

# Investigating the Effects of COVID-19 Quarantine in Migraine: An Observational Cross-Sectional Study from the Italian National Headache Registry (RICE)

**Marianna Delussi**

Universita degli Studi di Bari Aldo Moro

**Eleonora Gentile**

Universita degli Studi di Bari Aldo Moro

**Gianluca Coppola**

Universita degli Studi di Roma La Sapienza Facolta di Medicina e Psicologia

**Addolorata Maria Pia Prudeniano**

Azienda Ospedaliero Universitaria Policlinico Bari

**Innocenzo Rainero**

Universita degli Studi di Torino Scuola di Medicina

**Grazia Sances**

Fondazione Salvatore Maugeri Istituto Scientifico di Pavia Via Maugeri

**Chiara Abagnale**

Universita degli Studi di Roma La Sapienza Facolta di Medicina e Psicologia

**Valeria Caponnetto**

Universita degli Studi dell'Aquila

**Francesco De Cesaris**

Universita degli Studi di Firenze

**Ilaria Frattale**

Universita degli Studi dell'Aquila

**Elena Guaschino**

Fondazione Salvatore Maugeri Istituto Scientifico di Pavia Via Maugeri

**Andrea Marcinno'**

Universita degli Studi di Torino Scuola di Medicina

**Raffaele Omello**

Universita degli Studi dell'Aquila

**Francesca Pistoia**

Universita degli Studi dell'Aquila

**Alessia Putorti'**

Mondino Pavia

**Maria Elena Roca**

Azienda Ospedale Policlinico Bari

**Fausto Roveta**

Universita degli Studi di Torino Scuola di Medicina

**Maria Trojano**

Universita degli Studi di Bari Aldo Moro

**Francesco Pierelli**

Universita degli Studi di Roma La Sapienza Facolta di Medicina e Psicologia

**Pierangelo Geppetti**

Universita degli Studi di Firenze

**Simona Sacco**

Universita degli Studi dell'Aquila

**Marina De Tommaso** (✉ [marina.detommaso@uniba.it](mailto:marina.detommaso@uniba.it))

Universita degli Studi di Bari Aldo Moro <https://orcid.org/0000-0001-6567-5373>

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### Short report

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## Abstract

**BACKGROUND:** Previous studies during SARS and Ebola pandemics have shown that quarantine is associated with several negative psychological effects, such as post-traumatic stress symptoms, confusion and anger. These conditions may affect the course of many diseases, including migraine. Although it is possible that the quarantine measures for the current COVID-19 pandemic affect migraine burden, no information is currently available on this issue.

**AIM:** In this study, we aimed to: 1) explore the possible changes in migraine frequency, severity, and days with acute medication intake during quarantine period; 2) evaluate possible differences in migraine outcomes in consideration of lifestyle changes, emotions, pandemic diffusion, and COVID-19 infection.

**METHODS :** We interviewed patients who were included in the observational Italian Headache Registry (Registro Italiano Cefalee, RICE), retrospectively collecting information on main headache features, lifestyles factors, emotions, individual infection status, and perception of COVID-19 for two months before (pre-quarantine) and after the beginning of the quarantine (quarantine). Inclusion criteria were: age > 18, diagnosis of migraine without aura, migraine with aura and chronic migraine, last in-person visit more than 3 months preceding the beginning of quarantine.

**RESULTS:** A total of 433 migraine subjects agreed to be interviewed. We found an overall reduction in headache frequency and intensity during the quarantine, compared to pre-quarantine. There was a correlation between improvement and number of days of stay-at-home. When results were stratified for geographic area, we found a tendency towards worsening of headache frequency in northern Italy. Disgust regarding viral infection corresponded to a minor improvement in migraine.

### CONCLUSIONS

Migraine patients showed resilient behavior toward pandemic distress. Disgust regarding the contagion whereas potentially favoring defensive behavior, could potentially worsen migraine.

