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**ORIGINAL ARTICLE** 

# Occupational categories and cardiovascular diseases incidences: a cohort study in Iranian population

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#### Keywords

Occupation • ISCO category • Ischemic heart disease • Stroke

#### Summary

**Introduction**. In spite of traditional cardiovascular risk factor, the different occupations can play an important role in cardiovascular disease (CVDs) incidence. We aimed to assess the correlation between the occupational classes, based on the International Standard Classification of Occupation (ISCO), and CVDs in Iran as a developing country.

**Methods.** We followed the 2440 men, aged 35-65 years and without history of CVDs over fourteen years; 2001 to 2015 during the Isfahan Cohort Study. ISCO was used to classify occupations into 10 categories. Incidence rates of ischemic heart diseases and stroke were recorded. Socioeconomic demographic data including marital state, income and place of living and metabolic risk factors were also recorded.

**Results**. The mean age was  $46.97 \pm 8.31$  years old. 272 cardiovascular events (CVEs) were recorded that unstable angina was

## Introduction

Cardiovascular diseases (CVDs) including ischemic heart disease (IHD) and stroke are considered as a public health problem and were the most common underlying cause of death in the world [1]. The known risk factors for CVDs are genetics and family history, dyslipidemia, diabetes mellitus, hypertension, smoking and physical inactivity.

Nearly 80 percent of cardiovascular mortalities take place in countries with the low- and middle-income level which highlights socioeconomic status as a contributing and predictive factor on the CVDs. Given the significant role of occupation and career in the prediction of socio-economic status, it is only fair to discuss the occupational status as one of the main risk factors for cardiovascular disease and stroke. Numerous studies across the world have directly and indirectly, linked occupational factors and cardiovascular health condition. These studies identify factors such as shift work, overtime work, exposure to toxic chemicals and fumes, noise level, job stress, and sedentary behavior to be work-related environmental and psychosocial factors

the highest recorded with 49% prevalence and the fatal stroke had the lowest outbreak (1%). The unemployed/jobless group and elementary occupations (9th ISCO category) had higher and lower relative frequency in CVEs respectively. There was non-significant decrease in CVEs in all of categories except of 4<sup>th</sup> (clerical support workers) and 10th (armed forces) groups in comparison to unemployed/jobless subjects (P > 0.05). After considering of the group 7 as a reference group (most absolute CVEs frequency), in fully adjustment analysis group 4 had significant risk for CVEs (P = 0.04).

**Conclusions.** This study indicates that working as clerical support workers (4<sup>th</sup> ISCO category) is associated with higher significant risk for IHD and stroke incidence in comparison to craft and related trades workers (7<sup>th</sup> group of ISCO).

that associate with CVDs risk factors [2-6]. However, investigation of different occupational classes (based on professional skills or socioeconomic groups) instead of individual work space-related factors, gives us a broader view of the correlation between the risk of CVDs and occupational status [7, 8].

Therefore, the current study uses a cohort approach to describe the correlation between the occupational classes, based on the International Standard Classification of Occupation 2008 (ISCO-08), and CVDs in Iran as a developing country in the Middle East.

## Patients and methods

### THE POPULATION AND DATA COLLECTION

The Isfahan Cohort Study (ICS) is a population-based, longitudinal ongoing study that started with 6504 adults aged 35 and greater at baseline, living in urban and rural areas of three districts in central Iran who had participated in the baseline survey of a community trial for CVDs prevention and control, entitled Isfahan Healthy Heart Program (IHHP) [9, 10]. Ethical approval was obtained from the ethics committee of Isfahan Cardiovascular Research Center (ICRC), as World Health Organization (WHO) collaborating center. After obtaining informed written consent and the baseline survey in 2001, follow-up of the participants has been carried out every two years by telephone, or home interviews, physical and biochemical measurements and hospital events record until 2015.

Given that most subjects were housekeeping female, this study was conducted on men aged 35 to 65 years between inclusion age of study population and Iranian Ministry of Labour and Social Affairs retirement age law. In total, 2440 men subjects (employed and unemployed/ jobless) who did not have IHD and stroke were followed up for 14 years (2001 to 2015).

Questionnaires were completed for each person including age, occupations, marital state, income, place of living, smoking status and metabolic risk factors such as diabetes mellitus (DM), hypertension (HTN), dyslipidemia, metabolic syndrome and body mass index (BMI). Income was categorized based on the poverty boundary in Iran that was 5,000,000 Iranian Rials in 2001. A monthly income less than 5,000,000 was categorized as very low, 5,000,000 to 9,000,000 as low, 9,000,000 to 15,000,000 as middle, 15,000,000 to 20,000,000 was considered high and more than this level as very high income.

