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Complete List of Authors:	Alimohammadian, Masoomeh ; Tehran University of Medical Sciences, Department of Human Ecology, School of Public Health Majidi, Azam; Tehran University of Medical Sciences, Digestive Diseases Research Institute Yaseri, Mehdi; Tehran University of Medical Sciences, Department of Epidemiology and Biostatistics Ahmadi, Batoul; Tehran University of Medical Sciences, Department of Health Management and Economics, School of Public Health Islami, Farhad; Institute for Translational Epidemiology and Tisch Cancer Institute,, Icahn School of Medicine at Mount Sinai Delavari, Alireza; Tehran University of Medical Sciences, Digestive Diseases Research Institute Amani, Mohammad; Tehran University of Medical Sciences, Digestive Diseases Research Institute Derakhshan, Mohammad Feyz-Sani, Akbar; Tehran University of Medical Sciences, Digestive Diseases Research Institute Poustchi, Hossein; Tehran University of Medical Sciences, Digestive Diseases Research Institute Pourshams, Akram; Tehran University of Medical Sciences, Digestive Diseases Research Institute Khoshnia, Masoud; Tehran University of Medical Sciences, Digestive Diseases Research Institute Qaravi, Samad; Tehran University of Medical Sciences, Digestive Diseases Research Institute Abnet, Christian; National Cancer Institute, Division of Cancer Epidemiology and Genetics Dawsey, Sanford; National Cancer Institute, NIH, Division of Cancer Epidemiology & Genetics Brennan, Paul ; International Agency for Research on Cancer, Genetic Epidemiology Group Kamangar, Farin; Morgan State University, Department of Public Health Analysis, School of Community Health and Policy, Boffetta, Paolo; Institute for Translational Epidemiology and Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai Sadjadi, Alireza; Tehran University of Medical Sciences, Digestive Diseases Research Institute Malekzadeh, Reza; Tehran University of Medical Sciences, Digestive Diseases Research Institute

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Multimorbidity: A Neglected Issue among Middle-Age people- Results of gender differences investigation in a Large Population-Based Cross-Sectional Study in West Asia

Masoomeh Alimohammadian[1,2,3∞], Azam Majidi[2∞], Mehdi Yaseri[4], Batoul Ahmadi[5*] Farhad Islami[1,6], Alireza Delavari[1,2], Mohammad Amani[1,2], Mohammad H. Derakhshan[2,7], Akabar Feyz Sani[1,2], Hossein Poustchi[1,2], Akram Pourshams[1,2,8], Masoud Khoshnia[2,9], Samad Qaravi[2,9], Christian C. Abnet[10], Sanford M. Dawsey[10], Paul Brennan[11], Farin Kamangar[1,12], Paolo Boffetta[6], Alireza Sadjadi[1,2*], Reza Malekzadeh[1,2]

1. Digestive Disease Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
2. Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Human Ecology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
4. Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
5. Department of Health Management and Economics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
6. Institute for Translational Epidemiology and Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, NY, USA
7. Division of Cardiovascular and Medical Sciences, Section of Gastroenterology, University of Glasgow, Glasgow, UK.
8. Liver and Pancreaticbiliary Research center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
9. Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran
10. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA
11. International Agency for Research on Cancer, Genetic Epidemiology Group, Lyon, France
12. Department of Public Health Analysis, School of Community Health and Policy, Morgan State University, Baltimore, MD, USA

∞ These authors contributed equally to the work and share first authorship

* These authors share the corresponding position:

Corresponding Authors: Dr. Alireza Sadjadi**:** sadjadia@gmail.com and Dr. Batoul Ahmadi**:** ahmadiba@tums.ac.ir

ABSTRACT:

Objectives: Similar to other developing countries, transitions in lifestyle and health promotion have increased both, life-expectancy and the burden of chronic diseases in Iran.

Design: A cross-sectional analysis of Golestan cohort data

Setting: Community setting of Golestan Province, Iran

Study population: Residents of Golestan Province

Main outcome measures: This study investigates differences in multimorbidity and its determinants by gender and age-groups in northern Iran. Data were collected from 49,946 individuals (aged 40-75 years). Simple and multiple Poisson regression models with robust variances were used to examine the simultaneous effects of multiple factors.

Results: The overall prevalence of multimorbidity was 25.0% in women and 13.4% in men ($p< 0.001$), and it was higher in women at all ages groups. Although multimorbidity was associated with age, its prevalence was considerable even among younger participants (17.3% in women and 8.6% in men <50 years). With regard to the prevalence of multimorbidity, several factors showed a statistically significant interaction with gender. Former-smoking and being of Non-Turkmen ethnic groups, married, or physical inactivity showed a significant or stronger association with multimorbidity in men. Being of lower socioeconomic groups was associated with multimorbidity prevalence only in women. Higher educational levels (compared to illiteracy) showed an inverse association mainly in women ($p < 0.001$). Our study identified socioeconomic status, ethnicity, physical activity, marital status, educational level and smoking as determinants of gender differences in multimorbidity prevalence ($p< 0.01$).

Conclusion: Regarding gender and socioeconomic disparities, prevention and control of multimorbidity require gender-specific health policies and interventions, particularly among younger and middle-age groups.

Strengths and limitations of this study:

- Strengths of this study include data from a large, population-based cohort study with detailed data on sociodemographic, lifestyle and behavioral risk factors.
- All data were collected by interactive face-to-face interviews conducted by trained medically qualified researcher.
- Cross-sectional data analyses are susceptible to residual confounding and cannot establish the direction of an association.

- Another limitation of this investigation was "self- reporting method of gathered data, constraining us to access adequate documents about chronic diseases.

Keywords: Multimorbidity, Ageing, Gender differences, Golestan Cohort Study, Iran

SUMMARY:

What is already known about this subject?

- Limited evidence exists about gender and age differences in multimorbidity in developing countries

What does this study add?

- To address gender and age differences in multimorbidity in Iran as a sample developing country, we conducted a cross-sectional study in the baseline data of Golestan Cohort.
- Socioeconomic/educational status, ethnicity, physical activity and smoking were significant determinants of gender differences

How might this impact on clinical practice? (Recommendations for policy)

- Our findings confirm that multimorbidity is an important neglected health issue even in middle-age groups
- Control of multimorbidity require gender-specific health interventions, particularly in younger and middle-age groups

INTRODUCTION:

Chronic diseases not only cause physical and social complications in patients, but also they impose a huge burden on health systems. This burden could be further amplified by co-occurrence of two or more chronic diseases in one person, a condition that is known as multimorbidity [1-3]. Multimorbidity is associated with a higher mortality risk and increased utilization of healthcare services; therefore, it is a demanding situation for patients, their families, and healthcare providers [4-8].

In many developing countries, life expectancy has increased over the recent decades. On the other hand, the growing prevalence of multimorbidity has decreased the quality of life in patients with chronic diseases, especially in populations with limited resources [9, 10]. In cases of multimorbidity, the routine approach of dealing with a single disease at a time in the current clinical practice may lead to more unwanted side effects in patients and higher costs to patients and healthcare systems [11].

A limited number of studies have indicated a gender difference in patterns of multimorbidity [12]. This difference may be related to biological, socio-cultural, environmental, and economic factors. As these factors vary globally, their associations with multimorbidity may differ across populations [13-17]. Therefore more research needs to be conducted in this topic.

In an earlier study, we investigated the epidemiology of multimorbidity using the baseline data from the Golestan Cohort Study (GCS), a large-scale prospective study in West Asia [18]. In this article we applied numerous analyses to illuminate variability in the prevalence and determinants of multimorbidity in different ages, and also examine interactions between gender and multiple sociodemographic and lifestyle factors potentially associated with multimorbidity.

METHODS:

A total of 50,045 adults aged 40-75 years residing in Golestan province in northeastern Iran were enrolled in a cohort study from 2004 to 2008. The study protocol [19] and details of this study population are described elsewhere [18]. Trained staff used validated questionnaires to collect data on sociodemographic factors, lifestyle habits, occupation, physical activity, dietary habits, past medical history, and medications. A short physical exam was performed to measure blood pressure, height, and weight [19].

In this mainly rural population, physical activity was defined based on occupational activity and people were coded as “physically active” or “physically inactive”. Based on the two-step cluster

analysis using similarities of family assets, ethnicity, gender, employment status, appliance ownership, and surface area of the home, we categorized the socioeconomic status (SES) of participants as low, middle or high [20].

In this analysis, we included 49,946 (99.8%) participants that were Iranian citizens and excluded non- Iranians job seekers or refugees. Here, multimorbidity refers to the self-reported co-occurrence of two or more chronic diseases (mostly related to aging) [18] in the same person [7, 8, 21]. Based on the possibility of gathering valid self-reported data in the feasibility phase of GCS, self-reported information was collected for the following diseases: cardiovascular diseases (CVD), diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), chronic liver disease, tuberculosis (TB), gastroesophageal reflux disease (GERD), and cancers [19].

Statistical analysis: We estimated the proportion of multimorbidity among study participants by several sociodemographic and lifestyle factors. To evaluate the differences in distribution of factors between genders, we used t-test, Mann-Whitney or chi-square tests, whenever appropriate. We used simple and multiple Poisson regressions with robust variances, following the method presented by Barros and Hirakata [22], to examine the association between the studied factors and multimorbidity and calculated crude and adjusted prevalence ratios and 95% confidence intervals (CIs) in two genders. The gender difference between determinants of multimorbidity (commonly known as interaction or effect modification) was evaluated in separate multiple Poisson regression models.

In all analyses, the design effects were considered using the generalized estimating equations (GEE) method. All statistical analyses were performed using SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.). Two-sided p-values below 0.05 were considered as statistically significant.

RESULTS:

A total of 49,946 participants aged 40-75 years were included in the study, which 28,748 (57.6%) of participants were women. The prevalence of self-reported chronic diseases in those with multimorbidity and the gender difference are presented in Table 1.