## Introduction

COVID-19 (Kaur et al, 2020; Tian et al., 2020) was declared a global pandemic on March 11, 2020 by the World Health Organization. Italy, the first European country in which there was an outbreak of the pandemic, currently records a total of approximately 185,000 confirmed cases, and more than 24,000 patients with severe illness. The spread of COVID-19 in the Italian territory was markedly different, with northern Italy showing a much higher number of cases, as compared to central and southern Italy. On March 10, the Italian Government was the first in Europe to impose severe social-distancing orders. Social-distancing and mitigation strategies (Anderson et al., 2020; Nussbaumer-Streit et al, 2020; Parodi and Liu, 2020) aim to defer a major flow of patients, and reduce the demand for hospital admissions, while safeguarding the most vulnerable subjects (Bedford 2020).

Studies related to the 2003 outbreak of severe acute respiratory syndrome (SARS) in China and Canada, as well as the 2014 Ebola outbreak in Africa, reported that quarantine is associated with several negative psychological effects, such as post-traumatic stress symptoms, confusion, and anger (Hawryluck et al, 2004; Brooks et al, 2020), with a potential increase of suicidal risk (De Berardis et al, 2017). Changes in social behavior and work activities, the unavailability of a public health system for routine medical management, and widespread fear of infection could cause important psychosocial outcomes (Person et al., 2004; Shultz et al., 2016; Szperka *et al.*, 2020; Gautam et al, 2020), and could dramatically increase the burden of the disease. However, few data have been reported on the impact on migraine caused by psychosocial distress due to COVID-19 and long-term distancing measures.

In this study we aimed to: 1) explore whether the quarantine period affected frequency and severity of migraine and days with acute medication intake; 2) evaluate possible differences in migraine outcomes in consideration of changes in lifestyle, emotions, pandemic diffusion, and COVID-19 infection.

## Methods

### Study population and design

This observational cross-sectional study describes the impact of the COVID-19 pandemic and social distancing measures on headache features in migraine patients. It was conducted via a structured telephone interview in a sample of patients included in the Italian Registry of Headache (Registro Italiano delle Cefalee, RICE), which enrolls patients aged  $\geq 18$  years who visit headache treatment centers.

RICE is an observational registry, promoted and endorsed by the Italian Society for the Study of headaches (SISC), which records clinical data of consecutive patients with headache who refer to the member Headache Centers. The present ancillary sub-study is based on data from 7 headache centers in northern (Pavia and Turin), central (Florence and Latina), and southern (Avezzano-L'Aquila, and 2 centers in Bari) that enrolled patients who had entered the RICE at least three months before of the start of the quarantine (pre-quarantine) in Italy. The 7 centers are located in geographical areas that experienced markedly different impacts of COVID-19 outbreak: higher in the north, medium central, and lower in southern Italy (2020-<http://www.protezionecivile.gov.it/attivita-rischi/rischio-sanitario/emergenze/coronavirus>). For the present study, inclusion criteria were age  $\geq 18$  years, a diagnosis of migraine without aura, migraine with aura and chronic migraine according to the criteria of the International Classification of Headache Disorders, III edition (ICHD-III), most-recent in-person visit within the 3 months preceding the lockdown period. Exclusion criteria were ascertained comorbidity with other forms of primary headaches, psychiatric disorders according to DSMV, and liver, kidney and heart insufficiency.

### Telephone interviews and variables of interest

Telephone interviews were carried out by study investigators between March 27 and April 18, 2020. The interview was a web supported questionnaire, to be filled in during the telephone call. The questionnaire was administered in the Italian language (it is available in Italian and English in the Supplementary Materials). Variables of interest included frequency of headache expressed as average number of headache days per month, calculated during the 2 months preceding the quarantine (pre-quarantine) and in the time from the beginning of the quarantine (March 8, 2020 for Northern Italy, extended on March 10, 2020 to the rest of Italy). Patients were asked to report the intensity of headache and the use of symptomatic drugs during the pre-quarantine and quarantine times, according to their headache diaries. Questions included: number of the days of staying at home, current working conditions, level of risk contacts, individual infection, personal feelings on how COVID-19 affects migraine outcomes and/or migraine as a possible risk factor for COVID-19, fear of becoming infected, possible changes of daily behaviors (food intake habits, alcohol consumption, and sleep quality) as a result of social-distancing measures, emotions regarding the pandemic emergency (fear, disgust, anxiety, sadness, happiness) on a scale from 0 (no emotion) to 10 (maximum emotion), subjective evaluation of mood change (worsening, no change, improvement) (see the questionnaire in the Supplementary Section).