#### **OCCUPATIONAL CATEGORIES**

The International Standard Classification of Occupation (ISCO) was used to classify occupations into ten occupational categories. The ISCO is a standard and validated category based on skill specialization and skill level [11]. If a person had worked in more than one occupational category, the main job (more work time) was the basis for classification. The major groups of ISCO consist of: 1) legislators, senior officials and managers; 2) professionals; 3) technicians and associate professionals; 4) clerical support workers; 5) service workers and shop and market sales workers; 6) skilled agricultural, forestry and fishery workers; 7) craft and related trades workers; 8) plant and machine operators, and assemblers; 9) elementary occupations; and 10) armed forces [11]. A control group including unemployed/jobless people was also selected for analysis and comparison.

## FOLLOW-UP

Follow-up survey for cardiovascular events (CVE) including IHD and stroke was done along 14 years. The reported events were checked with the myocardial infarction (MI) and stroke registry database of the surveillance department, ICRC monthly in the three counties above. Two separate panels of specialists consisting of cardiologists and a neurologist reviewed and confirmed all relevant patient documents. The criteria for IHD were definite or probable acute MI, unstable angina (UA), and sudden cardiac death (SCD). The diagnosis of acute MI was based on the presence of at least two of the following criteria: 1) typical chest pain

lasting more than 30 min; 2) ST-segment elevation > 0.1mV in at least 2 adjacent electrocardiograph leads; and 3) an increase in serum levels of cardiac biomarkers including cardiac troponins, and creatine kinase (CK) and CK-MB [12]. The definition of UA required typical chest discomfort lasting more than 20 minute within the 24 h preceding hospitalization and representing a change in the usual pattern of angina or pain: occurring with a crescendo pattern, being severe and described as a frank pain [13]. The diagnosis of UA might be new or based on dynamic ST-interval, or T-wave changes in at least two contiguous ECG leads. Sudden cardiac death was defined as death within one hour of onset, a witnessed cardiac arrest, or abrupt collapse not preceded by > 1 hour of symptoms. Stroke was defined as a rapidonset focal neurological disorder persisting at least 24 h and had a probable vascular origin by WHO stroke definition [14].

#### STATISTICAL ANALYSIS

Continuous and categorical variables are reported as arithmetical mean value ± SD and absolute number (percent) respectively. Chi-square and independent T-test were used to compare risk factors between job categories (ISCO). The hazard ratio (HR) model with its 95% confidence interval (CI) for each ISCO category relative to the reference category was assessed when the control group (unemployed/jobless subjects) and 7th ISCO category (including most subjects and CVE) were selected as a reference category respectively. To adjust the potential confounding effects of the selected risk factors, adjusted cox regression models included age, socioeconomic and metabolic variables adjustment were performed. Statistical analysis was done by the Statistical Program for Social Sciences software 22 (SPSS 22). All differences were considered as statistically significant at a P value less than 0.050.

## Results

A total of 2440 males with mean age  $46.97 \pm 8.31$  years were classified and analyzed. 159 of them were unemployed or jobless who were considered as the control group. Table I presents the socioeconomic and metabolic characteristic of a participant in ISCO occupational categories. Except marital status and dyslipidemia, other basic characteristics had a significant difference between the groups (P < 0.005) (Tab. I). Income information was incomplete due to lack of representation of all individuals (especially those with high income). Most of the studied subjects were lived in the urban area, except for the 6<sup>th</sup> group who lived in the village according to their jobs (Tab. I).

In total, 272 CVE were recorded, as showed separately in Tab. II. The unstable angina was the highest recorded CVE with 49% prevalence, and the fatal stroke had the lowest outbreak (1%). The absolute frequency occurred in 7<sup>th</sup> group (craft and related trades workers) with 63 events; however, the unemployed/jobless group and