Table 1: Chronic conditions by gender in population with multimorbidity in the Golestan Cohort Study (GCS)

Chronic Conditions	Total (N=10,035)		Men (N=2,836)		Women (N=7,199)		Difference (Men vs. women)
	Number	%	Number	%	Number	%	%
GERD	7690	76.6	2030	71.6	5660	78.6	-7.1*
CVD	7379	73.5	1927	67.9	5452	75.7	-7.8*
Diabetes	2535	25.3	686	24.2	1849	25.7	-1.5
COPD	2203	22.0	653	23.0	1550	21.5	1.5
TB	1030	10.3	293	10.3	737	10.2	0.1
Cancers	102	1.0	34	1.2	68	0.9	0.3
CKD	72	0.7	27	1.0	45	0.6	0.3
Liver diseases	28	0.3	11	0.4	17	0.2	0.2

* P-value <0.001

The overall prevalence of multimorbidity was 25.0% in women and 13.4% in men with a difference of 11.7% (p <0.001). We showed the prevalence of multimorbidity in all study participants by gender and sociodemographic and lifestyle factors in Table 2. The prevalence of multimorbidity in age less than 50 years was 17.3% in women and 8.6% in men, but it was 40.6% in women and 20.2% in men above 60 years.

Table 2: The multimorbidity prevalence by gender, separated in different levels of sociodemographic & lifestyle factors

Variables	Levels	Total (N=49,946)		Men [2](N=21,198)		Women[2] (N=28,748)		Difference[4]
		No.	%	No.	%	No.	%	%
Age group	≤ 49	3215	13.9	779	8.6 [3]	2436	17.3 [3]	-8.7*
	50–60	3979	22.7	1040	14.2	2939	28.8	-14.6*
	61+	2841	30.4	1017	20.9	1824	40.6	-19.7*
Residential Area	Urban	7740	20.2	2189	13.3	5551	25.4	-12.2*
	Rural	2295	19.8	647	13.8	1648	23.9	-10.0*
Ethnicity	Turkmen	7308	19.6	2022	12.6	5286	24.9	-12.3*
	others [1]	2727	21.5	814	15.8	1913	25.4	-9.5*
Marital Status	Unmarried	8175	18.6	2756	13.4	5419	23.3	-10.0*
	Married	1860	30.6	80	14.2	1780	32.3	-18.1*
Education	Illiterate	8194	23.4	1623	15.6	6571	26.7	-11.1*
	≤ 5 years	1151	13.6	650	11.7	501	17.3	-5.5*
	6-12 years	585	10.9	467	10.8	118	11.1	-0.3
	University degree	105	9.9	96	10.3	9	6.9	3.5
Work Currently	Yes	8028	18.5	1989	11.3	6039	23.3	-12.0*
	No	2007	30.7	847	23.1	1160	40.5	-17.4*
SES	Good	3403	18.1	1103	12.7	2300	22.7	-10.0*
	Medium	4921	20.5	1297	13.3	3624	25.4	-12.1*
	Poor	1709	24.1	436	15.9	1273	29.2	-13.3*
Physical Activity	Yes	2100	13.3	1157	10.2	943	20.8	-10.6*
	No	7887	23.2	1673	17.0	6214	25.8	-8.8*
BMI	Underweight	413	17.4	175	14.1	238	21.0	-6.9*
	Normal	2669	14.9	1081	11.3	1588	19.2	-7.9*
	Overweight	3468	20.4	1045	14.4	2423	24.9	-10.6*
	Obese	3482	27.4	534	17.3	2948	30.7	-13.3*
Smoking	Never	8713	21.1	1662	12.8	7051	24.9	-12.1*
	Ex-smoker	676	21.2	621	20.3	55	44.0	-23.7*
	Light smoker	364	11.1	298	9.9	66	25.5	-15.6*
	Heavy smoker	281	13.0	255	12.1	26	44.8	-32.7*
Other tobacco use	No	872	19.7	663	17.7	209	30.8	-13.1*
	Yes	9163	20.1	2173	12.5	6990	24.9	-12.4*
Opium	No	8112	19.6	1765	11.7	6347	24.0	-12.3*
	Yes	1923	22.7	1071	17.4	852	36.2	-18.8*
Alcohol	No	9721	20.2	2527	13.0	7194	25.0	-12.1*
	Yes	314	18.2	309	18.2	5	25.0	-6.8

1. Other included: Persian, Turk, Sistani, Baluch and Kurdish; **2.** number of men/women participants in GCS; **3.** Number percentage) of multimorbidity among men/women population in the relevant variables level; **4.** Men vs. women; * p-value <0.001

The results from multiple Poisson regression models are shown in Table 3. The association between poor and middle socioeconomic status with multimorbidity prevalence was significantly stronger in women than men (p for interaction=0.033). On the other hand (based on p-value for interaction), the association between Non-Turkmen groups (0.003), being married (0.041), physical inactivity (0.009) and former smoking (0.033) and the prevalence of multimorbidity was statistically significant in men only, or was stronger in men than in women. There was an inverse association between education and multimorbidity prevalence mainly in women (p for interaction <0.001), although attending formal school for five or fewer years in men also showed a borderline, inverse association.

Table 3: Crude and adjusted prevalence ratio (PR) based on simple and multiple Poisson regression

		Men				Women				
		Crude		Adjusted[2]		Crude		Adjusted[2]		Interaction[3]
Variables	**Levels**	**PR**	**95% CI**	**PR**	**95% CI**	**PR**	**95% CI**	**PR**	**95% CI**	**P-value**
Age group	≤49	1		1		1		1		
	50-60	1.64	(1.50-1.80)**	1.46	(1.32-1.61)**	1.66	(1.58-1.76)**	1.51	(1.43-1.60)**	**0.282**
	61+	2.42	(2.20-2.65)**	1.87	(1.67-2.10)**	2.34	(2.20-2.49)**	2.06	(1.92-2.21)**	
Residential Area	Urban	1		1		1		1		
	Rural	1.04	(0.95-1.14)	0.93	(0.84-1.03)	0.94	(0.89-0.99)*	0.98	(0.92-1.05)	**0.280**
Ethnicity	Turkmen	1		1		1		1		
	Other[1]	1.26	(1.16-1.36) **	1.24	(1.14-1.35)**	1.02	(0.97-1.07)	1.09	(1.03-1.15)*	**0.003**
Marital Status	Unmarried	1		1		1		1		
	Married	0.94	(0.75-1.18)	1.22	(0.97-1.54)	0.72	(0.68-0.76)**	0.98	(0.92-1.04)	**0.042**
Education	Illiterate	1		1		1		1		
	≤ 5 years	0.75	(0.69-0.82) **	0.91	(0.82-1.00)**	0.65	(0.59-0.71)**	0.81	(0.73-0.89)**	**0.000**
	6-12 years	0.69	(0.63-0.77) **	0.91	(0.80-1.03)	0.42	(0.35-0.50)**	0.57	(0.47-0.69)**	
	University degree	0.66	(0.54-0.81) **	0.90	(0.72-1.13)	0.26	(0.13-0.50)**	0.37	(0.19-0.72)*	
Work Currently	Yes	1		1		1		1		
	No	2.04	(1.88-2.21)**	1.35	(1.23-1.48)**	1.74	(1.63-1.85)**	1.27	(1.18-1.35)**	**0.225**
SES	Good	1		1		1		1		
	Medium	1.05	(0.97-1.14)	0.95	(0.86-1.05)	1.12	(1.06-1.18)**	1.08	(1.02-1.14)*	**0.033**
	Poor	1.26	(1.12-1.40)**	1.04	(0.91-1.18)	1.28	(1.20-1.38)**	1.11	(1.03-1.19)*	
Physical Activity	Yes	1		1.00		1		1.00		
	No	1.66	(1.54-1.79)**	1.28	(1.18-1.39)**	1.24	(1.16-1.33)**	1.12	(1.04-1.21)*	**0.009**
BMI	Normal	1		1		1		1		
	Underweight	1.25	(1.06-1.46)	1.04	(0.89-1.22)	1.09	(0.95-1.25)	0.93	(0.81-1.07)	**0.594**
	Overweight	1.28	(1.17-1.39)**	1.46	(1.34-1.60)**	1.30	(1.22-1.38)**	1.43	(1.34-1.52)**	
	Obese	1.54	(1.39-1.71)**	1.85	(1.66-2.06)**	1.60	(1.50-1.70)**	1.87	(1.75-1.99)**	
Smoking	Never	1		1		1		1		
	Ex-smoker	1.59	(1.45-1.74)**	1.25	(1.13-1.39)**	1.77	(1.35-2.30)**	1.22	(0.93-1.59)	**0.033**
	Light smoker	0.77	(0.68-0.88)**	0.78	(0.69-0.89)**	1.02	(0.80-1.30)	0.89	(0.70-1.14)	
	Heavy smoker	0.95	(0.83-1.08)	0.87	(0.76-1.00)	1.80	(1.22-2.64)**	1.33	(0.90-1.96)	
Other tobacco use	No	1		1		1		1		
	Yes	1.42	(1.30-1.55)**	0.99	(0.89-1.09)	1.24	(1.08-1.42)*	0.98	(0.85-1.13)	**0.945**
Opium	No	1		1		1		1		
	Yes	1.49	(1.38-1.61)**	1.50	(1.37-1.64)**	1.51	(1.40-1.62)**	1.45	(1.35-1.57)**	**0.558**
Alcohol	No	1		1.00		1		1.00		
	Yes	1.40	(1.25-1.58)**	1.31	(1.15-1.49)**	1.00	(0.42-2.40)	0.94	(0.39-2.25)	**0.401**

1. Other included Persian, Turk, Sistani, Baluch and Kurdish; 2. Prevalence ratios were adjusted for baseline variables; 3. Difference between sexes (P-value for interaction refers to Wald test),

**: p-value <0.001; *: p-value <0.01

DISCUSSION:

We examined gender-related determinants of multimorbidity in a cross-sectional analysis of a large cohort study with more than 49,000 participants. Overall prevalence of multimorbidity was higher in women at all ages. Multimorbidity was not only prevalent in elderly people; interestingly it also affected younger cohort participants gender interacted with sociodemographic factors including ethnicity, marital status, educational level, socioeconomic status, physical activity, and smoking in terms of the prevalence of multimorbidity.

