chf).
Numerical: Mean ± SD.
Categorical: Percentage.

females but not in males. As this syndrome is an important predictor of future atherosclerotic cardiovascular diseases, interventions that target modifiable gendered factors may reveal significant upstream contributions in preventing the development of CVD.

Female sex has generally been thought to be a protective factor that decreases the risk of the development of MetS in fact the incidence and prevalence of MetS is higher in males than females. However, this sex-specific protection is lost after menopause at which time the female-specific risk of the development of MetS is reported to be equal to or in some cases greater than their male counterparts [28–30]. A study by Lobo et al. demonstrated that progesterone and estrogen, two hormones produced up to menopausal period are cardioprotective. Furthermore the reduction of these hormones post menopause results in abdominal obesity and reduced muscle weight, which in turn increases the risk of the development of MetS [31]. Another study by Ren et al. suggests that sex hormones in females may interact with various risk factors of cardiovascular disease (metabolic syndrome components) to improve outcomes and prevent further complications [32]. Importantly, our study demonstrated that beyond sex-specific hormonal changes (biological sex), psych-socio-cultural factor in effect contributed to a greater extent in females than in males to the development of MetS. Hence, although it is imperative to take into consideration sex differences in Mets development, psychosocial factors compound risk especially in females and must be considered in prevention and control.

Among the gender-related factors that impacted Mets in a sex-specific manner, our study demonstrated the importance of marital status. Males who were divorced or widowed were more likely to develop MetS compared to single and married males, while females who reported being married were at higher risk of the development of MetS in multivariable model. Similarly, a study by Chung et al. [33] concluded that divorced males are more at risk of MetS development compared to those who were married. Although the exact pathophysiology of such findings is not well understood [34,35], previous studies have found that the change in social circumstances are important indicators of metabolic syndrome. Earlier research generally indicates that men derive greater physical health benefits from marriage than women. For instance, married men tend to engage in less risky behaviors and consume heart healthy homemade food compared to their divorced counterparts [33,36]. Social support is theorized to influence health primarily by offering resources that help in evading disease risks, mitigating their effects, or shaping behaviors that either promote health or harm it [37]. Moreover, social support could directly affect various physiological systems, including the immune, neuroendocrine, and cardiovascular systems [38].

Indeed many social determinants of health are gendered [39]. We found that income, education, and occupation type were associated with MetS development, especially in females. For instance, amongst female participants reporting less formal education, a lower-income job and occupation significantly increased the risk of developing MetS.

Our study demonstrated that females with lower socioeconomic status are at higher relative risk of developing MetS compared to their male counterparts and moreover, gender-related factors play a more significant role in the Swiss population. A study in Korea [40] also showed the importance of socioeconomic status and its differing effect by sex for the development of MetS. Dallongeville et al. [41], also investigated the role of household income in over 3500 people in France and demonstrated that those with lower household income were at an increased risk of MetS. This relationship was more pronounced in female participants after adjusting for lifestyle variables. Furthermore, a recent Canadian study by Ridiger et al. [42] also revealed the importance of income and education in the development of MetS. As in our study, an inverse relationship between income, education level and subsequent risk of the development of MetS was demonstrated more so in females. Thus, the effect of gender-related factors on the development of MetS appears to be of greater magnitude in females as compared with males and such findings are consistent across several high-income countries.

Table 2
MetS components at baseline, and follow ups.