Variables	ISCO Categories (n)											
	1 <sup>st</sup> (86)	2 <sup>nd</sup> (160)	3 <sup>rd</sup> (13)	4 <sup>th</sup> (257)	5 <sup>th</sup> (458)	6 <sup>th</sup> (332)	7 <sup>th</sup> (710)	8 <sup>th</sup> (218)	9 <sup>th</sup> (8)	10 <sup>th</sup> (39)	Control (159)	P- value
Age (year)	45.62 ± 8.00	44.52 ± 5.48	47.23 ± 6.68	43.96 ± 6.58	47.81 ± 8.56	50.14 ± 9.08	44.86 ± 7.28	46.30 ± 7.77	47.87 ± 8.98	43.25 ± 6.02	57.23 ± 6.06	0.000
Marital status n (%): • married • single • divorced • dead spouse	84 (98) 2 (2) 0 0	160 (100) 0 0 0	13 (100) 0 0 0	253 (98) 4 (2) 0 0	449 (98) 9 (2) 0 0	327 (98) 3 (1) 0 2 (1)	707 (99.5) 3 (0.5) 0 0	214 (98) 3 (1.5) 1 (0.5) 0	8 (100) 0 0 0	39 (100) 0 0 0	157 (99) 0 0 2 (1)	0.067
Income n (%): • very low • low • moderate • high • very high	32 (37) 26 (30) 6 (7) 2 (2) 0	55 (34) 57 (35) 2 (1) 1 (1) 0	7 (54) 4 (31) 0 0 0	107 (42) 91 (35) 3 (1) 2 (1) 0	329 (72) 50 (11) 3 (1) 1 (0.5) 0	278 (84) 24 (7) 0 0 0	507 (71) 95 (13) 0 0 0	124 (57) 43 (20) 2 (1) 1 (1) 0	7 (87.5) 0 0 0 0	16 (41) 15 (38) 0 0 0	133 (84) 17 (11) 0 0 0	0.000
Place of living n (%): • urban • rural	76 (88) 10 (12)	138 (86) 22 (14)	10 (77) 3 (23)	215 (84) 42 (16)	375 (82) 83 (18)	68 (20) 264 (80)	529 (75) 181 (25)	166 (76) 52 (24)	7 (87.5) 1 (12.5)	34 (87) 5 (13)	144 (91) 15 (9)	0.000
Diabetes mellitus n (%)	5 (6)	10 (6)	3 (23)	12 (5)	46 (10)	21 (6)	35 (5)	17 (8)	1 (12.5)	3 (8)	33 (21)	0.000
Dyslipidemia n (%)	79 (92)	136 (85)	13 (100)	223 (87)	363 (79)	275 (83)	589 (83)	187 (86)	7 (87.5)	34 (87)	131 (82)	0.078
Hypertension n (%)	16 (19)	28 (17.5)	2 (15)	42 (16)	93 (20)	108 (33)	108 (15)	34 (16)	0	7 (18)	63 (40)	0.000
Smoker n (%): • current • former • never	34 (40) 7 (8) 45 (52)	42 (26) 13 (8) 105 (66)	3 (23) 0 10 (77)	75 (29) 20 (8) 162 (63)	143 (31) 39 (9) 275 (60)	123 (37) 24 (7) 184 (56)	253 (36) 70 (10) 387 (54)	93 (43) 18 (8) 106 (49)	3 (37.5) 0 5 (62.5)	15 (38.5) 5 (13) 19 (48.5)	42 (26) 20 (13) 96 (61)	0.028
BMI n (%): • normal • overweight • obese	39 (45) 28 (33) 19 (22)	77 (48) 68 (43) 15 (9)	4 (31) 6 (46) 3 (23)	112 (44) 111 (43) 34 (13)	192 (42) 203 (44) 63 (14)	189 (57) 112 (34) 31 (9)	353 (50) 285 (40) 72 (10)	76 (35) 100 (46) 42 (19)	3 (37.5) 3 (37.5) 2 (25)	9 (23) 20 (51) 10 (26)	60 (38) 71 (45) 28 (17)	0.000
Metabolic syndrome n (%)	12 (14)	26 (16)	3 (23)	34 (13)	89 (20)	43 (13)	78 (11)	44 (20)	0	10 (26)	53 (33)	0.000

Tab. I. Socioeconomic and metabolic characteristic of participant in ISCO occupational categories.

elementary occupations had higher and lower relative frequency in CVE respectively (Tab. II).

Table III presents crude, age-adjusted and fully adjusted (socioeconomic and metabolic variables) HR estimates among ISCO categories compared to unemployed/ jobless participants (control group). This analysis showed a non-significant decrease in CVE in all of categories except 4<sup>th</sup> (clerical support workers) and 10<sup>th</sup> (armed forces) groups (P > 0.050). After considering of the group 7 as a reference group, in fully adjustment analysis group 4 had significant risk for CVE(P = 0.044)analysis group - had significant increases in 2<sup>nd</sup>, 3<sup>rd</sup>, 6<sup>th</sup>, 8<sup>th</sup> and 10<sup>th</sup> groups (P > 0.05) (Tab.  $\frac{1}{4^{th}}$ ). (150) (13) (257)

3 (3)

.....