### Study outcomes

Study outcomes were: headache frequency and intensity, and days with acute medication intake during the 8 weeks preceding and during the social-distancing measures. Predictor variables were: migraine severity before the quarantine, lifestyle habits, emotions, severity of pandemic diffusion, and COVID-19 infection.

### Ethics

Local Ethic Committees of each recruiting center approved the RICE registry, and enrolled patients signed informed consent.

### Statistical analysis

In the absence of previous similar reports, and because of the descriptive nature of the study, the sample size was not calculated. Parametric distribution of data was evaluated by the Levene test for equality of variance. As the observation-period during quarantine varied across subjects, we normalized headache days for the effective period of observation (number of headache days / number of total days of observation x 30). We used ANOVA for repeated measures with condition before vs

during social distancing as factors. The effect of severity of migraine before quarantine, emotions, living behavior, and geographic area on primary outcomes was evaluated by the same repeated measures ANOVA model, introducing nominal variables as factors and quantitative variables as covariates. A complete factorial ANOVA model type III included in IBM SPSS software version 21 was used.

## Results

### Demographic data, working status, living conditions, and daily habits

**General.** A total of 433 migraine subjects agreed to be interviewed, while 10 patients did not give their consent. The mean interval elapsed between start of the quarantine and the time of the interview was  $31.9 \pm 4.5$  days without significant differences across participating centers. Baseline characteristics of enrolled patients are presented in Table 1.

Table 1  
Baseline characteristics of the included subjects

	<b>n = 433</b>
Gender, n (%)	
Female	333 (76.9)
Male	100 (23.1)
Age (years), mean $\pm$ SE	43.97 $\pm$ 0.63
BMI, mean $\pm$ SE	24.1 $\pm$ 0.002
Education years, n (%)	
0–5	16 (3.7)
6–8	84 (19.4)
9–13	175 (40.4)
>13	158 (36.5)
Days of social distancing, mean $\pm$ SE	29.27 $\pm$ 0.58
Home place, n (%)	
Countryside	76 (17.8)
City	183 (42.3)
Small town	174 (40.2)
No. of cohabiting family members during social distancing, mean $\pm$ SE	2.32 $\pm$ 0.13
Work, n (%)	
Unemployed	208 (48.0)
Employed	225 (52.0)
Employment, n (%)	
Work from home	89 (20.6)
At workplace	48 (11.1)
Unemployed (lost position)	88 (20.3)
Food intake, n (%)	
Increased	67 (15.5)
Reduced	153 (35.3)
Unchanged	213 (49.2)
Alcohol consumption, n (%)	
Reduced	85 (19.6)
Increased	13 (3.0)
Unchanged	344 (79.4)
Sleep quality, n (%)	
Improved	157 (36.3)

	n = 433
Worsened	45 (10.4)
Unchanged	229 (52.9)
Emotional reaction, mean ± SE	
Anger	4.15 ± 0.27
Disgust	3.39 ± 0.27
Fear	5.71 ± 0.28
Anxiety	5.86 ± 0.18
Sadness	5.40 ± 0.28
Happiness	4.67 ± 0.23

BMI indicates body mass index. Intensity of emotions related to the COVID-19 emergency are reported on a 0–10 scale.

