



# Economic burden of medication-overuse headache in Iran: direct and indirect costs

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## Abstract

**Background and objective** Medication-overuse headache (MOH) as a secondary chronic headache imposes a considerable burden on both individuals and societies. Nevertheless, little is known about the burden of MOH in Iran. Therefore, in the current study, we aimed to quantify the annual cost of MOH among Iranian patients.

**Methods** In this cross-sectional study, 84 patients were recruited. Demographic data, headache attack characteristics, related disability, and information about the economic burden of MOH were collected through face-to-face interview. Direct medical and nonmedical costs as well as indirect costs were included in our cost analysis. The prevalence-based approach was applied to estimate the economic burden of MOH.

**Results** We found that MOH patients in Iran spend averagely \$1046 for medical services, \$132 for nonmedical services, and \$1432 due to lost productivity per year. The per-person annual cost of MOH was US\$2610, and the total annual cost for Iran was \$10,179,000,000, with direct and indirect cost accounting for 45% and 55%, respectively.

**Conclusion** MOH leads to substantial healthcare costs and significant loss of productivity in Iran. Therefore, raising awareness in this area especially for policymakers can use in future health planning and lead to resource allocation in the field of disabling type of headache disorders such as MOH. Our findings also provide a different insight into the burden of MOH, which are likely closer to the actual costs in middle- and low-income countries, and also it could be a sample of such a study in western Asia.

**Keywords** Headache · Medication-overuse headache · MOH · Cost · Burden

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## Abbreviations

GBD	Global Burden of Disease
DALYs	Disability-adjusted life-years
MOH	Medication-overuse headache
TTH	Tension-type headache
MIDAS	Migraine Disability Assessment test
VAS	Visual analogue scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
GP	General practitioner
TCAs	Tricyclic antidepressants
GDP	Gross domestic product

## Introduction

Headache as one of the most common and debilitating neurological disorders affects 47% of the adult population globally [1]. Almost half of the world's adults experience headache at least once during their life [1]. However, lack of mortality and

periodic nature probably is the reason for overlooking the public health significance of headaches [1]. Based on the Global Burden of Disease (GBD) report, headache was ranked as the third cause of disability worldwide [2]. In accordance with these results, between 1990 and 2017 in Iran, headache was the most prevalent neurological disorder, which had the most significant role in disease burden in terms of disability-adjusted life-years (DALYs) [3].

Since headache disorders had a substantial burden, both for individuals and society, estimation of the economic impact of this disabling condition seems crucial. With the help of the “cost of illness” studies, the economic burden caused by illness is measured [4]. According to the results of the Eurolight project, which evaluated the cost of headache disorders in Europe, the highest mean per-person annual costs (direct and indirect) was reported for medication-overuse headache (MOH) (€3561), which was almost 3 times higher than the migraine annual cost (€1222) and more than tenfold that of tension-type headache (TTH) (€303) [5]. The report of GBD in 2016 introduced migraine as the second-largest contributor of disability mainly because MOH was characterized as a sequel of migraine and TTH [6].

MOH is a secondary chronic headache that resulted from the regular overuse of medication for the treatment of headache episodes [7]. However, as MOH usually occurs in the situation of frequent attacks of migraine headache, it might be recognized as a complication of chronic migraine disease [8]. The overall prevalence of MOH has been estimated to be about 1–2% of the general population [7]. However, the reported prevalence of this disorder in some countries, including Iran, was found to be higher [9]. MOH is not as prevalent as TTH or migraine but is generally noticeably more disabling [10]. The negative impact on the quality of life, disability, and workplace productivity was reported much higher in chronic migraine and chronic daily headache when accompanied by MOH [11]. Despite the fact that MOH could be largely treatable, only 10% of MOH patients were professionally diagnosed [1]. The underdiagnosed and consequently undertreated nature of this condition can lead to a considerable burden not only on individuals but also on societies through lost productivity. Thus, the attention should turn into revealing the true burden of such disabling headache disorders.