11 (7)

1 (8)

18 (7)

Unstable Angina n (%)

## Discussion

This prospective cohort study showed that working as clerical support workers (4th group of ISCO) is associated with higher significant risk for IHD and stroke incidence in comparison to craft and related trades workers (7th group of ISCO). This outcome also obtained for professional (2<sup>nd</sup> group), technicians and associate professionals (3<sup>rd</sup> group), skilled agricultural, forestry and fishery workers (6<sup>th</sup> group), plant and machine operators, and assemblers (8<sup>th</sup> group) and armed forces (10<sup>th</sup> group) with nonsignificant output in comparison to unemployed/ <sup>5<sup>th</sup></sup> joblessis subjects, all of the ISCO groups (except 4<sup>th</sup> and

0

4 (10)

18 (11)

134

13 (6)

.....

Unstable Angina n (%)	3 (3)	11 (7)	1 (8)	18 (7)	22 (5)	13 (4)	31 (4)	13 (6)	0	4 (10)	18 (11)	134
Tabiath! Nymachiatatata of card	iovæseular	events b	etween	the ISCO	categorie	es an of the cor	ntrolgroup	). 4 (2)	0	2 (5)	8 (5)	61
Fatal myocardial infarction n (%) Cardiovascular events	0	0	0	1 (0.5)	0	<del>3 (1)</del> ISCO Ca	2 (0.5) tegories (n)	<del>1 (0.5)</del>	0	0	0	7
Sudden cardiac death n (%) Non-fatal stroke n (%)	0 1 <sup>st</sup> (86)	2 <sup>nd</sup> 11(60)	1 (8) 3 <sup>rd</sup> (93)	1 (0.5) 4 <sup>th</sup> 52(57)	6 (1) 5 <sup>th</sup> (459)	8 (2) 6 <sup>th</sup> (3:52)	7 (1) 7 <sup>th</sup> (1/10))	4 (2) 8 <sup>th</sup> ( <b>218</b> )	9 <sup>th</sup> (89)	0 10 <sup>th</sup> (39)	4 (3) Control (1593)	31 Total 36
F8ff9lfat9rekAngli%a n (%)	13(1時)	110(7)	1 <b>Q</b> 8)	18 <sup>0</sup> (7)	220(5)	13Q(4)	\$1Q石)	13 <b>9</b> 6)	ø	4 (10)	18 (0:5)	134
Non-fatal myocardial infarction n (%)	6 (7)	5 (3)	0	8 (3)	11 (2)	6 (2)	11 (2)	4 (2)	0	2 (5)	8 (5)	61
Fatal myocardial infarction n (%)	0	0	0	1 (0.5)	0	3 (1)	2 (0.5)	1 (0.5)	0	0	0	7
Sudden cardiac death n (%)	0	0	1 (8)	1 (0.5)	6 (1)	8 (2)	7 (1)	4 (2)	0	0	4 (3)	31
Non-fatal stroke n (%)	0	1 (1)	0	5 (2)	9 (2)	2 (1)	11 (1)	3 (1)	0	0	5 (3)	36
Fatal stroke n (%)	1 (1)	0	0	0	0	0	1 (0.5)	0	0	0	1 (0.5)	3

22 (5)

13 (4)

31 (4)

Tab. III. Relation between ISCO occupational categories and cardiovascular events (ischemic heart dieses and stroke), unadjusted and adjusted hazard ratio (group control as reference).