Most of interviewed patients did not report changes in food intake, sleep, or alcohol assumption (Table 1). During quarantine, 177 subjects (55.1%) reported worsening, 42 (13.1%) no change, and 102 (31,8%) improvement in mood. Emotions scores related to pandemic are reported in Table 1

**Migraine during quarantine.** A reduction in the average number of days with headache, days with acute medication intake, and migraine intensity was observed during the quarantine compared to pre-quarantine (Table 2). Most patients subjectively reported that their migraines did not change after the start of quarantine. Most migraine patients did not consider migraine as a facilitating factor for COVID-19 infection (Supplemental Table 1). Two-hundred eighty-nine patients were taking preventive treatments for migraine; 88 discontinued treatment for different reasons, such as drug failure or difficulty in attaining the drugs (Supplemental Table 2) .

Table 2

Comparison of headache features before and during lockdown period. CM: Chronic Migraine patients; EM: Episodic Migraine patients. Data are reported as mean ± standard errors.

n° 433	Before	During	F	P value	EM	During	CM	During	F	P value
					Before		Before			
					n°331		n°102			
Monthly headache days	9.42 ± 0.43	8.28 ± 0.41	60.6	< 0.0001	5.10 ± 0.23	4.99 ± 0.35	21.6 ± 0.39	16.74 ± 0.59	59.6	< 0.0001
Acute medication days	8.32 ± 0.51	7.19 ± 0.54	21.7	< 0.0001	4.91 ± 0.46	4.2 ± 0.55	16.9 ± 0.78	13.2 ± 0.93	13.76	< 0.0001
Headache intensity	6.93 ± 0.10	6.71 ± 0.11	6	0.014	6.79 ± 0.11	6.5 ± 0.12	7.25 ± 0.25	6.95 ± 0.19	0.1	n.s.

**Effects of migraine severity, lifestyle habits, emotions and severity of pandemic diffusion on headache frequency.** Before the quarantine, 331 patients (xx%) reported episodic migraine, while the remainder were affected by chronic migraine. Improvement in headache frequency and analgesic consumption was higher in chronic than in episodic migraine patients (Table 2). Alcohol use, smoking, eating, and subjective perception of sleep quality did not affect headache frequency and intensity, use of symptomatic drugs, and/or working conditions. The improvement of headache frequency correlated with the number of stay-at-home days (ANOVA with repeated measures with days of social distancing as covariate F 37.07 p < 0.0001). Changes in headache parameters were similar among patients living in different urban areas and with different levels of education. Migraine features were not significantly different among northern, central and southern Italy before the quarantine period. (Supplemental Table 3). However, patients of northern Italy, the geographical area with the highest pandemic diffusion, showed

a tendency of increased headache frequency and use of acute medication (Table 4; Fig. 1). It should be noted that the number of days of effective stay-at-home were reduced in patients from northern Italy (Supplementary Table 3).

Table 4  
Comparison of headache features before and during lockdown period in the included patients. Data are reported as mean  $\pm$  standard errors.

	North (n = 105)		Center (n = 101)		South (n = 227)		F(geographic area)	P value	P value (Bonferroni)
	Before	During	Before	During	Before	During			
Monthly headache days	10.57 $\pm$ 0.81	11.03 $\pm$ 0.78	8.19 $\pm$ 0.84	6.02 $\pm$ 0.80	9.50 $\pm$ 0.56	7.78 $\pm$ 0.53	6	0.003	< 0.001 (South and Center vs North)
Acute medication days	10.21 $\pm$ 0.96	10.79 $\pm$ 1.02	7.29 $\pm$ 0.98	5.07 $\pm$ 1.04	7.46 $\pm$ 0.65	5.70 $\pm$ 0.69	3.6	0.027	< 0.01 (South and Center vs North)
Headache intensity	6.57 $\pm$ 0.19	6.59 $\pm$ 0.21	7.25 $\pm$ 0.21	7.03 $\pm$ 0.22	6.96 $\pm$ 0.21	6.50 $\pm$ 0.14	3	0.05	NS

There was a significant relationship between disgust against COVID-19 infection and increase in headache frequency (repeated measures ANOVA with disgust as covariate F 6.43 p 0.004).