So far, most of the studies concerning headache disorders burden are derived from the USA and Europe epidemiological surveys, and there are very few from the western Asia. [12–15]. However, the prevalence and burden of this disorder can vary significantly by geographic region, socioeconomic factors, and ethics [16, 17]. Furthermore, the surveys regarding the economic impact of MOH mostly addressed the direct costs only [18, 19], which based on evidence are relatively low in comparison with indirect costs [5]. Taken together, the mentioned facts emphasize the necessity of such studies, which can provide valuable information for health

policymakers and lead to allocating appropriate resources for headache disorder treatment and, finally, huge cost savings. Therefore, in the current study, we seek to investigate the burden of MOH by evaluating the annual direct and indirect costs among Iranian patients.

## Methods and materials

### Sample recruitment

This cross-sectional population-based study was conducted in May 2018. All referred patients to the headache clinic of Sina Hospital (affiliated by Tehran University of Medical Sciences) who have the inclusion criteria and are willing to participate were enrolled by conventional sampling. Included participants should be between 18 and 70 years old and have MOH based on the neurologist diagnosis according to the ICHD III criteria (beta version). Based on these criteria, the patient who suffers from MOH takes analgesics for more than 10 or 15 days a month according to the type of medication used, and this condition has been repeated for at least 3 months. Patients who were submitted to a withdrawal treatment in the last 3 months, who had other neurological disorders and/or any chronic or acute disorders including cardiovascular, respiratory, metabolic, renal, pulmonary, gastrointestinal disorders, and psychiatric problems, were excluded. The study was approved by the ethical committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1397.177); all patients signed an informed consent form prior to inclusion in the study.

### Research protocol

For the current study, patients were asked to fill in questionnaires that address demographic data, headache attack characteristics, related disability, and information about the economic burden. All questionnaires were completed through face-to-face interviews by the research team. In this study, we used a prevalence-based approach to estimate the economic burden of MOH. In the prevalence method, the total cost of MOH is calculated by multiplying the prevalence rate of disease by the mean annual per-person cost of illness. All the costs were converted to US dollars (US\$) using the average annual 2018 exchange rate (US\$1 = Rial 42,000). Costs included in our analysis were direct medical and nonmedical costs as well as indirect costs. The methods used for each cost category estimation are described below.

### Direct healthcare costs

Direct healthcare cost components included type and number of acute and prophylactic medication usage per month,

number of visits to health centers, the use of complementary therapies (including Botox injection, acupuncture, and occupational therapy), and diagnostic procedures including MRI, CT scan, and ophthalmology tests. For the estimation of medication price, we obtained data from Iran Food and Drug Administration website [20]. Unit costs of physician visits were extracted from Iran's tariff book. Since most laboratory tests, complementary medicine, and imaging techniques (CT and MRI) are done by private medical centers, the cost of each service was questioned from several private clinics and the average price was calculated. We also examined the cost of hospitalization of patients who suffered from headache in Sina hospital during the year 2018 and calculated the average cost per patient per day. In order to identify the cost of emergency room visits for each patient, we reviewed 12 short-term hospital admissions records and used the average charge as the cost per emergency room visits.

### Direct non-healthcare costs

Regarding the non-medical costs, the cost of commuting to a physician clinic including the trips from other cities, total times that the patient is suspended due to visit, and the number of visits to the pharmacy was questioned.

### Indirect costs

Indirect costs were referred to lost production due to absence from work or reduced productivity while working due to health conditions. Patients were asked to refer to how many workdays they lost in the previous 3 months and how many days they have been working with reduced productivity due to headache. To calculate indirect costs, we used the patient-reported income to extract the daily salaries of each patient which were lost due to illness. Since most patients consisted of housewives and unemployed women, we considered a cost equivalent to the minimum daily wage set by the Ministry of Labor to estimate their lost working days [21]. Since a family member usually accompanies the patient during visits, thus we estimated the time costs for an accompanying person by consideration of minimum daily wage and included those in calculating indirect costs.

### Instruments

Demographic questionnaire evaluated data regarding age, sex, job, marital status, education, economic status, smoking, and alcohol usage.

Migraine Disability Assessment test (MIDAS) assessed the impact of migraine on activity limitations like paid work, chores (housework), and nonwork activities (family, social, and recreation) in the prior 3 months. With the help of this questionnaire, the indirect costs of missing workdays could be

determined by exploring the number of days in which patients had no performance or less efficiency in daily activity due to headache. The validated translated form of the questionnaire was used [19].