Despite current perceptions, our study revealed that multimorbidity is not confined to elderly people, with even younger men and women cohort participants (age <50) suffering from this condition. Some studies have reported similar results but most are restricted to elderly people [23]. Our study showed that women had a greater burden of multimorbidity than men, consistent with Zielinski's report from a Swedish population [24]. One possible reason for higher rates of multimorbidity in women may be that they self-report more [25, 26]. According to Bertakis et al, women more often feel that their health is poor [27]. There is evidence that women use more health care facilities, particularly public funded health care than men [28, 29]. Other possible influences on this excess multimorbidity in women can be higher exposure to common risk factors for chronic diseases, or gender inequality in access to healthcare [7, 8, 12, 30-32].

We showed an association between low socioeconomic status (SES) and multimorbidity, which was statistically significant only for women. Earlier studies have associated low SES with higher multimorbidity [33, 34]. This may partly be explained by differences in lifestyle by SES. Low SES may reduce care-seeking in patients with chronic diseases [33]. This may produce a paradox, as lower usage of health care may translate to lower documented morbidity. Our finding that low and middle SES are associated with multimorbidity in women supports the assertion that women are at higher risk of adverse effects of poverty, payment inequality and health disparities [35]. Khanam et al also concluded that gender differences in SES, living and working environment, lifestyle factors and life-events may affect the occurrence and outcome of multimorbidity among women [36].

A previous study revealed that inactivity can increase the risk of breast and colorectal cancers, diabetes mellitus and ischemic heart diseases [37]. The findings of a study by Autenrieh et al. (2013) found an inverse association between physical activity and multimorbidity among men [26]. While in another study, multimorbidity was not associated with physical activity either in

men or women [38]. An association between sedentary occupations involving less physical activity and multimorbidity found in the current study which was more evident in men. This is may be due to the proportionately longer hours that men spent on their sedentary occupation.

In this study, with increasing the level of education, the prevalence ratio of multimorbidity significantly decreased, and this effect was more obvious in women; similarly other studies showed a decreased likelihood of multimorbidity in better-educated populations [30, 32, 39].

GCS included participants above 40 years, whose cultural, educational and social basis shaped around 1970s during which there was limited access to primary healthcare (PHC) facilities especially in rural areas [40]. However, after 1980s there was a remarkable improvement in health, life expectancy and communicable diseases control and socioeconomic status in Iran [20, 40]. Iran was among the few countries that reached WHO defined millennium development goals before 2015 [41]. As mentioned in the results education was defined as a protective factor for multimorbidity. Women's literacy rate in this population was less than 20% [19], while according to the latest reports women's literacy rate in Golestan province increased a great deal and reach to more than 80% [42]. These variations in health, education, and other socioeconomic status decreased health inequalities which may influence the pattern of diseases, including multimorbidity in the next generations. In this regard, Iran and similar countries need to adopt appropriate policies considering WHO recommendations.

Access to affordable health services, as a human right, is a requirement for quality of life. Despite the considerable progress in communities' health over the recent decades, the prevalence of chronic diseases is increasing [43]. Some global movements related to healthy life, underlined the need for multi-dimensionality collaborations for health promotion, as stated in the Ottawa Charter. For instance "Healthy-cities" project tries to integrate modern technologies and following sedentary life, over and done with encouraging people to use healthy life methods, such as involving in physical activity programs, increase level of health awareness and education and decrease social and health inequalities [43-47]. Considering findings of this study and recommendations of WHO (World Health Organization) [43] for our environment, we need specific national and sub-national health policy programs for men and women in different age-groups and socioeconomic status.

CONCLUSION:

Our findings confirm that multimorbidity is an important neglected health issue in all age-groups, specifically in women with lower socioeconomic status and educational level. Also men with low physical activity and former smokers are at higher risk of multimorbidity.
Defining priority interventions and multi-sectorial policies to tackle multimorbidity in both men and women, particularly younger populations are required. A desirable intervention would be development of a national health benefit service package recommended by WHO, emphasizing on health promotion to prevention with suitable approaches to chronic diseases and multimorbidity.

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Ethics approval: This study was approved by the ethics committee of the Digestive Diseases Research Institute, Tehran University of Medical Sciences (OHRP-IRB-00001641).

Contributorship Statement: MY analysed the data. MA and AM drafted the manuscript. AS, AM, MA, MA, MK, MHD provided scientific input. RM, FK, HP, AD, SQ provided expert clinical advice and interpretation of the data. PB, FK, RM, BA, AP, FI, PB, SMD provided expert guidance on health policy and delivery of healthcare and interpretation of the data. AS, MA, AM, FI were involved as methodologist in the interpretation of the research and the writing of the manuscript. All authors made critical revisions and provided intellectual content to the manuscript, approved the final version to be published and agreed to be accountable for all aspects of the work. AS and BA are the guarantor for this study.

Competing interests: all the authors have no conflicts of interest to declare.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3 4
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	3 (Ref. 19)
Study size	10	Explain how the study size was arrived at	3 (Ref. 19)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	3 (Ref. 19)
		(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	3 (Ref. 19)
		(*e*) Describe any sensitivity analyses	3 (Ref. 19)

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3 (Ref. 19)
		(b) Give reasons for non-participation at each stage	3 (Ref. 19)
		(c) Consider use of a flow diagram	3 (Ref. 19)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3 (Ref. 19) and Table. 2
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	*Cross-sectional study*—Report numbers of outcome events or summary measures	*4*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table. 2
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5 6 7
Generalizability	21	Discuss the generalisability (external validity) of the study results	7 8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

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Multimorbidity: A Neglected Issue among Middle-Age people- Results of gender differences investigation in a Large Population-Based Cross-Sectional Study in West Asia

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Complete List of Authors:	Alimohammadian, Masoomeh ; Tehran University of Medical Sciences, Department of Human Ecology, School of Public Health Majidi, Azam; Tehran University of Medical Sciences, Digestive Diseases Research Institute Yaseri, Mehdi; Tehran University of Medical Sciences, Department of Epidemiology and Biostatistics Ahmadi, Batoul; Tehran University of Medical Sciences, Department of Health Management and Economics, School of Public Health Islami, Farhad; Institute for Translational Epidemiology and Tisch Cancer Institute,, Icahn School of Medicine at Mount Sinai Delavari, Alireza; Tehran University of Medical Sciences, Digestive Diseases Research Institute Amani, Mohammad; Tehran University of Medical Sciences, Digestive Diseases Research Institute Derakhshan, Mohammad Feyz-Sani, Akbar; Tehran University of Medical Sciences, Digestive Diseases Research Institute Poustchi, Hossein; Tehran University of Medical Sciences, Digestive Diseases Research Institute Pourshams, Akram; Tehran University of Medical Sciences, Digestive Diseases Research Institute Sadjadi, Amir Mahdi Khoshnia, Masoud; Tehran University of Medical Sciences, Digestive Diseases Research Institute Qaravi, Samad; Tehran University of Medical Sciences, Digestive Diseases Research Institute Abnet, Christian; National Cancer Institute, Division of Cancer Epidemiology and Genetics Dawsey, Sanford; National Cancer Institute, NIH, Division of Cancer Epidemiology & Genetics Brennan, Paul ; International Agency for Research on Cancer, Genetic Epidemiology Group Kamangar, Farin; Morgan State University, Department of Public Health Analysis, School of Community Health and Policy, Boffetta, Paolo; Institute for Translational Epidemiology and Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai Sadjadi, Alireza; Tehran University of Medical Sciences, Digestive Diseases Research Institute Malekzadeh, Reza; Tehran University of Medical Sciences, Digestive Diseases Research Institute

Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy
Keywords:	Multimorbidity, Ageing, Gender differences, Golestan Cohort Study, Iran

Multimorbidity: A Neglected Issue among Middle-Age people- Results of gender differences investigation in a Large Population-Based Cross-Sectional Study in West Asia

Masoomeh Alimohammadian[1,2,3∞], Azam Majidi[1,2∞], Mehdi Yaseri[4], Batoul Ahmadi[5*], Farhad Islami[1,6], Alireza Delavari[1,2], Mohammad Amani[1,2], Mohammad H. Derakhshan[2,7], Akabar Feyz Sani[1,2], Hossein Poustchi[1,2], Akram Pourshams[1,2,8], AmirMahdi Sadjadi[1], Masoud Khoshnia[2,9], Samad Qaravi[2,9], Christian C. Abnet[10], Sanford M. Dawsey[10], Paul Brennan[11], Farin Kamangar[1,12], Paolo Boffetta[6], Alireza Sadjadi[1,2*], Reza Malekzadeh[1,2]

1. Digestive Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
2. Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Human Ecology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
4. Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
5. Department of Health Management and Economics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
6. Institute for Translational Epidemiology and Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, NY, USA
7. Division of Cardiovascular and Medical Sciences, Section of Gastroenterology, University of Glasgow, Glasgow, UK.
8. Liver and Pancreaticbiliary Research center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
9. Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran
10. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA
11. International Agency for Research on Cancer, Genetic Epidemiology Group, Lyon, France
12. Department of Public Health Analysis, School of Community Health and Policy, Morgan State University, Baltimore, MD, USA

∞These authors contributed equally to the work and share first authorship

* These authors share the corresponding position:

Corresponding Authors:

Dr. Alireza Sadjadi: sadjadia@gmail.com and **Dr. Batoul Ahmadi:** ahmadiba@tums.ac.ir

ABSTRACT:

Objectives:

Investigating the impact of gender and age-groups upon multimorbidity in northern Iran

Design: A cross-sectional analysis of Golestan cohort data.

Setting: Community setting of Golestan province, Iran

Study population: 49,946 individuals (aged 40-75 years)

Main outcome measures: Data related to Multimorbidity, defined as comorbidity of 2 or more chronic diseases, were collected in the beginning of a representative cohort study during 2003-2004. Simple and multiple Poisson regression models with robust variances were utilized to examine the simultaneous effects of multiple factors.