	Baseline				Follow up 1				Follow up 2			
	Overall	Males	Females	*P*	Overall	Males	Females	*P*	Overall	Males	Females	*P*
MetS score	0.9 ± 0.8	1.1 ± 0.7	0.7 ± 0.7	<0.001	1.5 ± 1.1	1.7 ± 1.1	1.3 ± 1,1	<0.001	1.2 ± 1.1	1.4 ± 1.1	1.1 ± 1.05	<0.001
MetS score Cat	*N* = 5195	*N* = 2281	*N* = 2914	<0.001	*N* = 3970	*N* = 1711	*N* = 2259	<0.001	*N* = 3568	*N* = 1495	*N* = 2073	<0.001
0	36	26.5	43.4		23	14.4	29.6		31.2	24.5	35.9	
1	36	39.1	33.6		29.3	28.6	29.8		31.9	30.4	33	
2	28	34.4	23		29.3	34.8	25.1		22.5	25.1	20.6	
3	–	–	–		13.9	15	12.4		11	15.2	8	
4	–	–	–		3.8	5.3	2.6		2.8	3.8	2.1	
5	–	–	–		0.7	0.9	0.5		0.6	0.9	0.3	
MetS Score components												
Waist Circumference (cm)	85.2 ± 11.1	91.7 ± 8.9	80.1 ± 9.9	<0.001	88.8 ± 11.4	93.9 ± 9.5	84.9 ± 11.1	<0.001	88.9 ± 12.1	95.04 ±10.3	84.4 ± 11.3	<0.001
SBP (mmHg)	124.7 ± 16.7	128.3 ± 15.3	121.7 ± 17.2	<0.001	123.9 ± 17.6	128.5 ± 15.9	120.4 ± 17.9	<0.001	124.9 ± 17.5	128.5 ± 16.3	122.2 ± 17.8	<0.001
DBP (mmHg)	77.6 ± 10.4	79.3 ± 10.2	76.2 ± 10.2	<0.001	77.2 ± 10.6	79.2 ± 10.4	75.6 ± 10.5	<0.001	76.9 ± 10.4	78.9 ± 10.5	75.4 ± 10.1	<0.001
Taking HTN Rx or BP≥130/85	*N* = 5195	*N* = 2281	*N* = 2914	<0.001	*N* = 3998	*N* = 1725	*N* = 2273 36.7	<0.001	*N* = 3694	*N* = 1558	*N* = 2136	<0.001
	38.6	45.2	33.5		43	51.4			48.5	56.8	42.4	
TG (mmol/L)	1.1 ± 0.7	1.3 ± 0.9	1 ± 0.4	<0.001	1.2 ± 0.8	1.4 ± 0.9	1.07±0.5	<0.001	1.2 ± 0.8	1.3 ± 0.9	1.1 ± 0.6	<0.001
HDL-C (mmol/L)	1.7 ± 0.4	1.5 ± 0.35	1.8 ± 0.4	<0.001	1.7 ± 0.5	1.4 ± 0.3	1.8 ± 0.4	<0.001	1.7 ± 0.5	1.4 ± 0.4	1.8 ± 0.4	<0.001
Fasting Glucose (mmol/L)	5.3 ± 0.7	5.4 ± 0.8	5.1 ± 0.6	<0.001	5.7 ± 0.8	5.8 ± 0.9	5.4 ± 0.6	<0.001	5.2 ± 0.7	5.4 ± 0.7	5.1 ± 0.6	<0.001
Fasting Glucose (mmol/L) ≥5.6	*N* = 5195	*N* = 2281	*N* = 2914	<0.001	*N* = 3988	*N* = 1719	*N* = 2269	<0.001	*N* = 3607	*N* = 1513	*N* = 2094	<0.001
	19.1	28.3	11.9		51.5	66	40.5		22.5	32.9	14.9	
Type2 DM or Taking meds	*N* = 5065	*N* = 2222	*N* = 2843	<0.001	*N* = 5066	*N* = 2223	*N* = 2843	<0.001	*N* = 5066	*N* = 2223	*N* = 2843	<0.001
	2	2.8	1.4		2.7	3.8	1.8		3.8	5.5	2.5	
Type2 DM/ Taking meds/ Glu≥5.6	*N* = 5195	*N* = 2281	*N* = 2914	<0.001	*N* = 3988	*N* = 1719	*N* = 2269	<0.001	*N* = 3617	*N* = 1520	*N* = 2097	<0.001
	19.7	28.9	12.4		51.7	66.2	40.7		23.3	34.3	15.3	

MetS score: 0–5.
Males: Waist Circ ≥102 cm + TG≥1.7 mmol/L+ HDL-C <1.03 + BP≥130/85 or use of antihypertensive drugs + Fasting Glu ≥5.6 mmol/L or medical treatment of hyperglycemia.
Females: Waist Circ ≥88 cm + TG≥1.7 mmol/L + HDL-C <1.3 + BP≥130/85 or use of antihypertensive drugs + Fasting Glu ≥5.6 mmol/L or medical treatment of hyperglycemia.
Numerical: Mean ± SD.
Categorical: Percentage.

Interestingly although being a current smoker was a risk factor for MetS in males, in females it acted as a protective factor. One explanation might be that females smoke less than males and therefore the metabolic effect of smoking is not significant. In the Nurses' health study, the association between smoking and diabetes was only significant for females who smoked >= 25 cig/d [43]. In a meta-analysis by Yuan et al. comparing the sex-specific association between smoking and type 2 diabetes mellitus, female smokers had similar risk of type 2 diabetes compared to their male counterparts. Hence it may be hypothesized that similar effect holds true for MetS. While being a current or former smoker increased the risk of MetS development, being an active smoker had 16 %, and 38 % higher risk of MetS compared to former and non-smokers. This finding was supported by Chen et al. [44] who investigated the risk of smoking in MetS development amongst Taiwanese people. They concluded that smoking cessation compared to actively smoking reduced the likelihood of MetS and its individual components in a dose dependent manner.

4.1. *Implications for public health*

Gender-related factors are important contributors to health disparities and disease outcome. The novelty of our study is the assessment of the role of gendered variables in the manifestation and progression of MetS in a sex-specific stratification. We demonstrated that female participants who report factors suggesting a disadvantaged social standing are at increased risk of developing MetS, which may potentially result in subsequent CVD.

Certain gender-related factors may be difficult to modify or would require systemic and cultural changes (changes in the social roles of men and women). However, those that are modifiable at the individual level should be targeted among individuals at risk for MetS through the implementation of disease prevention strategies. People to target are those with lower education and income through earlier screening and intervention, family education, social work services, choosing more affordable similar efficacious medications to improve compliance, implementing activity in usual daily life. These are some of the ways to implement health equity in clinical practice. As one size does not fit all, it can be envisioned that interventions will be sex-specific to reduce MetS risk. Hence, closer follow-up intervals, ensuring prescription of affordable medications, and exploring strategies for healthier lifestyle in these population, may reduce the likelihood of MetS incidence. Eventually, gender-related factors should be incorporated in calculating 10-year cardiac event risk such as in the Atherosclerotic cardiovascular disease (ASCVD) Score for enhanced prediction of future cardiovascular risk and implementation of preventive strategies.