Migraine characteristics questionnaire addressed the information on the number of years of migraine headache, the time since the diagnosis by a neurologist, the type of migraine prophylaxis, migraine characteristics during the last 3 months including the number of headache attacks per month, the mean severity of headache attacks based on visual analogue scale (VAS) (0 to 10), abortive drugs consumption and the frequency of use of these drugs per month, and the date and severity of the last headache attack and comorbidities.

Migraine-associated burden questionnaire was developed by the translation of the Eurolight study questionnaire as well as the opinions of neurologists and health economics experts. This questionnaire calculates the direct costs of headache both for medical and nonmedical services.

### Statistical analysis

Data were analyzed using the Statistics Package for the Social Sciences software release, 17.0 (SPSS, Chicago, IL, USA). Descriptive indicators such as absolute and relative frequency, mean, and standard deviation were used to describe the variables. By Kolmogorov–Smirnov and Shapiro tests, the normal distribution of data was assessed. In the case of normally distributed continuous data, parametric tests were applied, while Mann–Whitney and Kruskal–Wallis tests were used for non-normal distributed variables. Spearman correlation coefficient was applied for quantitative variables, and chi-square/Fisher's exact test was used to estimate the correlation between qualitative data.

## Results

### Patients' profile

A total of 84 patients referred to Sina Hospital Neurology Clinic and those who met the inclusion criteria were recruited. The demographic and socioeconomic characteristics of patients are summarized in Table 1. The median age of participants was 39 years with a male/female ratio of 1:4. Of the 84 MOH patients, 78 subjects (92.9%) suffered from chronic migraine, four patients (4.6%) had cluster headache, and two (2.3%) had a secondary headache due to increased intracranial pressure. Regarding the headache characteristics, the mean frequency of migraine attacks was 22.7 days per month and the mean severity of pain was 8.14 (SD = 1.86).

**Table 1** Demographic and socioeconomic characteristics of participants

Variables		N (%) = 84
Gender	Female	68 (81%)
	Male	16 (19%)
Marital status	Single	14 (16.7%)
	Married	66 (78.6%)
	Divorced	2 (2.4%)
	Widow	2 (2.4%)
Occupation	Employed	33 (39.3%)
	Housewife	34 (40.5%)
	Others	17 (20.2%)
Level of educations	High school diploma or less	41 (48.8%)
	Associate's degree	4 (4.8%)
	Bachelor's degree	21 (22.5%)
	Master's degree	9 (10.8%)
Socioeconomic status	Doctorate	4 (4.8%)
	Low	12 (22.2%)
	Medium	26 (48.1%)
	High	16 (29.6%)

### Healthcare resource utilization

Table 2 presents the estimation of healthcare resource utilization. Over 92% of the subjects used analgesics, while 25% of all patients used prophylactic agents prescribed by physicians in addition to the analgesics. Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most common analgesic medication used for headache attacks. The most common prescribed prophylactic drugs were propranolol and tricyclic antidepressants (TCAs). Only 14.5% of patients were seen by a general practitioner (GP) in the last year, while all patients are visited at least once a year by a neurologist with a mean annual frequency of  $5.01 \pm 4.8$ . Thirty-eight patients (46.3%) were visited by other specialists such as ophthalmologists and psychiatrists by an average number of 0.73 times ( $SD = 1.03$ ) per patient per year. As headache treatment, 43.7% of patients preferred complementary medicine, and on average, each patient received 4.47 visits last year.

The most commonly used complementary therapy was traditional medicine, with 28 (33.4) patients receiving at least one visit, and the mean number of traditional medicine visit sessions per patient was 1.53 ( $SD = 6.14$ ). Acupuncture comes in second place with 21 (24.6%) participants who had a mean annual frequency of  $1.69 \pm 4$  visits. Regarding hospitalization, patients mostly were admitted to the emergency room by a mean number of  $3.9 \pm 12.07$  per year. Among neurology ward hospitalized patients, more than half (56%) had readmission experience, with an average of 1.94 hospitalizations per year and the average length of stay in the hospital of 7.19 days.

Forty-six patients (55.4%) had blood tests at least once during the past year by a mean number of  $0.73 \pm 0.9$  times per year. Only one patient (1.3%) had no imaging history, and remaining patients experienced at least one type of imaging. However, the most common diagnosis services utilized by patients during the last year were brain MRI ( $1.99 \pm 2.15$ ).