Results: The overall prevalence of multimorbidity was 25.0% in women and 13.4% in men ($p< 0.001$), and it was higher in women at all ages groups. Although multimorbidity was associated with age, its prevalence was considerable even among younger participants (17.3% in women and 8.6% in men <50 years). With regard to the prevalence of multimorbidity, several factors showed a statistically significant interaction with gender. Former-smoking and being of Non-Turkmen ethnic groups, married, or physical inactivity showed a significantly stronger association with multimorbidity in men. Being of lower socioeconomic groups was associated with multimorbidity prevalence only in women. Higher educational levels (compared to illiteracy) showed an inverse association mainly in women ($p< 0.001$). Our study identified socioeconomic status, ethnicity, physical activity, marital status, educational level and smoking as determinants of gender differences in multimorbidity prevalence ($p< 0.01$).

Conclusion: Regarding gender and socioeconomic disparities, particularly among younger and middle-age groups, prevention and control of multimorbidity requires gender-specific health policies and interventions.

Strengths and limitations of this study:

- A large, population-based cohort study with detailed data on sociodemographic, lifestyle and behavioral risk factors provides a stronger insight to the analysis provided by this article.
- All data were collected by interactive face-to-face interviews conducted by trained medically qualified researcher.

- Cross-sectional data analyses are susceptible to residual confounding and cannot establish the direction of an association.
- Another limitation of this investigation was "self- reporting method of gathered data, constraining the research from accessing adequate documents about chronic diseases.

Keywords: Multimorbidity, Ageing, Gender differences, Golestan Cohort Study, Iran

SUMMARY:

What is already known about this subject?

- Limited evidence exists about gender and age differences in multimorbidity in developing countries

What does this study add?

- To address gender and age differences in multimorbidity in Iran as a sample developing country, a cross-sectional study in the baseline data of Golestan Cohort was conducted.
- Socioeconomic/educational status, ethnicity, physical activity and smoking were significant determinants of gender differences

How might this impact on clinical practice? (Recommendations for policy)

- The findings of this study confirm that multimorbidity is an important neglected health issue even in middle-age groups
- Control of multimorbidity require gender-specific health interventions, particularly in younger and middle-age groups

INTRODUCTION:

Occurrence of chronic diseases is not only cause physical complications and social difficulties for the patient, but it also results in a huge burden upon the health systems. This issue could be further amplified by co-occurrence of two or more chronic diseases in one person, a condition that is known as multimorbidity.[1-3] Multimorbidity is associated with a higher mortality risk and increased utilization of healthcare services; therefore, it is a demanding situation for patients, their families, and healthcare providers.[4-8]

Despite the rise in life expectancy among the developing countries over the last decades, the growing prevalence of multimorbidity has led to a decreased quality of life in patients with chronic diseases, especially in populations with limited resources.[9] [10] Patients with multimorbidity require specific medical care; however the current clinical practice lacks practical guidelines developed for management and treatment of patients who suffer from the mentioned condition.[11] In the current clinical practice, in cases of multimorbidity, the routine approach of dealing with a single disease at a time not only could cause higher cost to patients and healthcare systems but it also may lead to unwanted side effects.[12]

A limited number of studies have indicated a gender difference in patterns of multimorbidity.[13] This difference may be related to biological, socio-cultural, environmental, and economic factors. As these factors vary globally, their associations with multimorbidity may differ across populations.[14-18] Therefore, more research needs to be conducted in this topic.

The epidemiology of multimorbidity had been previously studied using the baseline data from the Golestan Cohort Study (GCS), a large-scale prospective study in Western Asia.[19] In this article we applied numerous analyses to illuminate variability in the prevalence and determinants of multimorbidity in different ages, and also further examine interactions between gender and multiple sociodemographic and lifestyle factors potentially associated with multimorbidity.

METHODS:

A total of 50,045 adults aged 40-75 years residing in Golestan province in northeastern Iran were enrolled in a cohort study from 2004 to 2008. This analysis included 49,946 (99.8%) participants that were Iranian citizens and excluded non- Iranians job seekers or refugees. The study protocol[20] and details of this study population are described elsewhere. [19] Trained staff utilized validated questionnaires to collect data on sociodemographic factors, lifestyle habits, occupation,

physical activity, dietary habits, past medical history, and medications. A short physical exam was performed to measure blood pressure, height, and weight.[20]

In this mainly rural population, physical activity was defined based on occupational activity and people were coded as "physically active" or "physically inactive". Based on the two-step cluster analysis using similarities of family assets, ethnicity, gender, employment status, appliance ownership, and surface area of the home, the socioeconomic status (SES) of participants was categorized as low, middle or high.[21]

Here, multimorbidity refers to the self-reported co-occurrence of two or more chronic diseases (non-acute conditions)[19] in the same person.[7 8 22] Based on the possibility of gathering valid self-reported data in the feasibility phase of GCS, self-reported information was collected for the following diseases: cardiovascular diseases (CVD), diabetes (type I and II), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), chronic liver disease, tuberculosis (TB), gastroesophageal reflux disease (GERD), and cancers.[20]

Statistical analysis: The proportion of multimorbidity among participants was estimated by several sociodemographic and lifestyle factors. In order to evaluate the differences in distribution of factors between genders, t-test, Mann-Whitney or chi-square tests, were applied whenever appropriate.

There are some occasions in which odds ratio could be misleading, thus a model was initiated which can provide the prevalence ratio. Simple and multiple Poisson regressions were used with robust variances, following the method presented by Barros and Hirakata[23], in order to examine the association between the studied factors and multimorbidity and calculated crude and adjusted prevalence ratios and 95% confidence intervals (CIs) in two genders. The gender difference between determinants of multimorbidity (commonly known as interaction or effect modification) was evaluated in separate multiple Poisson regression models.

In all analyses, the design effects were considered using the generalized estimating equations (GEE) method. The GEE (Generalized Estimating Equation) is a generalization of the GLM that could handle the correlation of observation. The assumption of the GLM is the independence of observation which could be violated in studies where there are Intra cluster correlations in cluster sampling or randomization and in longitudinal analysis when repeated measurements are performed from a subject.[24 25] All statistical analyses were performed using SPSS software (IBM

Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.). Two-sided p-values below 0.05 were considered as statistically significant.

RESULTS:

A total of 49,946 participants aged 40-75 years were included in the study, which 28,748 (57.6%) of participants were women. The prevalence of self-reported chronic diseases in those with multimorbidity and the gender difference are presented in supplementary Table.

The overall prevalence of multimorbidity was 25.0% in women and 13.4% in men with a difference of 11.7% ($p < 0.001$). Table 1 represents the prevalence of multimorbidity in all study participants by gender and sociodemographic and lifestyle factors. The prevalence of multimorbidity in age less than 50 years was 17.3% in women and 8.6% in men, but it was 40.6% in women and 20.2% in men above 60 years.

Table 1: The multimorbidity prevalence by gender, separated in different levels of sociodemographic & lifestyle factors

		Total		Men		Women		
		Overall	Multimorbidity	Overall	Multimorbidity	Overall	Multimorbidity	Diff.**
Variables	**Levels**	N=49,946	%	N=21,198	%	N=28,748	%	%
Age group	40-49	23074	13.9	9012	8.6	14062	17.3	-8.7*
	50–60	17512	22.7	7321	14.2	10191	28.8	-14.6*
	61-75	9360	30.4	4865	20.9	4495	40.6	-19.7*
Residential Area	Urban	38354	20.2	16514	13.3	21840	25.4	-12.2*
	Rural	11592	19.8	4684	13.8	6908	23.9	-10.0*
Ethnicity	Turkmen	37253	19.6	16051	12.6	21202	24.9	-12.3*
	others [1]	12693	21.5	5147	15.8	7546	25.4	-9.5*
Marital Status	Unmarried	43873	18.6	20634	13.4	23239	23.3	-10.0*
	Married	6073	30.6	564	14.2	5509	32.3	-18.1*
Education	Illiterate	35060	23.4	10406	15.6	24654	26.7	-11.1*
	≤ 5 years	8449	13.6	5545	11.7	2904	17.3	-5.5*
	6-12 years	5376	10.9	4317	10.8	1059	11.1	-0.3
	University degree	1061	9.9	930	10.3	131	6.9	3.5
Work Currently	Yes	43415	18.5	17529	11.3	25886	23.3	-12.0*
	No	6530	30.7	3668	23.1	2862	40.5	-17.4*
SES	Good	18831	18.1	8703	12.7	10128	22.7	-10.0*
	Medium	24001	20.5	9748	13.3	14253	25.4	-12.1*
	Poor	7105	24.1	2741	15.9	4364	29.2	-13.3*
Physical Activity	Yes	15838	13.3	11308	10.2	4530	20.8	-10.6*
	No	33947	23.2	9852	17.0	24095	25.8	-8.8*
BMI	Underweight	2380	17.4	1245	14.1	1135	21.0	-6.9*
	Normal	17871	14.9	9596	11.3	8275	19.2	-7.9*
	Overweight	16993	20.4	7271	14.4	9722	24.9	-10.6*
	Obese	12694	27.4	3081	17.3	9613	30.7	-13.3*
Smoking	Never	41323	21.1	13018	12.8	28305	24.9	-12.1*
	Ex-smoker	3189	21.2	3064	20.3	125	44.0	-23.7*
	Light smoker	3272	11.1	3013	9.9	259	25.5	-15.6*
	Heavy smoker	2161	13.0	2103	12.1	58	44.8	-32.7*
Other tobacco use	Yes	4427	19.7	3749	17.7	678	30.8	-13.1*
	No	45519	20.1	17449	12.5	28070	24.9	-12.4*
Opium	Yes	8489	19.6	6138	11.7	2351	24.0	-12.3*
	No	41457	22.7	15060	17.4	26397	36.2	-18.8*
Alcohol	Yes	1721	20.2	1701	13.0	20	25.0	-12.1*
	No	48225	18.2	19497	18.2	28728	25.0	-6.8

1. Other included: Persian, Turk, Sistani, Baluch and Kurdish; **. Men vs. women;* p-value <0.001

The results from multiple Poisson regression models are shown in Table 2. The association between poor and middle socioeconomic status with multimorbidity prevalence was significantly stronger in women than men (p for interaction=0.033). On the other hand (based on p-value for interaction), the association between Non-Turkmen groups (0.003), being married (0.041), physical inactivity (0.009) and former smoking (0.033) and the prevalence of multimorbidity was statistically significant in men only, or was stronger in men than in women. There was an inverse association between education and multimorbidity prevalence mainly in women (p for interaction <0.001), although attending formal school for five or fewer years in men also showed a borderline, inverse association.