Patients reporting mood improvement showed a tendency to reduced headache frequency (repeated measures ANOVA with mood perception as factor: F 5.43 p 0.001). However, the Bonferroni test among the different mood perceptions did not show any significant difference. Patients who subjectively reported a worsening of their migraine showed an objective increase in headache frequency (Repeated measures ANOVA with subjective impression of migraine severity as factor: F 35.58 p < 0.0001: Bonferroni test: got worse vs improved p < 0.01). However, patients feeling migraine as a facilitating factor for infection showed a tendency toward frequency increase (ANOVA with perception of migraine as risk factor : F 3.59 p 0.012 Bonferroni test: n.s.). Emotions against pandemic and subjective perception of mood and disease severity did not influence the change of headache features in chronic, compared to episodic, migraine.

**COVID-19 infection in migraine sample.** In the overall sample, 5 patients reported to have been infected by SARS-CoV-2 (Table 5). Those patients did not report substantial changes in their migraines after infection.

Table 4  
Characteristics of migraine patients positive to SARS-CoV-2 infection. Changes refer to quarantine measures compared with the two previous months.

	Age	Sex	Geographic area	Symptomatic	COVID-19 Outcome	Migraine frequency change (%)	Mean intensity change (points)	Change in use of symptomatic drugs (%)
Patient 1	22	F	South	No		-18	0.38	-75
Patient 2	56	F	North	No		-20	1	0
Patient 3	47	F	South	Yes	Under treatment	-20	0.88	0
Patient 4	44	F	North	Yes	Recovered	-40	1	-32
Patient 5	46	F	North	Yes	Under treatment	-30	0.5	0

## Discussion

The results of the present study show a resilient behavior of migraine patients in response to quarantine for the COVID-19 pandemic, given that headache frequency, days with acute medication intake, and headache intensity improved during the social distancing measures. Resilience prevailed in chronic migraine patients and in the areas where there was the lowest prevalence of COVID-19, and was positively influenced by the number of days of stay-at-home orders. Disgust toward infection corresponded to an attenuation of headache improvement.

**Migraine during quarantine.** The interview was conducted on migraine patients previously enrolled in RICe, which guaranteed the presence of accurate clinical features previously recorded. This represents a point of strength, as compared to interviews administered to the general population (Potter et al., 2019). The general improvement of headache frequency and intensity during lockdown confirms results obtained in smaller Italian migraine samples (Parodi et al., 2020). The viral diffusion may contribute to the onset of stress-related disorders (Horesh and Brown, 2020; Szperka *et al.*, 2020), which may worsen migraine (Peterlin et al., 2009). The development of a resilient behavior associated with COVID-19 (Horesh and Brown, 2020) may have also involved migraine patients. Resilience mechanism could enhance the threshold of migraine onset and subjective feeling of its intensity. In fact, resilience ability is generally associated with better outcome in patients with chronic pain (France *et al.*, 2020).

**Effects of migraine severity, lifestyle habits, emotions, and severity of pandemic diffusion on headache frequency.** In a previous large global cross-sectional study, patients with frequent migraine showed greater resilience in response to negative events, such as treatment failures (Martelletti et al., 2018). The present results confirm that resilient behavior against the pandemic could prevail in more severe migraines. Psychological features of migraine patients, underlying a favorable outcome under the current dramatic epidemics, were not recorded in previous visits of the RICe database, though this could be subject for further studies in a possible scenario of pandemic persistence (Lipsitch et al., 2020). A correlation between the emotional impact of pandemic situation and its effect on migraine features was not found. However, the perception that migraine could facilitate COVID-19 infection, possibly causing additional stress, negatively affected the improvement of headache frequency. The pandemic emergency did not seem to cause particular sleep disruption in our migraine sample, an effect attributable to the resilient reaction.