### Direct healthcare and non-healthcare cost of MOH patients

Table 3 displays the annual per-person direct cost for patients with MOH in Tehran, Iran. The total cost of MOH-related healthcare resource utilization was \$1046. Hospitalization has the biggest proportion of total healthcare costs (\$507). Furthermore, every patient averagely spent \$132 per year for transportation during the treatment (non-healthcare costs).

### Annual indirect cost of MOH patients

According to our survey results (during past 3 months), 24 patients (28.6%) have been absent from work at least once and the mean number of days lost per patient was 4.55 days ( $SD = 12.65$ ). The indirect cost of absence from work was estimated at \$73 for each patient over 3 months. Accordingly, the indirect annualized cost of absenteeism from work was estimated at \$293 per patient. In our study, 28 (33.3%) patients reported more than 50% loss of function. The mean number of days that each patient experienced more than 50% decrease in workplace performance during the 3 months was 7.98 days ( $SD = 14.73$ ). Adding the burden of lost or reduced productivity at home as well as lost productivity due to accompanying the patient, the total annual indirect cost was estimated \$1432 per patient (Table 4).

### Per-person and global 1-year MOH cost estimation

According to our study, the total direct costs of diagnostic and medical treatment per person per year would be an average of \$1046. Also, the total sum of nonmedical direct costs per patient per year is on average \$132. Indirect costs due to lost workdays reduced productivity at work or home, and wasted time of the person who accompanied patients was \$1432 per year. Taken together, evidence suggests that each MOH patient spends an average of \$2610 per year (Table 5). Figure 1 depicts the components of the total cost of MOH, including both direct and indirect costs. As shown in the figure, indirect costs represented the main part of the costs, about 55%.

MOH generally has a prevalence of between 1 and 2% worldwide [7], and since it is secondary to primary chronic headache, in societies where chronic headaches are more common, MOH will be more prevalent. The prevalence of MOH in Iran has also been reported to be 4.9% [9]. Taking into account the country's population census data of 79,926,270



**Table 2** Health resource utilization estimates by MOH patients

Health resources		N (%) / mean $\pm$ SD
Prophylactic drugs (percentage)	Propranolol	25.5%
	TCA	24.1%
	SSRI	13.3%
	SNRI	13.3%
	Gabapentin	7.2%
	Valproate	16.9%
	Topiramate	10.8%
	Other	31.2%
Abortive drugs (percentage)	NSAIDs	92.8%
	Triptans	37.3%
	Ergotamin	15.7%
	Corticosteroids	13.3%
	Opioids	14.5%
Average number of visits by physician per patient per year (mean $\pm$ SD)	Others	20.5%
	General practitioner	0.67 $\pm$ 2.2
	Neurologist	5.01 $\pm$ 4.8
Average frequency of complementary medicine per patient per year (mean $\pm$ SD)	Other specialists	0.73 $\pm$ 1.03
	Botox	0.84
	Traditional medicine	1.53 $\pm$ 6.14
	Acupuncture	1.69 $\pm$ 4.1
	Homeopathy	0.62 $\pm$ 4.07
Average number of hospitalizations per patient per year (mean $\pm$ SD)	Others	0.57 $\pm$ 2.5
	Admitted to the clinic	3.16 $\pm$ 7.36
	Emergency admission	3.9 $\pm$ 12.07
Average number of diagnostic measures per patient (mean $\pm$ SD) per year	Admitted to ward	0.37 $\pm$ 0.9
	MRI	1.99 $\pm$ 2.15
	CT Scan	0.76 $\pm$ 1.30
	Neck X-ray	0.13 $\pm$ 0.37
	EEG	0.97 $\pm$ 1.46
Average number of blood test per patient per year (mean $\pm$ SD)	Others	0.12 $\pm$ 0.36
	Lab test	0.73 $\pm$ 0.9

based on the latest census [22], an estimated number of MOH patients in Iran would be about 3,900,000. Accordingly, considering the cost per person of \$2610 per year, the total annual cost of patients with MOH is \$10,179,000,000.

## Discussion

Our results estimated that the per-person annual cost of MOH was US\$2610 in 2018 and the total annual cost for Iran was \$10,179,000,000, with direct and indirect cost

accounting for 45% and 55%, respectively. This study showed that MOH leads to substantial healthcare costs as well as significant loss of productivity. MOH patients in Iran spend averagely \$1046 for medical services, \$132 for nonmedical services, and \$1432 due to lost productivity per year.