Analysis	ISCO categories (n)											
	1 <sup>st</sup> (86)	2 <sup>nd</sup> (160)	3 <sup>rd</sup> (13)	4 <sup>th</sup> (257)	5 <sup>th</sup> (458)	6 <sup>th</sup> (332)	7 <sup>th</sup> (710)	8 <sup>th</sup> (218)	9 <sup>th</sup> (8)	10 <sup>th</sup> (39)		
Model 1 HR (95% CI)	0.43 (0.21-0.87)*	0.35 (0.2-0.63)*	0.66 (0.16-2.76)	0.5 (0.31-0.80	)* 0.39 (0.25-0.60	)* 0.40 (0.24-0.64)*	0.32 (0.21-0.49)*	0.45 (0.27-0.75)*	-	0.61 (0.25-1.44)		
Model 2 HR (95% CI)	0.69 (0.34-1.41)	0.70 (0.38-1.29)	0.99 (0.23-4.14)	0.97 (0.59-1.6	2) 0.59 (0.38-0.92	)* 0.53 (0.33-0.87)*	0.60 (0.39-0.94)*	0.79 (0.46-1.34)	-	1.38 (0.56-3.37)		
Model 3 HR (95% CI)	0.78 (0.36-1.67)	0.88 (0.46-1.65)	0.93 (0.22-3.94)	1.21 (0.72-2.0	4) 0.69 (0.44-1.08	0.79 (0.46-1.34)	0.78 (0.49-1.22)	0.95 ( 0.55-1.62)	-	1.51 (0.61-3.69)		
Mtalysisunadjusted analysis (Crude Model); model 2; age adjusted analysis; model 3: multivariate (socioeconomic and metala00 talegosias)(m)ted analysis; ': p-values less than 0.05.												
	1 <sup>st</sup> (86)	2 <sup>nd</sup> (160)	3 <sup>rd</sup> (13)	4 <sup>th</sup> (257)	5 <sup>th</sup> (458)	6 <sup>th</sup> (332)	7 <sup>th</sup> (710)	8 <sup>th</sup> (218)	9 <sup>th</sup> (8)	10 <sup>th</sup> (39)		
Take IV:Relation between ISC0300 cupational categories and cardiovascular events dischemic heart cheses and strake 75 unadjusted and acies ted												
hvazcerelHrateics 6groc	ଧା <b>ଡ଼</b> ଡି.ସ୍ଟୋରା Meefene	270 (CE) 8-1.29) 0.	99 (0.23-4.14) 0.9	07 (0.59-1.62) 0.5	59 (0.38-0.92)° 0.	53 (0.33-0.87)* 0.6	60 (0.39-0.94)* 0.	.79 (0.46-1.34)	-	1.38 (0.56-3.37)		
Model 3 HR (95% CI) ( Analysis	0.78 (0.36-1.67) 0	.88 (0.46-1.65) 0.	93 (0.22-3.94) 1.2	21 (0.72-2.04) 0.6	59 (0.44-1.08) 0. ISCO	79 (0.46-1.34) 0.7 categories (n)	8 (0.49-1.22) 0.	95 ( 0.55-1.62)	-	1.51 (0.61-3.69)		
Model 1: unadjusted analys	sis (Crude Model); mo 1 <sup>st</sup> (86)	del 2: age adjusted an 2 <sup>nd</sup> (160)	alysis; model 3: multi 3 <sup>rd</sup> (13)	variate (socioecono 4 <sup>th</sup> (257)	mic and metabolic v 5 <sup>th</sup> (458)	riables) adjusted analy 6 <sup>th</sup> (332)	sis; *: p-values less th 7 <sup>th</sup> (710)	an 0.05. 8 <sup>th</sup> (218)	9 <sup>th</sup> (8)	10 <sup>th</sup> (39)		
Model 1 HR (95% CI)	1.31 (0.67-2.57)	1.08 (0.63-1.85)	2.02 (0.49-8.29)	1.52 (1.00-2.32)*	1.18 (0.81-1.72)	1.22 (0.79-1.88)	1.00	1.38 (0.87-2.19)	-	1.86 (0.80-4.30)		
Model 2 HR (95% CI)	1.14 (0.58-2.23)	1.16 (0.68-1.99)	1.63 (0.40-6.70)	1.61 (1.05-2.46)*	0.97 (0.66-1.43)	0.89 (0.57-1.38)	1.00	1.30 (0.82-2.08)	-	2.28 (0.98-5.28)		
Model 3 HR (95% CI)	0.99 (0.48-2.04)	1.12 (0.64-1.96)	1.20 (0.29-4.96)	1.55 (1.01-2.40)*	0.88 (0.60-1.31)	1.01 (0.64-1.31)	1.00	1.21 ( 0.76-1.95)	-	1.93 (0.83-4.49)		
Model 1: unadjusted analysis (Crude Model); model 2: age adjusted analysis; model 3: multivariate (socioeconomic and metabolic variables) adjusted analysis; *: p-values less than 0.05.												

10<sup>th</sup> groups) had a non-significant protective correlation with IHD and stroke incidence.