The improvement of headache severity was correlated with the effective number of days of stay-at-home (Wilkins and Beaudet, 1998; Santos et al., 2014). The resilient behavior against migraine worsening for pandemic distress could thus be enhanced during effective social distancing. We did not find an association between headache improvement, work activity, and lifestyle habits. Nevertheless, staying at home, even if forced, could globally influence trigger factors and the ability to rest, possibly decreasing the risk of recurrence. This result could be taken into consideration for the social management of public health during pandemics (Parodi and Liu, 2020).

The headache centers cooperating in data collection see patients coming from different Italian regions, so we considered the place of residence at the time of public restrictive measures. Residents in regions with higher pandemic diffusion seemed to express a less resilient behavior. As an adjunctive result, we also observed that patients in northern Italy reported fewer days of social distancing, which were associated with a positive outcome of migraine. We could thus suppose that the severity of pandemic diffusion could change environmental situation and personal habits (Motta Zanin et al., 2020), also exerting an influence on the resilient behavior.

The expression of disgust was slightly associated with migraine frequency increase. Disgust is an emotional response of rejection or revulsion to something potentially contagious or offensive (Badour and Feldner, 2018). It is a system that evolved to motivate infectious disease avoidance and combat the behavioral causes of infectious and chronic disease, such as pandemic flu (Curtis, 2011). While it could help in assessing avoidance behavior during pandemic infections, it is a cause of distress (Curtis, 2011), which could have a negative impact on migraine frequency and attenuate the resilient reaction.

**COVID-19 infection in migraine sample.** Although the present study was not designed to assess the frequency of infection in the migraine population, because of the relatively small sample, we did find 5 out of 433 migraine patients positive for SARS-CoV-2

infection (1.15%). At the time we collected data, there were about 185,000 infected in the general Italian population (0,3%), with a slight prevalence in males (51,7%), and a median age of 62 years (Italian Healthy System and Civil Protection report <http://www.protezionecivile.gov.it/attivita-rischi/rischio-sanitario/emergenze/coronavirus>). However, the percentage of asymptomatic persons among the general population is an unresolved issue, so present data do not enable any type of speculation about the prevalence of SARS-CoV-2 infection in migraine patients. Recent reviews about the main symptoms of COVID-19 stated that headache occurs in nearly 10% of patients, while migraine is not included within the comorbidities that aggravate symptomatic patients (Sanyaolu et al, 2020). Further studies and meta analyses are needed to establish prevalence and clinical aspects of COVID-19 in the migraine population.

### **Study limitations**

The main limitation of the present study is the small number of patients interviewed. This limitation was determined by the restricted time window of the interview, limited to the time of the restrictive measures, also termed “phase I”, enforced by the Italian Government, and by the fact that enrolled cases were solely those patients who had previously given their informed consent to the RICe study, and therefore could be enrolled in the present sub-study. Additional limitations could be scarce reliability of headache diaries during the pandemic, and the short amount of time for evaluation of migraine outcome during the social and health emergency (1 month on average). This study was conducted in tertiary headache centers and included patients with high monthly attack frequency, not representative of migraine in the general population. Finally, the text of interview was only partially validated among Italian citizens (Motta Zanin et al., 2020).

## **Conclusions**

We found that, on average, migraine patients expressed resilient behavior with regards to pandemic distress, with a reduction in migraine severity indices. Resilience also emerged in the maintenance of habitual lifestyles during social distancing, but was less evident in people with a limited number of days of staying at home. The present data could help in the future reorganization of services, healthcare workforce, and ongoing management of migraine (Bhaskar et al, 2020). The spontaneous limitation of migraine burden during quarantine could favor patient follow-up via the use of telemedicine visits (Szperka *et al.*, 2020), reliable diaries, and frequent remote contacts after an initial in-person visit.

## **Abbreviations**

RICe

Registro Italiano Cefalee- Italian Headache Registry

SISC

Società Italiana Studio Cefalee-Italian Society for Headache Study

## **Declarations**

Ethics approval and consent to participate

Local Ethic Committees of each recruiting center approved the RICe registry; signed informed consent was requested to be included in the RICe registry.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

#### Funding

No funding sources were provided.