Table 3
Sex differences in gender-related variables in participants with and without MetS.

	Overall			Males			Females		
	MetS –	MetS +	*P*-value	MetS –	MetS +	*P*-value	MetS –	MetS +	*P*-value
Employment Status	*N* = 2335	*N* = 898	<0.001	*N* = 891	*N* = 479	0.001	*N* = 1444	*N* = 419	<0.001
Employed	76.1	69.0		87	80.5		69.3	55.7	
Working hours	*N* = 1916	*N* = 673	0.1	*N* = 840	*N* = 422	0.01	*N* = 1076	*N* = 251	0.06
Part time	7.2	9.2		2.7	5.7		10.7	15.1	
Full time	92.8	90.8		97.3	94.3		89.3	84.9	
Occupation category	*N* = 1971	*N* = 708	<0.001	*N* = 852	*N* = 436	0.004	*N* = 1119	*N* = 272	<0.001
Low	20.1	29.5		24.4	31.7		16.8	26.1	
Middle	60.7	55.5		47.3	46.8		71.0	69.5	
High	19.2	15		28.3	21.6		12.2	4.4	
Marital Status	*N* = 2488	*N* = 975	0.08	*N* = 966	*N* = 524	0.001	*N* = 1552	*N* = 451	0.2
Never Married	18.9	15.8		16.7	15.8		20.3	16.6	
Divorced/Widowed	22.0	24.0		13.0	20.0		27.6	29.9	
Married	59.1	57.7		70.3	64.1		52.1	53.4	
Education Level	*N* = 2518	*N* = 974	<0.001	*N* = 965	*N* = 524	<0.001	*N* = 1553	*N* = 451	<0.001
Mandatory	13.1	21.9		10.3	16.8		14.8	27.9	
Apprenticeship	32.9	38.7		32.6	37.8		33.1	39.7	
High School	28.4	22.3		25.8	22.9		30	21.5	
University	25.6	17.1		31.3	22.5		22.1	10.9	
Income	*N* = 2092	*N* = 651	<0.001	*N* = 830	*N* = 361	0.001	*N* = 1262	*N* = 290	<0.001
Low	21.8	31.6		14.3	21.6		26.8	44.1	
Middle	44.4	43.6		42.5	44.0		45.6	43.1	
High	33.7	24.7		43.1	34.3		27.6	12.8	
Domestic status	*N* = 2439	*N* = 792	<0.001	*N* = 933	*N* = 419	<0.001	*N* = 1506	*N* = 373	<0.001
Living Alone	29.5	35.1		17.5	23.6		37	48	
Single parent	6.6	4.0		3.5	2.6		8.5	5.6	
Couple	33.9	37.1		36.5	41.8		32.2	31.9	
Couple with children	30	23.7		42.4	32		22.3	14.5	
Smoking	*N* = 2519	*N* = 975	0.1	*N* = 966	*N* = 524	<0.001	*N* = 1553	*N* = 451	0.1
Never	44.1	40.2		41	31.9		46	49.9	
Former	31.6	33.3		34.8	35.9		29.6	30.4	
Smoker	24.3	26.5		24.2	32.3		24.4	19.7	
Alcohol intake			<0.001			0.06			0.8
	5.9 ± 7.4	7.2 ± 9.3		8.9 ± 9.1	9.9 ± 10.8		4.1 ± 5.2	3.9 ± 5.8	
Antidepressant use	*N* = 2519	*N* = 976	0.008	*N* = 966	*N* = 524	0.003	*N* = 1553	*N* = 452	0.06
	6.7	9.4		3.9	7.6		8.5	11.5	
Major Depressive Disorder	*N* = 2322	*N* = 842	0.1	*N* = 889	*N* = 457	0.4	*N* = 1.433	*N* = 385	0.5
	41.8	39.1		29.8	32.2		49.2	47.3	
Generalized Anxiety Disorder	*N* = 2317	*N* = 836	0.3	*N* = 885	*N* = 452	1	*N* = 1432	*N* = 384	0.06
	2.2	2.9		1.9	1.8		2.3	4.2	

Occupation Categories: "High" (entrepreneurs, professionals, higher managers), "Middle" (self-employed, lower managers, skilled clerks), and "Low" (unskilled clerks, farmers, skilled manual workers, unskilled manual workers) levels.
Income Categories: Low= <4999 chf, Middle (5000 chf – 9499 chf), High (>9500 chf).
Values are all percent.

4.2. Limitations

While the longitudinal method, random selection of participants and inclusion of gender-related variables are strengths of this study that enabled the assessment of the role of sex and gender in the development of MetS, this study was from a single center cohort in one country and the lack of diversity may be seen as a limitation of the study. Despite these limitations, the results resonated with previous literature in middle- and high-income countries and add to the literature by highlighting the sex-specific role of gender-related factors in the development of MetS. Future multicenter investigations including more diverse populations are warranted to assess the intersectionality of race/culture/country with gender and sex.