Based on our researches, studies on the relationship between classified occupations (especially based on skill) like ISCO category and CVDs, were few [15]. Most studies have examined the risk factors of occupational and environmental conditions and the occurrence of CVE and mortality [16, 17].

A case-control study was carried out by Malinauskiene et al. in Lithuania a country in a transition market economy to investigate the risk of a first time MI among different occupational categories in 25-64 yearold men. The occupational category used by them was ISCO. They showed that legislators, senior officials, and managers (1<sup>st</sup> ISCO category), professionals (2<sup>nd</sup> ISCO category), and plant and machine operators and assemblers (8<sup>th</sup> ISCO category) had a significantly higher risk of non-fatal first time MI compared to craft and related trades workers (7<sup>th</sup> ISCO category). The 4<sup>th</sup> ISCO category also had a non-significant increase risk for MI incidence. Their main explanation was the existence of occupational-psychological stressors, especially in the first category [15].

Our analysis did not show any significant predominance of metabolic and socioeconomic risk factors in group 4 and 7 (as baseline group). Therefore, it is not possible to associate this relationship with risk factors of the groups. These findings could be explained by the inactive and stressful nature of such occupations in Iran society.

In a prospective study by Li et al. in Japan, male workers with 40-59 years old were classified into manual and non-manual classes. The CVE including stroke, MI and SCD were assessed and did not reveal significant inequalities in the rate of cardiovascular events [18]. However, the incidence rate of MI in manual workers was non-significantly lower compared to non-manual workers. Their results were in contrast to another industrial county in Europe and United States of America (USA) that manual worker have a higher risk for cardiovascular risk factors and events [19-23]

Zhang et al. in a large prospective study USA showed that male white-collar occupations were associated with increased risk of SCD, when compared to bluecollar occupations. Since differences in conventional risk factors did not explain this elevated risk, they hypothesized that other factors such as behavioral and psychosocial stressors in the workplace warrants further investigation [24]. We also rely on the same reasoning to explain the meaningful association between group four and cardiovascular events.

To the best of our knowledge this study is among the first studies in Iran, the Middle East, and other developing countries that assess the relationship between occupations and cardiovascular disease. Given the occupational structure and cultural context of the area, we applied the ISCO classification which is a standard occupation classification and took into consideration the socioeconomic status of the individuals [11, 25]. As we mentioned earlier, Malinauskiene et al. has utilized this classification in Lithuania while most of the studies use more simplified models which could be one of the contributions of this study.

This study suffers from several limitations, first of all, there might be a misclassification of occupations because people might not have reported their jobs correctly. Secondly, some of the participants changed their job in the middle of the study and we decided to consider their former job if they spent longer time in that position. Thirdly, analyzing the sub-categories of ISCO was not in the scope of this study and we suggest future studies to focus on that.

## Conclusions

This study indicates that working as clerical support workers (4<sup>th</sup> group of ISCO) is associated with higher significant risk for IHD and stroke incidence in comparison to craft and related trades workers (7<sup>th</sup> group of ISCO). In comparison to unemployed/jobless subjects, there was not a significant correlation between the nature of occupational categories and CVE incidence.

## Acknowledgements

The authors would like to thank Minoo Dianatkhah for helping with the statistical analysis. This project would not have succeeded without the sincere effort of ICS staff, especially Mansoureh Boshtam. We also gratefully acknowledge Ladan Ghahramani for her cooperation in editing this paper.

Funding sources: this work was supported by the Isfahan Cardiovascular Research Institute.

Ethical approval: all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this study, ethical approval was obtained from the Ethics Committee of Isfahan Cardiovascular Research Center (ICRC), as WHO collaborating center.

# Conflict of interest statement

The authors declare no conflict of interest.

## Authors' contributions

RG, MA, MKA and MS contributed to the conception and design of the study. NS, MS, MT and HR designed and contributed the Isfahan Cohort Study. MKA and RG conducted the data analysis and drafted the manuscript, and all authors revised it.

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Received on August 3, 2019. Accepted on February 11, 2020.

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How to cite this article: Ghahramani R, Aghilinejad M, Kermani-Alghoraishi M, Roohafza HR, Talaei M, Sarrafzadegan N, Sadeghi M. Occupational categories and cardiovascular diseases incidences: a cohort study in Iranian population. J Prev Med Hyg 2020;61:E290-E295. https://doi.org/10.15167/2421-4248/jpmh2020.61.2.1359

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