#### Authors' contributions

**Marianna Delussi and Eleonora Gentile equally contributed** : study design, interview preparation, patient selection and study coordination

**Marina de Tommaso**, study coordination, manuscript preparation, data analysis, manuscript editing

**Pierangelo Geppetti and Simona Sacco** : manuscript preparation, data analysis, manuscript editing

**Innocenzo Rainero, Gianluca Coppola, Grazia Sances , Maria Pia Prudenzano**: manuscript preparation and editing

**Francesco Pierelli and Maria Trojano**: study design, manuscript editing

**Raffaele Omello**: study design, statistical analysis

**Chiara Abagnale, Valeria Caponnetto, Francesco De Cesaris, Iaria Frattale, Elena Guaschino, Andrea Marcinnò, Francesca Pistoia, Alessia Putortì, Maria Elena Roca, Fausto Roveta**: patient selection, manuscript editing and preparation, telephone interviews

**Chiara Lupi**: RICE data, patient selection, telephone interviews

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#### Conflict of interest

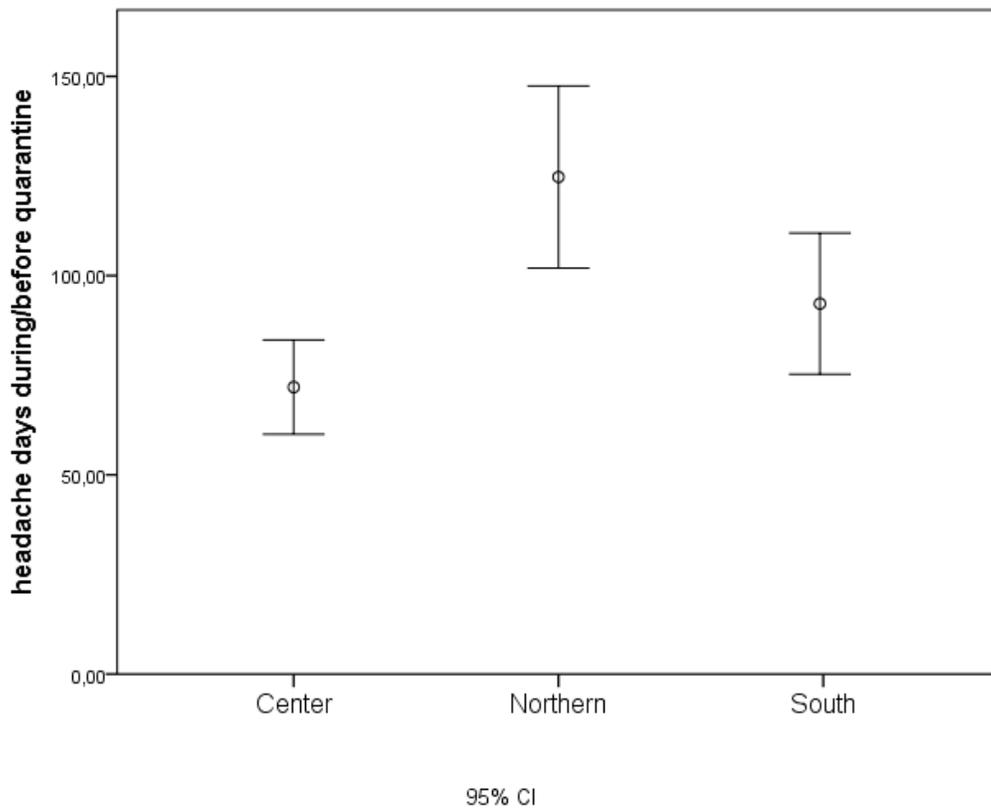
No author declares conflict of interest

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## Figures



**Figure 1**

Change of days with headache in migraine patients divided into geographic area of residence. The indexes express the percent ratio between normalized headache days before and after the date of the social-distancing orders.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SurveySup.docx](#)
- [SupplementalTables.docx](#)