Table 2: Crude and adjusted prevalence ratio (PR) based on simple and multiple Poisson regression

		Men				Women				
		Crude		Adjusted[2]		Crude		Adjusted[2]		Interaction[3]
Variables	**Levels**	PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI	P-value
Age group	40-49	**Ref.**		**Ref.**		**Ref.**		**Ref.**		
	50-60	1.64	(1.50-1.80)**	1.46	(1.32-1.61)**	1.66	(1.58-1.76)**	1.51	(1.43-1.60)**	0.282
	61-75	2.42	(2.20-2.65)**	1.87	(1.67-2.10)**	2.34	(2.20-2.49)**	2.06	(1.92-2.21)**	
Residential Area	Urban	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.280
	Rural	1.04	(0.95-1.14)	0.93	(0.84-1.03)	0.94	(0.89-0.99)*	0.98	(0.92-1.05)	
Ethnicity	Turkmen	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**0.003**
	Other[1]	1.26	(1.16-1.36) **	1.24	(1.14-1.35)**	1.02	(0.97-1.07)	1.09	(1.03-1.15)*	
Marital Status	Unmarried	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**0.042**
	Married	0.94	(0.75-1.18)	1.22	(0.97-1.54)	0.72	(0.68-0.76)**	0.98	(0.92-1.04)	
Education	Illiterate	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**0.000**
	≤ 5 years	0.75	(0.69-0.82) **	0.91	(0.82-1.00)**	0.65	(0.59-0.71)**	0.81	(0.73-0.89)**	
	6-12 years	0.69	(0.63-0.77) **	0.91	(0.80-1.03)	0.42	(0.35-0.50)**	0.57	(0.47-0.69)**	
	University degree	0.66	(0.54-0.81) **	0.90	(0.72-1.13)	0.26	(0.13-0.50)**	0.37	(0.19-0.72)*	
Work Currently	Yes	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.225
	No	2.04	(1.88-2.21)**	1.35	(1.23-1.48)**	1.74	(1.63-1.85)**	1.27	(1.18-1.35)**	
SES	Good	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**0.033**
	Medium	1.05	(0.97-1.14)	0.95	(0.86-1.05)	1.12	(1.06-1.18)**	1.08	(1.02-1.14)*	
	Poor	1.26	(1.12-1.40)**	1.04	(0.91-1.18)	1.28	(1.20-1.38)**	1.11	(1.03-1.19)*	
Physical Activity	Yes	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**0.009**
	No	1.66	(1.54-1.79)**	1.28	(1.18-1.39)**	1.24	(1.16-1.33)**	1.12	(1.04-1.21)*	
BMI	Normal	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.594
	Underweight	1.25	(1.06-1.46)	1.04	(0.89-1.22)	1.09	(0.95-1.25)	0.93	(0.81-1.07)	
	Overweight	1.28	(1.17-1.39)**	1.46	(1.34-1.60)**	1.30	(1.22-1.38)**	1.43	(1.34-1.52)**	
	Obese	1.54	(1.39-1.71)**	1.85	(1.66-2.06)**	1.60	(1.50-1.70)**	1.87	(1.75-1.99)**	
Smoking	Never	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**0.033**
	Ex-smoker	1.59	(1.45-1.74)**	1.25	(1.13-1.39)**	1.77	(1.35-2.30)**	1.22	(0.93-1.59)	
	Light smoker	0.77	(0.68-0.88)**	0.78	(0.69-0.89)**	1.02	(0.80-1.30)	0.89	(0.70-1.14)	
	Heavy smoker	0.95	(0.83-1.08)	0.87	(0.76-1.00)	1.80	(1.22-2.64)**	1.33	(0.90-1.96)	
Other tobacco use	No	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.945
	Yes	1.42	(1.30-1.55)**	0.99	(0.89-1.09)	1.24	(1.08-1.42)*	0.98	(0.85-1.13)	
Opium	No	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.558
	Yes	1.49	(1.38-1.61)**	1.50	(1.37-1.64)**	1.51	(1.40-1.62)**	1.45	(1.35-1.57)**	
Alcohol	No	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.401
	Yes	1.40	(1.25-1.58)**	1.31	(1.15-1.49)**	1.00	(0.42-2.40)	0.94	(0.39-2.25)	

1. Other included Persian, Turk, Sistani, Baluch and Kurdish; 2. Prevalence ratios were adjusted for baseline variables; 3. Difference between sexes (P-value for interaction refers to Wald test),

**: p-value <0.001; *: p-value <0.01

DISCUSSION:

This study examined gender-related determinants of multimorbidity in a cross-sectional analysis of a large cohort study with more than 49,000 participants. Overall prevalence of multimorbidity was shown to be higher in women at all ages. Multimorbidity was not only prevalent in elderly people; interestingly it also affected younger cohort participants. Gender interacted with sociodemographic factors including ethnicity, marital status, educational level, socioeconomic status, physical activity, and smoking in terms of the prevalence of multimorbidity. Past smoking habit, being of Non-Turkmen ethnic groups, being married or physically inactive showed a significant association with multimorbidity in men. Being of lower socioeconomic groups was associated with multimorbidity prevalence only in women.

Despite current perceptions, this study revealed that multimorbidity is not confined to elderly people, since even the younger men and women among the cohort participants (age <50) also suffered from this condition. Some studies have reported similar results but most are restricted to elderly people.[26] This research presented that women had a greater burden of multimorbidity than men, consistent with Zielinski's report from a Swedish population.[27] A potential cause for more significant prevalence of multimorbidity among women could be their relatively higher tendency to share their conditions in self-reports.[28 29] According to Bertakis et al, women more often feel that their health is poor.[30] There is evidence that women use more health care facilities, particularly public funded health care in comparison to men.[31 32] Other possible influences on this excess multimorbidity in women can be higher exposure to common risk factors for chronic diseases, or gender inequality in access to healthcare.[7 8 13 33-35]

The study showed an association between low socioeconomic status (SES) and multimorbidity, which was significantly associated with being women. Earlier studies have associated low SES with higher multimorbidity.[36 37] This may partly be explained by differences in lifestyle by SES. Low SES may reduce care-seeking in patients with chronic disease.[36] This may produce a paradox, as lower usage of health care may translate to lower documented morbidity. This study's findings which indicated that low and middle SES are associated with multimorbidity in women supports the assertion that women are at higher risk of adverse effects of poverty, payment inequality and health disparities.[38] Khanam et al. also concluded that gender differences in SES, living and working environment, lifestyle factors and life-events may affect the occurrence and outcome of multimorbidity among wome.[39]

A previous study revealed that inactivity may increase the risk of breast and colorectal cancers, diabetes mellitus and ischemic heart diseases.[40] The findings of a study by Autenrieh et al. (2013) discovered an inverse association between physical activity and multimorbidity among men.[29] While in another study, multimorbidity was not associated with physical activity either in men or women.[41] An association between sedentary occupations involving less physical activity and multimorbidity found in the current study which was more evident in men. This may be due to the proportionately longer hours that men spent on their sedentary occupation.

In this study, with increasing the level of education, the prevalence ratio of multimorbidity significantly decreased, and this association was more obvious in women; similarly other studies showed a decreased likelihood of multimorbidity in better-educated populations.[33 35 42]

GCS included participants above 40 years, whose cultural, educational and social basis shaped around 1970s during which there was limited access to primary healthcare (PHC) facilities especially in rural area.[43] However, after 1980s there was a remarkable improvement in health, life expectancy and communicable diseases control and socioeconomic status in Iran.[21 43] Iran was among the few countries that reached WHO defined millennium development goals before 2015.[44] As mentioned in the results, education was defined as a protective factor for multimorbidity. Women's literacy rate in this population was less than 20% [20], while according to the latest reports women's literacy rate in Golestan province increased a great deal and reach to an excess of 80%.[45] These variations in health, education, and other socioeconomic status decreased health inequalities which may be influential to the pattern of diseases, including multimorbidity in the next generations. In this regard, Iran and similar countries need to adopt appropriate policies considering WHO recommendations.

Access to affordable health services, as a human right, is a necessity for a better quality of life. Despite the considerable progress in communities' health over the recent decades, the prevalence of chronic diseases is increasing.[46] Some global movements related to healthy life, underlined the need for multi-dimensionality collaborations for health promotion, as stated in the Ottawa Charter. For instance "Healthy-cities" project tries to integrate modern technologies and following sedentary life, over and done with encouraging people to use healthy life methods, such as involving in physical activity programs, increase level of health awareness and education and decrease social and health inequalities.[46-50] Considering findings of this study and recommendations of WHO (World Health Organization) [46] for the environment, a specific

national and sub-national health policy programs for men and women in different age-groups and socioeconomic status is required.

CONCLUSION:

The findings of this study confirm that multimorbidity is an important neglected health issue in all age-groups, specifically in women with lower socioeconomic status and educational level. Also men with low physical activity and former smokers are at higher risk of multimorbidity. Defining priority interventions and multi-sectorial policies to tackle multimorbidity in both men and women, particularly younger populations are required. A desirable intervention would be development of a national health benefit service package recommended by WHO, emphasizing on health promotion to prevention with suitable approaches to chronic diseases and multimorbidity.

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Ethics approval: This study was approved by the ethics committee of the Digestive Diseases Research Institute, Tehran University of Medical Sciences (OHRP-IRB-00001641).