5. Conclusions

This study has demonstrated that gender-related factors are associated with the development of MetS, especially in female individuals. By recognizing gendered social and economical disparities, particularly amongst those in poor socio-economic environments, the prevention and management of MetS might be improved. There is a need for stratifying health related risk prediction by sex. Furthermore, gendered determinants of health are an essential part of clinical decision making and development of intervention, as they contribute to the development of the MetS and, likely eventual cardiovascular diseases especially in females.

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Ethics

The data utilized for the analysis of this study has been approved by institutional ethics review board.

CRediT authorship contribution statement

Pouria Alipour: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Zahra Azizi:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Valeria**

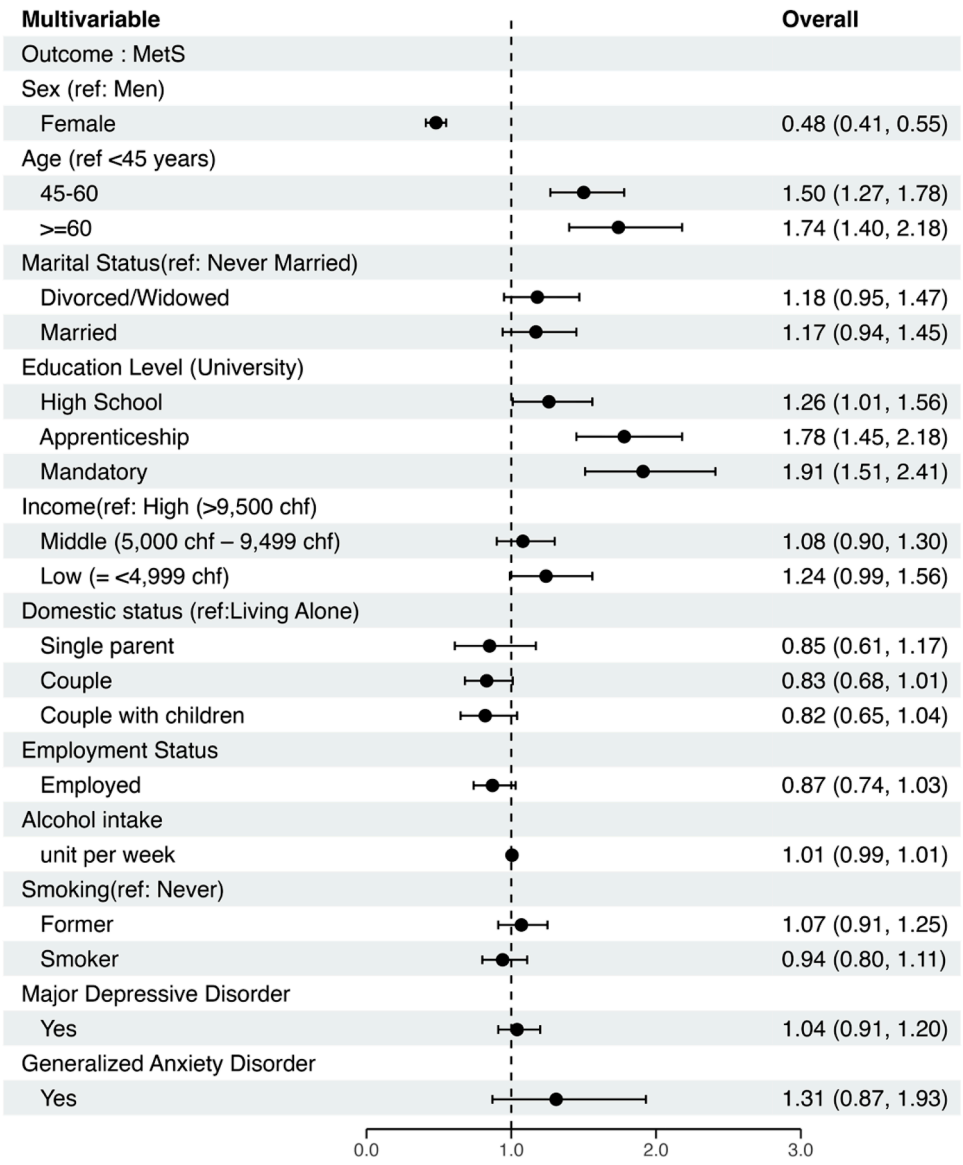


Fig. 3. Association between Gender-related Factors and risk of developing MetS
The results are presented as Odds Ratio (95 % Confidence Interval)
MetS score: 0–5, MetS positive: MetS score ≥3 MetS score components: Males: Waist Circ ≥102 cm + TG≥1.7 mmol/L + HDL-C <1.03 + BP≥130/85 or use of antihypertensive drugs + Fasting Glu ≥5.6 mmol/L or medical treatment of hyperglycemia Females: Waist Circ ≥88 cm + TG≥1.7 mmol/L+ HDL-C <1.3 + BP≥130/85 or use of antihypertensive drugs + Fasting Glu ≥5.6 mmol/L or medical treatment of hyperglycemia.