So far, some European studies evaluated annual per person and the total burden of MOH. In the following, we compare our results with those economical cost estimation (Table 6). Eurolight project was a cross-sectional survey of over 8000 participants seeking monetary costs of headache disorders in 8 European countries [5]. They found that the mean annual per-person cost of MOH was about €3561. According to the Eurolight report, indirect cost accounted for 92% in which the most important cost contributors were attributable to reduced productivity (€1669) and absenteeism (€1623). Despite the huge size and geographical scope of Eurolight, this study was conducted between November 2008 and August 2009, so it has been a long time since this information was released. Another study regarding the calculation of the economic burden of MOH was conducted by D'Amico et al. in 2017 [23]. In this study, the annual cost of the disease was estimated at €10,730 per patient, which was much higher than the amount reported by the Eurolight. The reason for this wide disparity lies in the more detailed evaluation of patients' drug profiles, considering average reduction lower than 50% along with lost days, as well as collecting samples from a third-party referral center rather than the general population. It should also be noted that in D'Amico study, all included patients had a particularly severe disease profile and were at the time point of withdrawal and this can maximize the cost of the disease. In the most recently published reports concerning the burden of MOH, the cost was estimated at €10,553 per patient per year in Italy [24]. Direct (medical and nonmedical) and indirect costs accounted for 48.5% and 51.5% of the total cost, respectively.

The results of these European studies are in the upper range of results reported by our survey, which might be explained by some reasons. First, differences in burden costs between studies can be caused by the differences in wage levels among countries. For example, in Raggi A et al. study, the average daily income of Italy in 2019 was \$137, while Iranian minimum daily wage in our study was much less. This can lead to a lower estimation of disease burden especially regarding the indirect cost, which served as the main contributor to the economic cost. In the Eurolight study, Lithuania is a good witness to this claim. The annual cost of migraine per patient was €1222 for the pooled sample; however for Lithuania, as the only country from Central and Eastern Europe, the mean per-person annual cost of migraine was €297, which

**Table 3** Direct healthcare and non-healthcare cost of MOH per patient

Services		Mean frequency per year	Cost unit (\$)	Mean annual cost (\$)	Percentage of total healthcare cost (%)	Total cost (\$)
Direct healthcare cost						
Visits	General practitioner	0.7	6	4	0.3	59
	Neurologist	5.01	9.5	48	4.5	
	Other specialists	0.73	9.5	7	0.6	
Medications	Prophylactic	—	—	83	7.9	228
	Acute	—	—	65	6.2	
	Botox	0.84	95	80	7.6	
Complementary medicine	Traditional medicine	1.53	13	20	1.9	58
	Acupuncture	1.69	9	16	1.5	
	Homeopathy	0.62	8	5	0.4	
	Others	0.57	30	17	1.6	
Blood test	Laboratory	0.73	42	31	2.9	31
Hospitalization	Clinic	3.16	9	30	2.8	507
	Emergency room	3.9	41	159	15	
	Ward	0.37	859	318	30	
Imaging studies	MRI	1.99	39	77	7.3	163
	CT scan	0.76	54	41	3.9	
	Neck X-ray	0.13	8	1	0.09	
	EEG	0.97	37	36	3.4	
	Others	0.12	67	8	0.7	
Total cost	-	-	-	-	100	1046
Direct non-healthcare costs						
Transportation	For physician visits	6.39	7	46	34.8	132
	For complementary medicine	4.47	7	32	24.2	
	For hospitalization	7.51	7	54	40.9	
Total cost	-	-	-	-	100	132

is less than one-fourth of the cost reported overall. A probable explanation is that the average daily income earned in Lithuania is notably lower than in other countries. Second, in line with wage differences, medical services tariff including medication price, diagnosis

procedure, and the cost of a doctor's visits in Iran is much lower than European countries. Third, different methodological approaches and instruments for evaluating the MOH burden could be another cause of difference across studies. For example, in the case of Italian study, which

**Table 4** Annual indirect cost of MOH patients

Cost attributed to patients	Day number per year	Cost per year	Percentage (%)
Absenteeism	18.20	293	20
Reduced workforce (more than 50%)	31.92	330	23
Lost productivity at home	55.60	419	29
Reduced productivity at home (more than 50%)	88.56	359	25
Total cost	1401		
Cost attributed to patients	Mean hours per year	Mean cost per year	Percentage (%)
Lost productivity due to accompanying the patient	65.36	31	2
Total cost	31		