Contributorship Statement: MY analyzed the data. MA, AM and AMS drafted the manuscript. AS, AM, MA, MA, MK, MHD provided scientific input. RM, FK, HP, AD, SQ provided expert clinical advice and interpretation of the data. PB, FK, RM, BA, AP, FI, PB, SMD provided expert guidance on health policy and delivery of healthcare and interpretation of the data. AS, MA, AM, FI were involved as methodologist in the interpretation of the research and the writing of the manuscript. All authors made critical revisions and provided intellectual content to the manuscript, approved the final version to be published and agreed to be accountable for all aspects of the work. AS and BA are the guarantor for this study.

Competing interests: all the authors have no conflicts of interest to declare.

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Supplementary Table 1: Chronic conditions by gender in population with Multimorbidity in the Golestan Cohort Study (GCS)

Chronic Conditions	Total (N=10,035)		Men (N=2,836)		Women (N=7,199)		Difference (Men vs. women)
	Number	%	Number	%	Number	%	%
GERD	7690	76.6	2030	71.6	5660	78.6	-7.1*
CVD	7379	73.5	1927	67.9	5452	75.7	-7.8*
Diabetes	2535	25.3	686	24.2	1849	25.7	-1.5
COPD	2203	22.0	653	23.0	1550	21.5	1.5
TB	1030	10.3	293	10.3	737	10.2	0.1
Cancers	102	1.0	34	1.2	68	0.9	0.3
CKD	72	0.7	27	1.0	45	0.6	0.3
Liver diseases	28	0.3	11	0.4	17	0.2	0.2

* P-value <0.001

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3 4
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	3 (Ref. 19)
Study size	10	Explain how the study size was arrived at	3 (Ref. 19)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	3 (Ref. 19)
		(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	3 (Ref. 19)
		(*e*) Describe any sensitivity analyses	3 (Ref. 19)

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3 (Ref. 19)
		(b) Give reasons for non-participation at each stage	3 (Ref. 19)
		(c) Consider use of a flow diagram	3 (Ref. 19)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3 (Ref. 19) and Table. 2
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	*Cross-sectional study*—Report numbers of outcome events or summary measures	*4*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table. 2
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5 6 7
Generalizability	21	Discuss the generalisability (external validity) of the study results	7 8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

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Multimorbidity as an Important Issue among Women: Results of Gender Difference Investigation in a Large Population-Based Cross-Sectional Study in West Asia

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Complete List of Authors:	Alimohammadian, Masoomeh ; Tehran University of Medical Sciences, Department of Human Ecology, School of Public Health Majidi, Azam; Tehran University of Medical Sciences, Digestive Diseases Research Institute Yaseri, Mehdi; Tehran University of Medical Sciences, Department of Epidemiology and Biostatistics Ahmadi, Batoul; Tehran University of Medical Sciences, Department of Health Management and Economics, School of Public Health Islami, Farhad; Institute for Translational Epidemiology and Tisch Cancer Institute,, Icahn School of Medicine at Mount Sinai Derakhshan, Mohammad Delavari, Alireza; Tehran University of Medical Sciences, Digestive Diseases Research Institute Amani, Mohammad; Tehran University of Medical Sciences, Digestive Diseases Research Institute Feyz-Sani, Akbar; Tehran University of Medical Sciences, Digestive Diseases Research Institute Poustchi, Hossein; Tehran University of Medical Sciences, Digestive Diseases Research Institute Pourshams, Akram; Tehran University of Medical Sciences, Digestive Diseases Research Institute Sadjadi, Amir Mahdi Khoshnia, Masoud; Tehran University of Medical Sciences, Digestive Diseases Research Institute Qaravi, Samad; Tehran University of Medical Sciences, Digestive Diseases Research Institute Abnet, Christian; National Cancer Institute, Division of Cancer Epidemiology and Genetics Dawsey, Sanford; National Cancer Institute, NIH, Division of Cancer Epidemiology & Genetics Brennan, Paul ; International Agency for Research on Cancer, Genetic Epidemiology Group Kamangar, Farin; Morgan State University, Department of Public Health Analysis, School of Community Health and Policy, Boffetta, Paolo; Institute for Translational Epidemiology and Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai Sadjadi, Alireza; Tehran University of Medical Sciences, Digestive Diseases Research Institute Malekzadeh, Reza; Tehran University of Medical Sciences, Digestive Diseases Research Institute

Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy
Keywords:	Multimorbidity, Gender differences, Golestan Cohort Study, Iran

Multimorbidity as an Important Issue among Women: Results of Gender Difference Investigation in a Large Population-Based Cross-Sectional Study in West Asia

Masoomeh Alimohammadian[1,2,3∞], Azam Majidi [1,2∞], Mehdi Yaseri[4], Batoul Ahmadi[5*], Farhad Islami [1,6], Mohammad H. Derakhshan[2,7], Alireza Delavari[1,2], Mohammad Amani[1,2], Akabar Feyz Sani[1,2], Hossein Poustchi[1,2], Akram Pourshams[1,2,8], Amir Mahdi Sadjadi[1], Masoud Khoshnia[2,9], Samad Qaravi[2,9], Christian C. Abnet[10], Sanford M. Dawsey[10], Paul Brennan[11], Farin Kamangar[1,12], Paolo Boffetta[6], Alireza Sadjadi[1,2*], Reza Malekzadeh[1,2]

1. Digestive Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
2. Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Human Ecology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
4. Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
5. Department of Health Management and Economics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
6. Surveillance and Health Service Research, American Cancer Society, Atlanta, USA
7. Division of Cardiovascular and Medical Sciences, Section of Gastroenterology, University of Glasgow, Glasgow, UK
8. Liver and Pancreatic Biliary Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
9. Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran
10. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA
11. International Agency for Research on Cancer, Genetic Epidemiology Group, Lyon, France
12. Department of Public Health Analysis, School of Community Health and Policy, Morgan State University, Baltimore, MD, USA

[∞]These authors contributed equally to this work and share first authorship.

[*]Corresponding Authors:

Dr. Alireza Sadjadi: sadjadia@gmail.com and Dr. Batoul Ahmadi: ahmadiba@tums.ac.ir

ABSTRACT:

Objectives: This study investigated the impact of gender on multimorbidity in northern Iran.

Design: A cross-sectional analysis of the Golestan cohort data.

Setting: Golestan Province, Iran

Study population: 49946 residents (age: 40-75 years) of Golestan Province, Iran.

Main outcome measures: Researchers collected data related to multimorbidity, defined as co-existence of two or more chronic diseases in an individual, at the beginning of a representative cohort study which recruited its participants from 2004-2008. The researchers utilized simple and multiple Poisson regression models with robust variances to examine the simultaneous effects of multiple factors.

Results: Women had a 25.0% prevalence of multimorbidity, whereas men had a 13.4% prevalence (p<0.001). Women of all age-groups had a higher prevalence of multimorbidity. Of note, multimorbidity began at a lower age (40-49 years) in women (17.3%) compared to men (8.6%) of the same age (p<0.001). This study identified significant interactions between gender as well as socioeconomic status (SES), ethnicity, physical activity, marital status, education level, and smoking (p<0.01).

Conclusion: Prevention and control of multimorbidity requires health promotion programs to increase public awareness about the modifiable risk factors, particularly among women.

Strengths and limitations of this study:

- A large, population-based cross-sectional study with detailed data on sociodemographic, lifestyle and behavioral risk factors provides a stronger insight to the analysis provided by this article.
- Trained, qualified medical researchers collected all of the data by interactive face-to-face interviews.
- Cross-sectional data analyses are susceptible to residual confounding and cannot determine the direction of an association.
- Another limitation of this investigation was the possible recall bias resulted from the method of gathering medical history (self-report).

Keywords: Multimorbidity, Gender differences, Golestan Cohort Study, Iran

SUMMARY:

What is already known about this subject?

- Limited evidence exists about the relationship between multimorbidity and gender differences in developing countries.

What does this study add?

- We conducted a cross-sectional analysis on the baseline data from the Golestan Cohort Study to address gender differences in multimorbidity in Iran as a developing country.
- Significant determinants of gender differences in multimorbidity included SES, educational status, ethnicity, physical activity, and smoking.

How might this impact clinical practice? (Recommendations)

- The findings of this study confirm that multimorbidity is an important health issue, which requires gender-specific health interventions, particularly for the middle-aged population.

INTRODUCTION:

Chronic diseases not only induce physical complications and social hardship for patients, but also develop remarkable burden for health systems. This issue can be further intensified by multimorbidity, the simultaneous occurrence of two or more chronic diseases in one person.[1-3] Multimorbidity is associated with a higher mortality risk and increased utilization of healthcare services; therefore, it is a demanding situation for patients, their families, and healthcare providers.[4-8]

Despite the increase in life expectancy among developing countries over the last decades, the growing prevalence of multimorbidity has led to a decreased quality of life in patients with chronic diseases, especially in populations with limited resources.[9,10] Patients with multimorbidity require specific medical care; however, the current clinical practice lacks practical guidelines to manage and treat these patients.[11-14] Current clinical practices for patients with multiple chronic diseases routinely deal with each individual disease rather than multiple diseases, and can result in increased expenses for patients and healthcare systems, and possibly lead to unwanted adverse effects.[13,15,16]

Previous studies have shown a gender difference in patterns of multimorbidity. A systematic review of most previous studies indicated that women had a greater prevalence of multimorbidity compared to men.[17] This difference might be related to biological, sociocultural, environmental, or economic factors. As these factors vary globally, their associations with multimorbidity might differ across populations.[18-22] Therefore, more research should be conducted on this topic.

We used baseline data from the Golestan Cohort Study (GCS), a large-scale prospective study in Western Asia, to explore the epidemiology of multimorbidity.[23] In this article we used detailed statistical analyses to examine the variability of the prevalence and determinants of multimorbidity among different age groups. We also investigated interactions between gender and multiple sociodemographic and lifestyle factors potentially associated with multimorbidity.