Raparelli: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Colleen M. Norris:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Alexandra Kautzky-Willer:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Karolina Kublickiene:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Maria Trinidad Herrero:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Khaled El Emam:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Peter Vollenweider:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Martin Preisig:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Carole Clair:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Louise Pilote:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

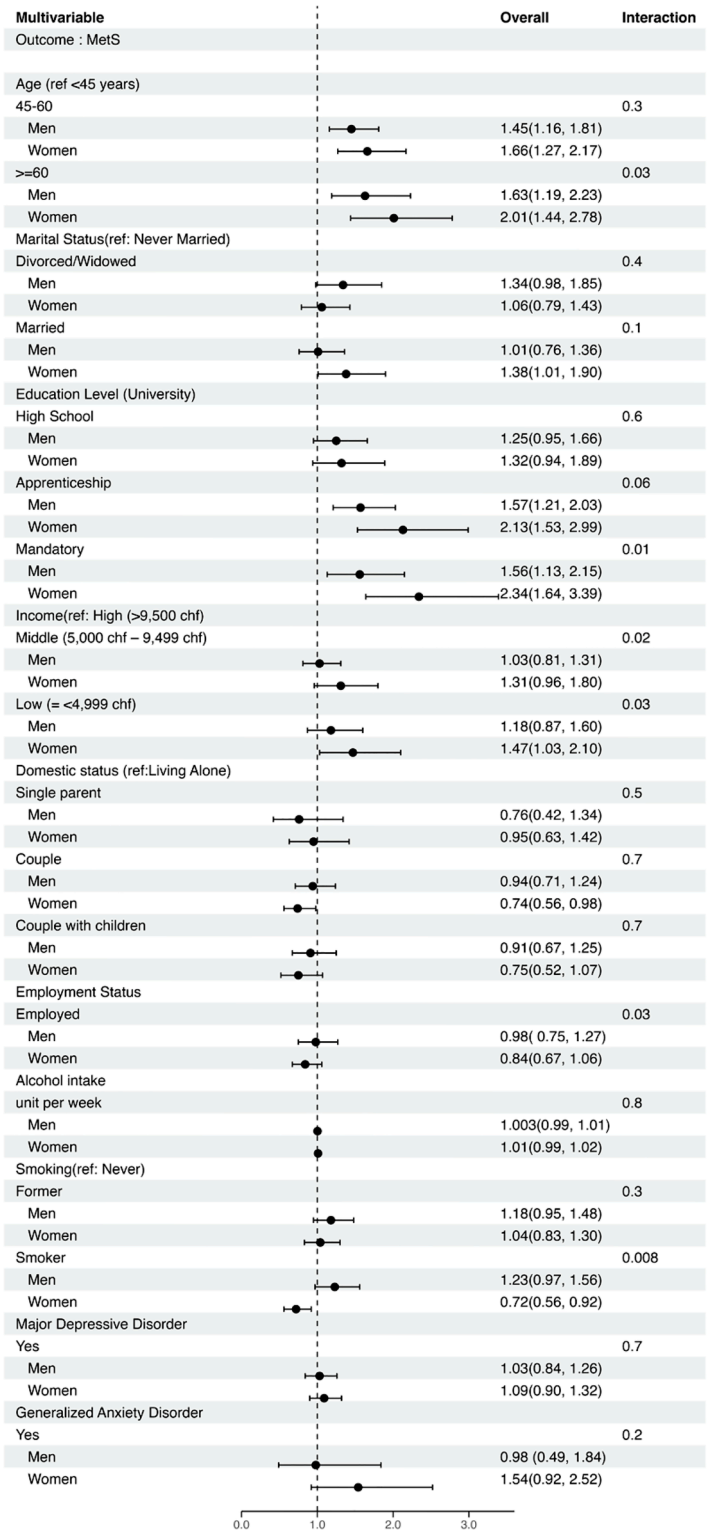


Fig. 4. Sex-Stratified Multivariable Models for Association between Gender-related Factors and risk of developing MetS
The results are presented as Odds Ratio (95% Confidence Interval), and *p*-value has been reported for interaction with sex. MetS score: 0–5, MetS positive: MetS score ≥3 MetS score components: Males: Waist Circ ≥102 cm + TG≥1.7 mmol/L+ HDL-C <1.03 + BP≥130/85 or use of antihypertensive drugs + Fasting Glu ≥5.6 mmol/L or medical treatment of hyperglycemia Females: Waist Circ ≥88 cm + TG≥1.7 mmol/L + HDL-C <1.3 + BP≥130/85 or use of antihypertensive drugs + Fasting Glu ≥5.6 mmol/L or medical treatment of hyperglycemia *P*-value for interactions with sex: Model for interaction: Gender $Variable_n$+Sex+Gender $Variable_n$*Sex+ Gender variables $_{a+b+c+..}$