**Table 5** Total annual cost of MOH per patients in Iran

Cost components	Cost (US\$)
Direct healthcare cost	1046
Direct non-healthcare cost	132
Indirect cost	1432
Total cost	2610

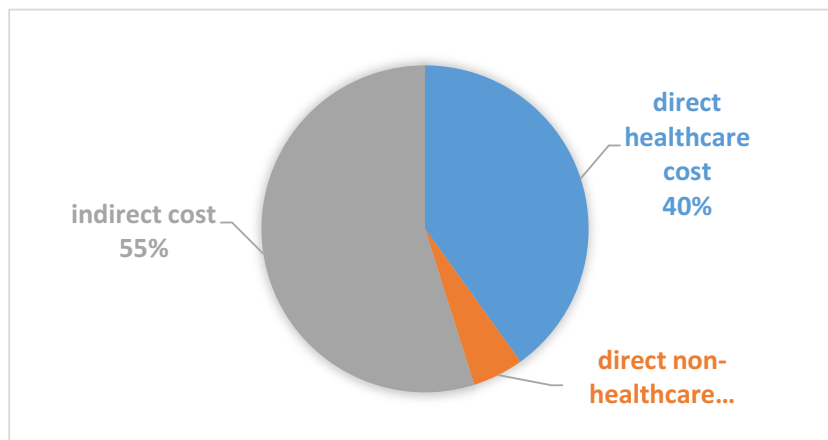
had notably higher annual burden per patient compared with our survey and the Eurolight project, all enrolled MOH patients were submitted to a large number of diagnostic procedures in the year of cost calculation, while in Iran, after definitive diagnosis of migraine, paraclinical examinations are very limited, and MRI, as one of the most expensive imaging techniques, is not usually performed. Fourth, most of our research participants consisted of women of productive age. But unlike the abovementioned studies, half of the women in our study were not employed. Using the minimum daily wage tariff for estimation of productivity lost for this group could lead to the lower estimates of indirect costs, despite the high number of the day lost due to headaches.

Taken together, it is important to note that comparing the net costs between the countries may cause misunderstanding and does not indicate the impact of the economic burden for each country. Therefore, to standardize the costs, it is better to consider other economic indicators that could provide a more appropriate and pragmatic vision for cost analysis. According to the most recent available World Bank data (which was attributable to 2017), adjusted net national income per capita in Iran was \$4238 per year, while in the case of Italy, this index reaches \$26,537 [25]. Keeping this in mind, the relatively small cost of \$2610 per patient per year has a substantially higher percentage of Iranian annual income compared with Italy (\$11,454 of \$26,537). Also, expressing the costs based on the gross domestic product (GDP) per capita of the

countries showed that the mean annual cost of each MOH patient in Italy was almost 30% of their GDP per capita in 2019 (GDP: \$32,946) [26], while in case of Iran, it was about 45% in 2017 (GDP: \$5627) [27]. In fact, this could show clearly that, although the net burden of MOH is high overall, the meaning and value of the cost for Iran and maybe for many middle- and low-income countries are significantly greater than the high-income countries.

Another point that should be considered for an economic cost comparison between countries is paying attention to the total cost of disease based on the prevalence rate. For example, the cost of a disease per patient may not be very high in one country, but due to the high prevalence, a large economic burden will be imposed on the health system and society. This specifically holds true for Iran. In this regard, although the annual cost per person in Iran was much lower than the estimated cost for the Italian population (\$2610 vs. €10,553), through a higher prevalence rate (3.9 million vs. 1.28 million citizens) the total burden of MOH across Iran became closer to Italy.