METHODS:

This cross-sectional study analyzed baseline data from the GCS. We analyzed data from 49946 Iranians, aged 40-75 years, who resided in Golestan Province in northeastern Iran. Participants had no current or previous diagnosis of any upper gastrointestinal cancers. The original cohort recruited its participants from 2004-2008. [24] The details of this study have been described elsewhere. [23]

Body mass index (BMI) was defined as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (>30 kg/m^2). We divided participants into the following age clusters (age at the time of the interviews): 40-49, 50-60, and 61-75 years. In this mainly rural population, physical activity was defined based on occupational activity as follows: physically active (heavy or intense activity during employment) or physically inactive (all other participants). Participants' socioeconomic status (SES) comprised three levels (low, middle or high) according to the two-step cluster analysis [25] with the use of similarities for family assets, ethnicity, sex, employment status, age at onset of the first job, home ownership status and house size (surface area), and age.

Based on the possibility of gathering valid self-reported data during the feasibility phase of the GCS, we collected self-reported information for the following chronic diseases: cardiovascular disease (CVD), diabetes (types I and II), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), chronic liver disease, tuberculosis (TB), gastroesophageal reflux disease (GERD), and cancers.[24] Respondents reported the presence of regurgitation or heartburn during the past 1-2 years, via a standard GERD questionnaire.[26,27] Participants who reported any symptoms during the mentioned time period were considered to have GERD.

In this study, we defined multimorbidity as the simultaneous occurrence of two or more of the above mentioned chronic diseases (non-acute conditions)[23] in the same person.[7,8,28]

Statistical analysis: We estimated multimorbidity among participants according to several sociodemographic and lifestyle factors. The Student's t-test, Mann-Whitney, or chi-square tests evaluated differences in the distribution of respondents according to sociodemographic factors and lifestyle factors between men and women whenever appropriate.

Occasions exist in which the odds ratio can be misleading. Hence, we have used a model that could provide the prevalence ratio. Simple and multiple Poisson regressions were used with robust variances according to the method presented by Barros and Hirakata.[29] We sought to examine the possibility of a gender-based association between the studied factors and multimorbidity, calculated crude and adjusted prevalence ratios and test it with interaction (effect modification) test, and 95% confidence intervals. The gender differences between determinants of multimorbidity (i.e., interaction or effect modification) were evaluated in separate multiple Poisson regression models.

We have considered the design effects according to the generalized estimating equations (GEE) method for all analyses. This method is a generalization of the GLM that can handle the correlation of observation. The assumption of the GLM is the independence of observation which could be violated in studies that have intra-cluster correlations in cluster sampling or randomization, as well as in longitudinal analysis of repeated measurements obtained from a subject.[30,31] All statistical analyses were performed using SPSS software (IBM Corporation, released 2013, IBM SPSS Statistics for Windows, version 22.0; Armonk, NY, USA). Two-sided *p*-values less than 0.05 were considered statistically significant.

RESULTS:

This cross-sectional study enrolled 49946 participants (aged: 40-75 years) who predominantly resided in rural areas. Women comprised 28748 (57.6%) participants. The supplementary table shows the prevalence of self-reported chronic diseases in those with multimorbidity and the gender differences.

The results indicated an overall age-sex standardized prevalence for multimorbidity of 19.4% (95% CI: 19.1% to 19.8%). Women had almost twice the prevalence (25.0%) compared to men (13.4%), with a difference of 11.7% (95% CI: 11.0% to 12.4%), ($p<0.001$). Table 1 shows the prevalence of multimorbidity in all study participants according to gender, sociodemographic and lifestyle factors. Women had evidence of more multimorbidity in all age-groups. Of note, compared to men, multimorbidity in women began at an earlier age (40-49 years). In this age group, 17.3% of women had multimorbidity compared to 8.6% for men ($p<0.001$).

Table 1: Prevalence of multimorbidity by gender according to sociodemographic and lifestyle factors

		Total		Men		Women		Difference	
		Overall	Multimorbidity	Overall	Multimorbidity	Overall	Multimorbidity	Men vs. Women	p-value
Variables	**Levels**	N=49946	(%)	N=21198	(%)	N=28748	(%)	(%)	
Age (years)	40-49	23074	13.9	9012	8.6	14062	17.3	-8.7*	<0.001
	50-60	17512	22.7	7321	14.2	10191	28.8	-14.6*	<0.001
	61-75	9360	30.4	4865	20.9	4495	40.6	-19.7*	<0.001
Residential area	Rural	38354	20.2	16514	13.3	21840	25.4	-12.2*	<0.001
	Urban	11592	19.8	4684	13.8	6908	23.9	-10.0*	<0.001
Ethnicity	Turkmen	37253	19.6	16051	12.6	21202	24.9	-12.3*	<0.001
	Other[1]	12693	21.5	5147	15.8	7546	25.4	-9.5*	<0.001
Marital status	Unmarried	43873	18.6	20634	13.4	23239	23.3	-10.0*	<0.001
	Married	6073	30.6	564	14.2	5509	32.3	-18.1*	<0.001
Education	Illiterate	35060	23.4	10406	15.6	24654	26.7	-11.1*	<0.001
	≤5 years	8449	13.6	5545	11.7	2904	17.3	-5.5*	<0.001
	6-12 years	5376	10.9	4317	10.8	1059	11.1	-0.3	0.761
	University degree	1061	9.9	930	10.3	131	6.9	3.5	0.219
Employed	Yes	43415	18.5	17529	11.3	25886	23.3	-12.0*	<0.001
	No	6530	30.7	3668	23.1	2862	40.5	-17.4*	<0.001
Socioeconomic status (SES)	Good	18831	18.1	8703	12.7	10128	22.7	-10.0*	<0.001
	Medium	24001	20.5	9748	13.3	14253	25.4	-12.1*	<0.001
	Poor	7105	24.1	2741	15.9	4364	29.2	-13.3*	<0.001
Physical activity	Yes	15838	13.3	11308	10.2	4530	20.8	-10.6*	<0.001
	No	33947	23.2	9852	17.0	24095	25.8	-8.8*	<0.001
Body mass index (BMI)	Underweight	2380	17.4	1245	14.1	1135	21.0	-6.9*	<0.001
	Normal	17871	14.9	9596	11.3	8275	19.2	-7.9*	<0.001
	Overweight	16993	20.4	7271	14.4	9722	24.9	-10.6*	<0.001
	Obese	12694	27.4	3081	17.3	9613	30.7	-13.3*	<0.001
Smoking[2]	Never	41323	21.1	13018	12.8	28305	24.9	-12.1*	<0.001
	Ex-smoker	3189	21.2	3064	20.3	125	44.0	-23.7*	<0.001
	Light smoker (<20 cigarettes/day)	3272	11.1	3013	9.9	259	25.5	-15.6*	<0.001
	Heavy smoker (≥20 cigarettes/day)	2161	13.0	2103	12.1	58	44.8	-32.7*	<0.001
Other tobacco use	Yes (ever)	4427	19.7	3749	17.7	678	30.8	-13.1*	<0.001
	No (never)	45519	20.1	17449	12.5	28070	24.9	-12.4*	<0.001
Opium	Yes (ever)	8489	19.6	6138	11.7	2351	24.0	-12.3*	<0.001
	No (never)	41457	22.7	15060	17.4	26397	36.2	-18.8*	<0.001
Alcohol	Yes (ever)	1721	20.2	1701	13.0	20	25.0	-12.1*	<0.001
	No (never)	48225	18.2	19497	18.2	28728	25.0	-6.8	0.435

1. Other: Persian, Turk, Sistani, Baluch, and Kurdish; **2.** Individuals were defined as smokers if they had used cigarettes at least once weekly for 6 months. * $p<0.001$

Table 2 shows the results from multiple Poisson regression models. Men who were ex-smoker, non-Turkmen, married and physically inactive had significantly higher chance of multimorbidity. Being in lower socioeconomic groups showed an association with multimorbidity only in women. Higher educational levels (compared to illiteracy) showed an inverse association with multimorbidity, mainly in women (p<0.001).

Based on interaction analysis, a significantly stronger association existed between poor/middle SES with multimorbidity in women compared to men (p=0.033). The associations between non-Turkmen ethnicity groups (p=0.003), married status (p=0.041), physical inactivity (p=0.009), and ex- smoking (p=0.033) and the prevalence of multimorbidity was statistically significant in men only, or stronger in men compared to women. There was an inverse association between education and multimorbidity mainly in women (p for interaction <0.001).

Table 2: Crude and adjusted prevalence ratio (PR) based on simple and multiple Poisson regression.