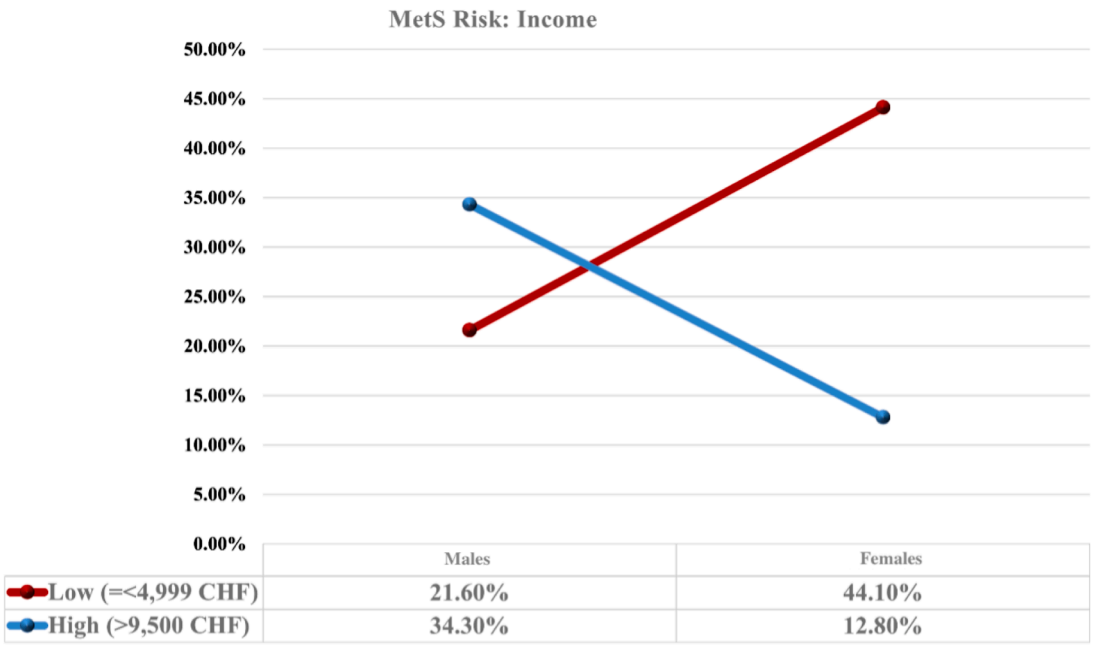


Fig. 5. Absolute risk of MetS in males and females in different categories of income.

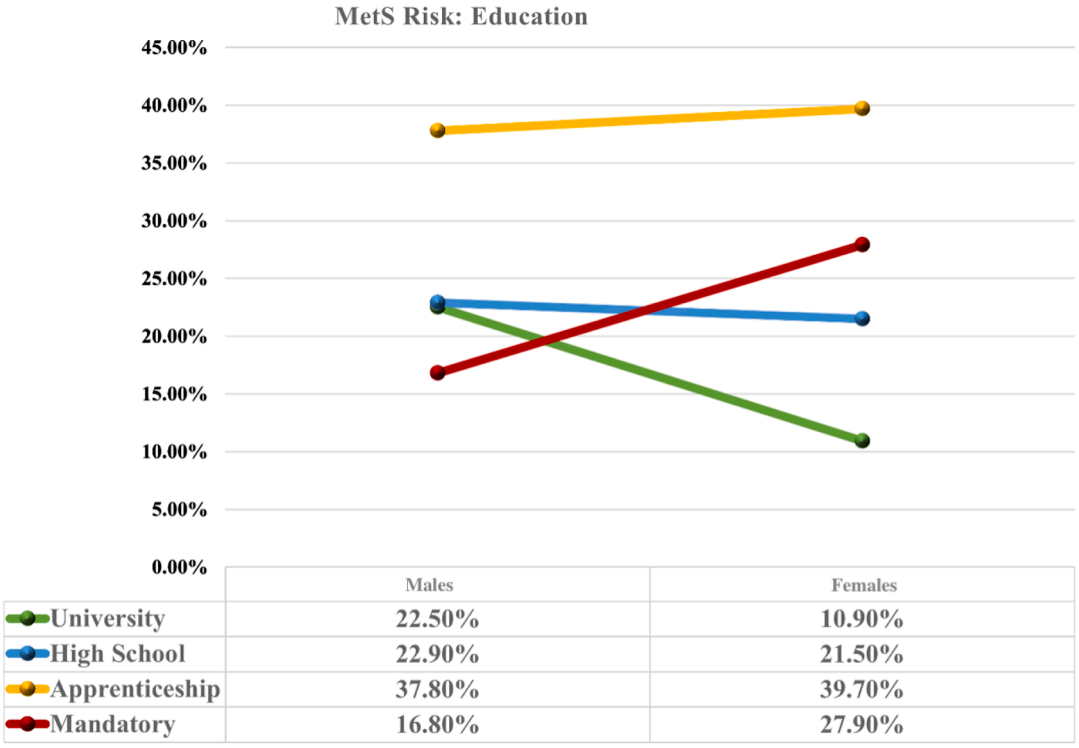


Fig. 6. Absolute risk of MetS in males and females in different categories of education.