Regardless of the mentioned differences, the fact that most MOH-related burden is attributable to indirect costs is common among all studies, and previous reports even in European countries demonstrated that indirect cost constituted the greatest part of the total burden, although the magnitude of indirect cost contribution was varied among studies. Eurolight showed the highest percentage of indirect costs (92%). However, in their sample, non-pharmacological treatments and direct nonmedical costs did not take into account, which can probably lead to a miscalculation in favor of indirect costs. The clear impact of gender inequalities on total expense and its contributors should not also be neglect. Males not only displayed a higher total cost than females but also, because of the higher level of salary, had higher indirect costs attributable to lost workdays [28]. In D'Amico et al. study [23], the indirect cost was accounted for 80% of the total cost for men, while in women, only 49% of the total cost was attributable to indirect cost, so the high percentage of women in our study

**Fig. 1** Total cost components of MOH during 2018 in Iran

**Table 6** Summary of research that report annual per-person and total cost of MOH

Authors (years of evaluation)	Population	Annual per-person cost	Total cost
Linde M. et al. (2008–2009)	8 European countries (Eurolight project)	€3561	–
D'Amico et al. (-)	Italy	€10,730	–
Raggi A et al. (2015–2017)	Italy	€10,553	€13.5 billion
Togha M. et al. (2018)	Iran	\$2610 (~€2210)	\$10 billion (~€8.5 billion)

can partially explain the smaller difference between the two categories of costs (45% vs. 55%).

Ninety-three of our participants suffered from chronic migraine. This finding is in line with the fact that MOH never develops *de novo* and can be recognized as a chronic migraine complication rather than a simple type of secondary headache. Interestingly, previous research demonstrated that primary chronic migraine is also rare, and chronic migraine usually progresses from episodic migraine. Given the high burden of chronic migraine accompanied by MOH and relatively lower cost of episodic migraine treatment compared with chronic one, it is not far from the mind that the prevention of migraine chronification can contribute to substantial cost saving.

Factors like ethnicity, geography, economic aspects of countries, healthcare structure, and costs of services across countries can be the source of huge differences in terms of disease burden [16, 29]. However, most information regarding headache disorders burden was derived from the USA and Europe so far, and the studies on MOH burden are scarce from our neighbor countries and our region. Therefore, our results are of importance for two main reasons: first, our findings transfer valuable information to policymakers and could be used in future health planning. Second, they provide a different insight into the cost of MOH, which is likely closer to the actual expenditure in middle- and low-income countries. Another strength of this study is the definite diagnosis of MOH by an expert neurologist based on ICHD-III beta criteria rather than a questionnaire-based diagnosis. Additionally, with the help of cross-sectional design and face-to-face interviews, there are more possibilities for detailed data collection regarding direct non-healthcare costs, productivity loss, and even cost of time wasted by the person accompanying the patient. However, some limitations have to be acknowledged. Our results depend on patient reports by using a retrospective questionnaire, and this method can introduce recall bias. Furthermore, our samples were collected from the third-level referral center, and about 30% of our patients were people who came to Tehran from another city, so some of these participants may have severe disease which can lead to overestimation of the cost. Finally, it should be noted that determining the cause of cost differences and the direction of the events is not easy to understand. Higher indirect costs in developed countries may reflect the high cost of the lost opportunities

due to the high GDP per capita and high wages. But lower costs in developing countries could be also due to a lower number of missed workdays as a result of economic pressure and not necessarily lower salary or a better outcome. Therefore, estimating and interpreting the economic costs of disease should be specific to each nation or at least similar areas in terms of income and development indexes.

## Conclusion

In the current study, we delivered an estimation of MOH cost in Iran that showed the mean annual cost of \$2610 per patient mostly due to indirect costs (55%). Based on the previously reported prevalence of MOH in Iran (4.9%), the total annual cost of patients is about \$10 billion. Our findings unambiguously reveal that the economic burden of this headache disorder in Iran is high. Therefore, raising awareness in this area especially for policymakers can lead to resource allocation in the field of disabling type of headache disorders such as MOH and implementation of effective management for prevention of migraine chronification. Our study is one of the few ones regarding the burden of a disabling headache that may track the attention for doing such studies in our geographic regions.

**Authors' contribution** All authors contributed to the study conception and design. Material preparation and data collection were performed by Fatemeh Nadjafi-Semnani. Zahra Mohammadshirazi and Niusha vahidpour were also involved in data collection process. Data analysis was performed by Ali Akbari-sari and Rajabali Daroudi. The first draft of the manuscript was written by Mansoureh Togha and Fahimeh Martami. All authors read and approved the final manuscript.

**Data availability** Not applicable.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval** The study was approved by the ethical committee of Tehran University of medical sciences (IR.TUMS.MEDICINE.REC.1397.177).

**Consent to participate** All patients signed an informed consent form prior to inclusion in the study.



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