		Men				Women				
		Crude		Adjusted[2]		Crude		Adjusted[2]		Interaction[3]
Variables	**Levels**	PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI	*p-value*
Age (years)	40-49	**Ref.**		**Ref.**		**Ref.**		**Ref.**		
	50-60	1.64	(1.50-1.80)**	1.46	(1.32-1.61)**	1.66	(1.58-1.76)**	1.51	(1.43-1.60)**	0.282
	61-75	2.42	(2.20-2.65)**	1.87	(1.67-2.10)**	2.34	(2.20-2.49)**	2.06	(1.92-2.21)**	
Residential area	Rural	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.280
	Urban	1.04	(0.95-1.14)	0.93	(0.84-1.03)	0.94	(0.89-0.99)*	0.98	(0.92-1.05)	
Ethnicity	Turkmen	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**0.003**
	Other[1]	1.26	(1.16-1.36) **	1.24	(1.14-1.35)**	1.02	(0.97-1.07)	1.09	(1.03-1.15)*	
Marital status	Unmarried	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**0.042**
	Married	0.94	(0.75-1.18)	1.22	(0.97-1.54)	0.72	(0.68-0.76)**	0.98	(0.92-1.04)	
Education	Illiterate	**Ref.**		**Ref.**		**Ref.**		**Ref.**		
	≤5 years	0.75	(0.69-0.82) **	0.91	(0.82-1.00)	0.65	(0.59-0.71)**	0.81	(0.73-0.89)**	**0.000**
	6-12 years	0.69	(0.63-0.77) **	0.91	(0.80-1.03)	0.42	(0.35-0.50)**	0.57	(0.47-0.69)**	
	University degree	0.66	(0.54-0.81) **	0.90	(0.72-1.13)	0.26	(0.13-0.50)**	0.37	(0.19-0.72)*	
Employed	Yes	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.225
	No	2.04	(1.88-2.21)**	1.35	(1.23-1.48)**	1.74	(1.63-1.85)**	1.27	(1.18-1.35)**	
Socioeconomic status (SES)	Good	**Ref.**		**Ref.**		**Ref.**		**Ref.**		
	Medium	1.05	(0.97-1.14)	0.95	(0.86-1.05)	1.12	(1.06-1.18)**	1.08	(1.02-1.14)*	**0.033**
	Poor	1.26	(1.12-1.40)**	1.04	(0.91-1.18)	1.28	(1.20-1.38)**	1.11	(1.03-1.19)*	
Physical activity	Yes	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**0.009**
	No	1.66	(1.54-1.79)**	1.28	(1.18-1.39)**	1.24	(1.16-1.33)**	1.12	(1.04-1.21)*	
Body mass index (BMI)	Normal	**Ref.**		**Ref.**		**Ref.**		**Ref.**		
	Underweight	1.25	(1.06-1.46)	1.04	(0.89-1.22)	1.09	(0.95-1.25)	0.93	(0.81-1.07)	0.594
	Overweight	1.28	(1.17-1.39)**	1.46	(1.34-1.60)**	1.30	(1.22-1.38)**	1.43	(1.34-1.52)**	
	Obese	1.54	(1.39-1.71)**	1.85	(1.66-2.06)**	1.60	(1.50-1.70)**	1.87	(1.75-1.99)**	
Smoking	Never	**Ref.**		**Ref.**		**Ref.**		**Ref.**		
	Ex-smoker	1.59	(1.45-1.74)**	1.25	(1.13-1.39)**	1.77	(1.35-2.30)**	1.22	(0.93-1.59)	
	Light smoker (<20 cigarettes/day)	0.77	(0.68-0.88)**	0.78	(0.69-0.89)**	1.02	(0.80-1.30)	0.89	(0.70-1.14)	**0.033**
	Heavy smoker (≥20 cigarettes/day)	0.95	(0.83-1.08)	0.87	(0.76-1.00)	1.80	(1.22-2.64)**	1.33	(0.90-1.96)	
Other tobacco use	No (never)	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.945
	Yes (ever)	1.42	(1.30-1.55)**	0.99	(0.89-1.09)	1.24	(1.08-1.42)*	0.98	(0.85-1.13)	
Opium	No (never)	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.558
	Yes (ever)	1.49	(1.38-1.61)**	1.50	(1.37-1.64)**	1.51	(1.40-1.62)**	1.45	(1.35-1.57)**	
Alcohol	No (never)	**Ref.**		**Ref.**		**Ref.**		**Ref.**		0.401
	Yes (ever)	1.40	(1.25-1.58)**	1.31	(1.15-1.49)**	1.00	(0.42-2.40)	0.94	(0.39-2.25)	

1. Other: Persian, Turk, Sistani, Baluch, and Kurdish; 2. Prevalence ratios were adjusted for baseline variables; 3. Difference between sexes (*p*-value for interaction refers to the Wald test),

*: $p<0.01$; **: $p<0.001$

DISCUSSION:

This study examined gender-related determinants of multimorbidity in a cross-sectional analysis of a large cohort study that had more than 49000 participants. Women of all ages had a higher overall prevalence of multimorbidity. Multimorbidity was not only prevalent in elderly people; it also affected participants aged 40-49 years. Gender interacted with sociodemographic factors of ethnicity, marital status, educational level, SES, physical activity, and smoking in terms of multimorbidity prevalence. Past smoking history, non-Turkmen ethnic groups, married status, and physical inactivity showed significant associations with multimorbidity in men. Lower socioeconomic groups were associated with multimorbidity, only in women.

Despite current perceptions, this study revealed that multimorbidity was not confined to elderly people. The results showed that middle-age cohort participants (age <50) of both genders also suffered from this condition, and this observation has been supported by another study. [32] We observed that women had a greater burden of multimorbidity which supported the results from a study by Zielinski et al. on a Swedish population.[33] A potential cause for more significant prevalence of multimorbidity among women could be their relatively higher tendency to share their conditions in self-reports.[34,35] There is evidence that women use more health care facilities, particularly public funded health care compared to men. [36-38] Possible influences for this excess multimorbidity in women could be higher exposure to common risk factors for chronic diseases or gender inequality in access to healthcare. [7,8,39-42] It is worth mentioning that this information is related to data collected approximately ten years ago at a subnational level.

This study showed a significant association between low SES and multimorbidity among women. Earlier studies suggested an association between low SES and multimorbidity.[43,44] This might partially be explained by differences in lifestyle attributed to SES. Low SES might reduce care-seeking in patients with chronic diseases.[43] This might produce a paradox, as lower health care use might translate to lower documented morbidity. This study's findings indicated that low and middle SES had an association with multimorbidity in women, which has supported the assertion that women are at higher risk for the adverse effects of poverty, payment inequality, and health disparities.[45] Khanam et al. concluded that gender differences in SES, living and working environments, lifestyle factors, and life-events might affect the occurrence and outcome of multimorbidity among women.[46]

A previous study revealed that inactivity might increase the risk of breast and colorectal cancers, diabetes mellitus, and ischemic heart diseases.[47] Autenrieth et al. discovered an inverse

association between physical activity and multimorbidity among men.[35] Another study reported no association between multimorbidity and physical activity for either men or women.[48] We observed an association between sedentary occupations that involved decreased physical activity and multimorbidity, which was more evident in men. This might be due to the proportionately longer hours that men spend at sedentary occupations.

In this study the prevalence ratio of multimorbidity significantly decreased with increased education level; the association was more obvious in women. Similarly, other studies showed a decreased likelihood of multimorbidity among better-educated populations.[39,42,49]

The GCS enrolled participants above 40 years of age whose cultural, educational and social basis was shaped around the 1970s – a time of limited access to primary healthcare (PHC) facilities, particularly in rural areas.[50] However, after the 1980s, there was a substantial improvement in health, life expectancy, control of communicable diseases, and SES in Iran.[25,50] Iran was among the few countries that reached WHO defined millennium development goals prior to 2015.[51] We observed that education was defined as a protective factor for multimorbidity. In this population, women had a literacy rate of less than 20%.[24] The latest report, released in 2014, has shown tremendous increase in women's literacy in Golestan Province, which is over 80%.[52] The improvements in health, education, and other SES have decreased health inequalities which may influence disease patterns, including multimorbidity, in succeeding generations.

Access to affordable health services, as a human right, is a necessity for improved quality of life. Despite the considerable progress in community health in recent decades, there is an increasing prevalence of chronic diseases.[53] Some global movements related to healthy lifestyles have underlined the need for multi-dimensionality collaborations for health promotion as stated in the Ottawa Charter.[53-57] The findings of this study and recommendations by WHO [53] indicate that specific national and sub-national health policies for men and women of different age-groups and SES should be implemented.

The possible changes in demographic characteristics and lifestyle habits of the Iranian population over the past decades and the current study sampling methods (regional vs. national) should be taken into consideration. Future studies that assess more representative samples or at the national level are recommended.

CONCLUSION

The findings of this study confirm that multimorbidity is an important health issue for all individuals above 40 years of age, with particular emphasis for women with lower SES and educational levels. Men with decreased physical activity, married, and former smokers have shown a higher risk for multimorbidity.

Defining priority interventions and multi-sectorial policies that tackle multimorbidity in both men and women, as well as increased attention to middle-aged populations are required. In order to control multimorbidity, particularly in women, we recommend the use of health promotion and educational methods to enhance public awareness about modifiable risk factors such as physical activity and smoking.

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Ethics approval: The Ethics Committee of the Digestive Diseases Research Institute, Tehran University of Medical Sciences approved this study (OHRP-IRB-00001641).

Contributorship statement: MY analyzed the data. MA, AM and AMS drafted the manuscript. AS, AM, MA, MA, MK, and MHD provided scientific input. RM, FK, HP, AD, and SQ provided expert clinical advice and data interpretation. PB, FK, RM, BA, AP, FI, PB, and SMD provided expert guidance on health policy and delivery of healthcare and interpretation of the data. AS, MA, AM, and FI were involved as methodologists in research interpretation and manuscript writing. All authors made critical revisions and provided intellectual content to the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of this work. AS and BA are the guarantors for this study.

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Supplementary Table 1: Chronic conditions by gender in population with Multimorbidity in the Golestan Cohort Study (GCS)

Chronic Conditions	Total (N=10,035)		Men (N=2,836)		Women (N=7,199)		Difference (Men vs. women)
	Number	%	Number	%	Number	%	%
GERD	7690	76.6	2030	71.6	5660	78.6	-7.1*
CVD	7379	73.5	1927	67.9	5452	75.7	-7.8*
Diabetes	2535	25.3	686	24.2	1849	25.7	-1.5
COPD	2203	22.0	653	23.0	1550	21.5	1.5
TB	1030	10.3	293	10.3	737	10.2	0.1
Cancers	102	1.0	34	1.2	68	0.9	0.3
CKD	72	0.7	27	1.0	45	0.6	0.3
Liver diseases	28	0.3	11	0.4	17	0.2	0.2

* P-value <0.001

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3 4
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	3 (Ref. 19)
Study size	10	Explain how the study size was arrived at	3 (Ref. 19)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	3 (Ref. 19)
		(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	3 (Ref. 19)
		(*e*) Describe any sensitivity analyses	3 (Ref. 19)

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3 (Ref. 19)
		(b) Give reasons for non-participation at each stage	3 (Ref. 19)
		(c) Consider use of a flow diagram	3 (Ref. 19)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3 (Ref. 19) and Table. 2
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	*Cross-sectional study*—Report numbers of outcome events or summary measures	*4*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table. 2
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5 6 7
Generalizability	21	Discuss the generalisability (external validity) of the study results	7 8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8