Appendix 1. Sensitivity analysis on age group less than 50 years old and more than 50 years old

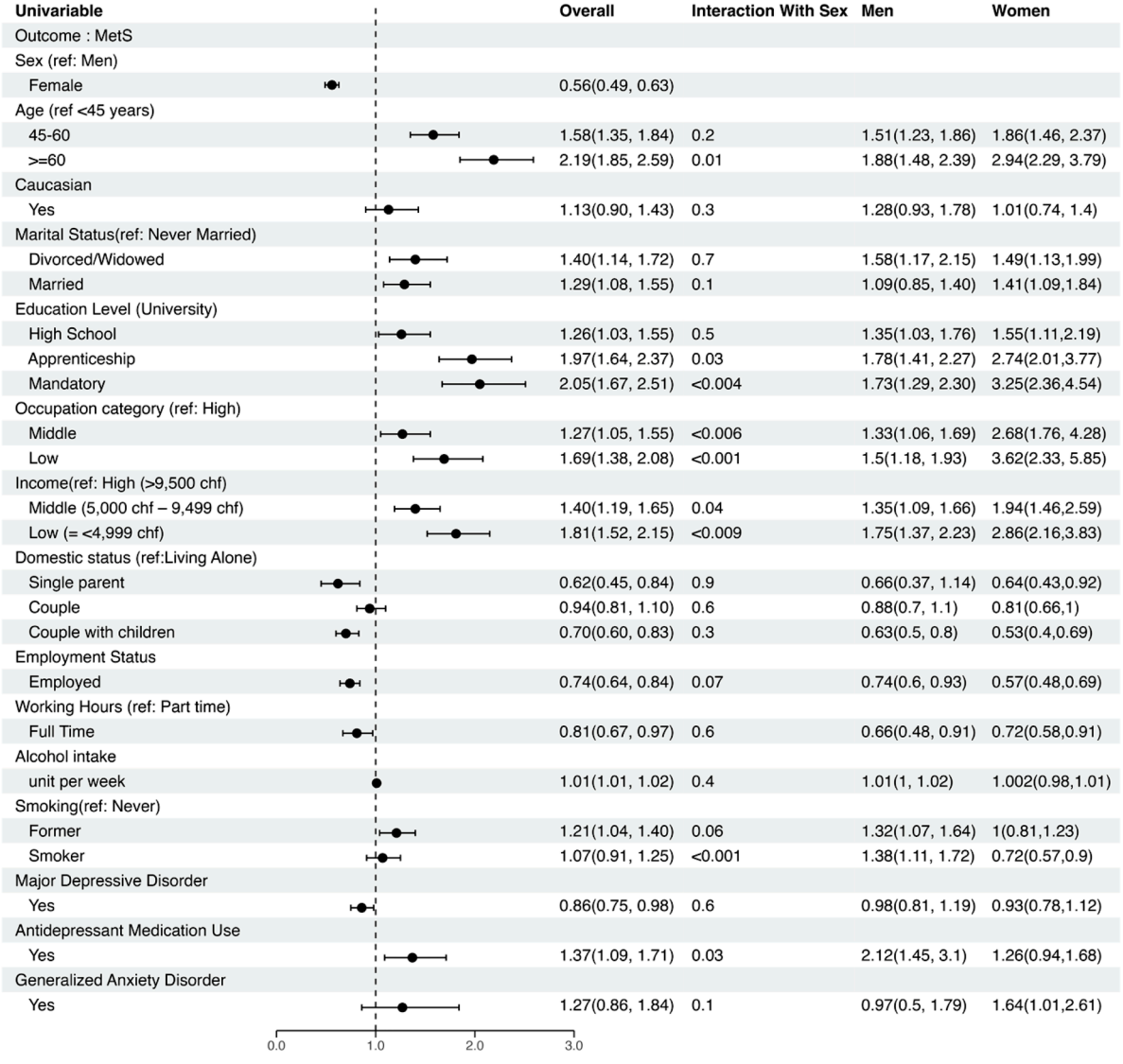
	< 50 years old (*N* = 2635)		**≥50 years old (*N* = 2560)**	
Multivariable	Overall OR (95 %CI)	Interaction with Sex P Value	Overall OR (95 %CI)	Interaction with Sex P Value
Sex *(ref: male)*	0.38(0.3,0.47)		0.56(0.46,0.69)	
Marital Status *(ref: Never Married)*				
Divorced/Widowed	1.21(0.88,1.67)	0.4	1.15(0.86,1.55)	0.3
Married	1.27(0.95,1.71)	0.5	1.14(0.83,1.56)	0.3
Education Level *(University)*				

(*continued on next page*)

(*continued*)

High School	1.06(0.78,1.44)	0.5	1.44(1.06,1.95)	0.7
Apprenticeship	1.57(1.18,2.1)	0.09(F)	1.93(1.45,2.59)	0.6
Mandatory	1.58(1.12,2.23)	0.003(F)	2.15(1.56,2.99)	0.7
Income *(ref:* High (>9500 chf*)*				
Middle (5000 chf – 9499 chf)	1.11(0.86,1.42)	0.03(F)	1.16(0.86,1.57)	0.9
Low (= <4999 chf)	1.12(0.8,1.56)	0.04 (F)	1.38(0.99,1.93)	0.7
Domestic status *(ref: Living Alone)*				
Single parent	0.96(0.64,1.41)	0.7	0.8(0.36,1.66)	0.1
Couple	0.81(0.58,1.12)	0.3	0.88(0.68,1.13)	0.4
Couple with children	0.82(0.59,1.13)	0.6	0.73(0.5,1.06)	0.7
Employment Status (employed)	0.77(0.57,1.03)	0.7	0.92(0.76,1.1)	0.2
Alcohol intake (unit per week)	1(0.99,1.01)	0.2	1.008(0.99,1.01)	0.4
Smoking *(ref: Never)*				
Former	1.19(0.93,1.53)	0.1	1.03(0.84,1.25)	0.7
Smoker	1.3(1.02,1.66)	0.01(M)	0.72(0.57,0.91)	0.2
MDD	0.99(0.81,1.22)	0.9	1.06(0.88,1.28)	0.7
Generalized Anxiety Dx	1.44(0.75,2.59)	0.2	1.19(0.7,1.98)	0.8

Appendix 2. Bivariate analysis to assess role of gendered factors in developing MetS



The results are presented as Odds Ratio (95 % Confidence Interval), and p-value has been reported for interaction with sex.
MetS score: 0–5,
MetS positive: MetS score ≥3
MetS score components:

Males: Waist Circ ≥102 cm + TG≥1.7 mmol/L + HDL-C <1.03 + BP≥130/85 or use of antihypertensive drugs + Fasting Glu ≥5.6 mmol/L or medical treatment of hyperglycemia

Females: Waist Circ ≥88 cm + TG≥1.7 mmol/L + HDL-C <1.3 + BP≥130/85 or use of antihypertensive drugs + Fasting Glu ≥5.6 mmol/L or medical treatment of hyperglycemia

P-value: Model for interaction: Variable+Sex+Variable*Sex

Appendix 3. Factors associated with MetS prevalence: interaction with sex in multivariable models

MetS Prevalence	Interaction Models Odds Ratio (95 % CI)
Age	
45–60	1.21(0.74, 1.98)
>=60	0.99(0.55, 1.76)
Female Sex (vs. Male reference sex)	0.40(0.31, 0.52)
Age*Sex	1.16(0.84, 1.60)
45–60*Sex	1.46(1.02, 2.09)
>=60*Sex	
Marital Status (ref: Never Married)	
Divorced/Widowed	1.55(0.78, 3.10)
Married	0.76(0.42, 1.38)
Female Sex (vs. Male reference sex)	0.41(0.29, 0.58)
Marital Status*Sex	0.85(0.55, 1.30)
Divorced/Widowed*Sex	1.34(0.92, 1.95)
Married*Sex	
Smoking (ref: Never)	
Former	1.33(0.81, 2.18)
Smoker	2.17(1.29, 3.64)
Female Sex (vs. Male reference sex)	0.58(0.46, 0.72)
Smoking*Sex	0.87(0.64, 1.19)
Former*Sex	0.57(0.41, 0.79)
Smoker*Sex	
Domestic Status (ref: Living Alone)	
Single parent	0.61(0.18, 1.98)
Couple	0.78(0.46, 1.32)
Couple with children	0.89(0.50, 1.57)
Female Sex (vs. Male reference sex)	0.47(0.37, 0.60)
Domestic Status *Sex	1.21(0.61, 2.42)
Single parent*Sex	1.04(0.75, 1.43)
Couple*Sex	0.93(0.64, 1.34)
Couple with children*Sex	
Education (ref: University)	
High School	1.12(0.59, 2.12)
Apprenticeship	1.06(0.59, 1.90)
Mandatory	0.87(0.44, 1.72)
Female Sex (vs. Male reference sex)	0.36(0.25, 0.51)
Education*Sex	1.11(0.72, 1.72)
High School*Sex	1.45(0.98, 2.17)
Apprenticeship*Sex	1.71(1.10, 2.67)
Mandatory*Sex	
Income (ref: High (>9500 chf)	
Middle (5000 chf – 9499 chf)	0.61(0.36, 1.03)
Low (= <4999 chf)	0.70(0.39, 1.25)
Female Sex (vs. Male reference sex)	0.34(0.25, 0.46)
Income*Sex	1.51(1.06, 2.17)
Middle (5000 chf – 9499 chf) *Sex	1.52(1.04, 2.23)
Low (= <4999 chf) *Sex	
Alcohol Intake	1.007(0.98, 1.03)
Female Sex (vs. Male reference sex)	0.48(0.40, 0.58)
Alcohol Intake*Sex	0.99(0.97, 1.01)
Employment Status	1.46(0.89, 2.41)
Female Sex (vs. Male reference sex)	0.60(0.46, 0.77)
Employment *Sex	0.72(0.54, 0.97)
MDD	1.13(0.73, 1.74)
Female Sex (vs. Male reference sex)	0.49(0.40, 0.58)
MDD*Sex	0.95(0.72, 1.24)
GAD	0.63(0.15, 2.45)
Female Sex (vs. Male reference sex)	0.47(0.41, 0.55)
GAD*Sex	1.56(0.70, 3.57)

Model for interactions with country: repeated set of multivariable models, including two-way interactions between each variable and sex adjusted for other covariates

Sex refers to Female Sex (vs. male reference sex)

$Variable_n$+Sex+ $Variable_n$*Sex+ variables $_{a\ +\ b\ +\ c}$+.

MetS~Age+Sex+Age*Sex+ MDD+Smoking+Houshold size+ Education+Income+Domestic status+ …

MetS~MDD+Sex+MDD*Sex+Age+ Smoking+Houshold size+ Education+Income+ Domestic status+…

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