

Migraine and Stress – An Explorative Cross-Country Study of External Stress Factors

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Research article

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Abstract

Background

According to the Global Burden of Disease 2016 project, migraine ranks first for 15-49 years and second for all ages. The project has reported no significant relation with socio-economic status of a country. To the contrary, migraine ranks first for all ages in low- and middle-income countries suffering from civic unrest and conflict. This raises the question whether external stress factors may be correlated with migraine years lived with disability (YLD).

Methods

In the absence of cross-country studies on migraine and stress, this is a unique exploratory study. The analysis uses two country groups: developed countries (including some middle-income countries) and developing (middle- and low-income) countries. For the first group, proxy variables for stress are included that relate to flexible and highly competitive labour markets (productivity and unemployment), whereas for the second group, proxy variables are used that relate to conflict and migration. The data were analysed with multiple ordinary least squares cross-section regressions.

Results

The results show a positive relationship between the stress variables on the one hand and migraine YLD on the other hand for both country groups. Almost all results are statistically significant at $p<0.01$.

Conclusions

The findings from the exploratory cross-country analysis suggest that societal stress factors may be potential candidates for modifiable factors for the prevalence and severity of migraine at the country level.

Background

According to the Global Burden of Disease 2016 project, migraine ranks first for the age group of 15 to 49 years while it ranks second for all ages, measured as Years Lived with Disability (YLD).¹ An insightful GBD study focusing on migraine reveals that there are 1.04 billion migraine patients worldwide and together they suffer from 45.1 million years lived with disability.² Interestingly, migraine ranks high in all countries in the world and, contrary to beliefs, is not a typical western lifestyle disease. It is listed in the top five most debilitating diseases in every country (except for one in which it takes the sixth place). Migraine ranks equally high in developing countries, even though diseases such as malaria and anaemia are widespread in the developing world. The GBD-migraine study has found that at the cross-country level, there is no significant relationship between the prevalence of migraine and socio-economic status. The socio-economic development of a country “is not a major determinant of the size of the headache burden”, the authors conclude (p. 971).²

The causes of the debilitating chronic disease are still largely unknown. In addition, there is no effective treatment yet. As a consequence, migraine patients often suffer for years if not decades, which explains the high ranking in terms of disability. Studies into possible causes, comorbidities, and treatments are largely limited to clinical studies (RCTs and cohort studies) and health surveys. There are no systematic cross-country analyses available with country-level data of risk factors for migraine. Clinical studies suggest three categories of candidates for modifiable risk factors: metabolic factors (including obesity and insulin resistance), mental health factors (including depression, anxiety, and insomnia), and hormone factors (oestrogen, which may be influenced by industrial food and certain chemicals in the environment; and cortisol, a key stress hormone).^{3–8} Of all these modifiable risk factors, chronic stress is increasingly mentioned as a key mechanism in the development and chronification of migraine.⁹

A few small cohort studies have shown statistically significant relationships between migraine and external stress factors, in particular work-related stress^{10,11} and stress from civil war, terrorism, and combat.^{12–14} Why is migraine the number one chronic disease among those of working age in developed countries, where work-related stress is ubiquitous? And why is migraine the number one chronic disease in developing countries suffering from conflict or civic unrest or large refugee inflows, such as Afghanistan, Syria, Venezuela, Colombia, Jordan, Iraq, Lebanon and Palestine? In this article, I will explore the extent to which external stress factors are related to migraine at the cross-country level. The results should be taken with much caution – they are exploratory in character. The purpose of the present study is not to establish causality, but to complement findings from clinical research and country-level survey studies. The results suggest that future research on migraine and stress may be advised to take external stressors, at the societal level, into account.

Literature review

Although the ultimate cause of migraine is still unknown, the neurophysiology of migraine has been described in much detail over the past decade. Migraine is a neurological disease with a cascade of effects in the brain, in which the HPA-axis (Hypothalamic-Pituitary-Adrenal axis) and the trigeminal nerve (with one of the branches behind the eyes, where migraine headache is often located) play a key role.^{15–18} Genetic research shows more and more genes that are related to migraine, while the fact that some patients develop migraine late in their lives whereas others report an end to the attacks suggests that epigenetic factors may play a role too.¹⁹

The HPA-axis appears to play a crucial role not only in the stress response but also in migraine, through the hypothalamus, which is responsible for regulating the autonomic and central nervous system as well as some metabolic processes (for example the regulation of glucose and insulin). Indeed, just before a migraine attack, patients often crave sweets while during the attack most patients feel nauseous. The HPA-axis is the key mechanism of the body's response to acute stress, which may be caused by any stressor, consciously (an explosion or threat of dismissal) or unconsciously (feeling unsafe or work deadlines). But when the number of stressors becomes too high or a single stressor occurs with a high frequency, stress may become chronic. In that case, the HPA-axis is overactive and the body does not

have sufficient time to recover and to bring cortisol, blood pressure, glucose, oestrogen, pulse, and breathing back to normal values.²⁰⁻²² In that case, stress researchers refer argue that the brain fails to regulate the tress response adequately which is referred to as allostatic overload.²²

Allostatic overload is visible in the brain. Neuroimages of individuals suffering from chronic stress show structural and functional changes in the amygdala, hippocampus and prefrontal cortex.²² Over the past decade, allostatic overload has also been related to migraine, not only from migraine to stress, but more importantly, from stress to migraine, which suggests a possible causal path.^{7,15,23} The brains of migraine patients appear to be highly sensitive, or hyperexcitable, in particular the hypothalamus, amygdala, and prefrontal cortex showing similar structural and functional changes as in the brains of those suffering from chronic stress.^{18,24} As the authors of a review study conclude, "being a migraineur means having subtle differences in brain structure and function even outside of attacks. (p. 559)²⁵" This implies, the authors, continue, that migraineurs are particularly susceptible to environmental changes, which includes the work environment and the political context, which may lead "to inappropriate processing or interpretation of stressful information. (p. 593)²⁵" Therefore, Bruce McEwen, one of the first stress researchers, emphasizes that our environments need to change if we want to reduce sustained stress and its effect on various diseases. He refers to policies that help to increase people's "healthspan" rather than their "lifespan", by "providing opportunities for individuals to experience better working and living environments. (p. 23)²⁴"

The modern flexible work context as well as civic unrest and conflict with subsequent insecurity and refugee flows are clearly external stressors for large populations. They may, therefore, have an aggregate effect on the prevalence of migraine as well as on the severity of it, expressed together in YLD. But there are no studies available that have explored possible relationships between the prevalence or severity of migraine on the one hand and such external stressors in society on the other hand. There is a clear need for cross-country studies into these relationships. A recent editorial in *Neurology* concludes that various external factors "can affect the threshold for migraines, including stressful life events. (p. 53)²⁶" Researchers have pointed in particular at work-related stress in the western world, related to an individualist, competitive work culture in ever more flexible and insecure labour markets, with continued outsourcing of low skilled work and job replacement by modern technology.²⁷ For the developing world, basic insecurity of life is likely to be a source of chronic stress, related to civil war, violent conflict, weak states, or large refugee flows due to crises in neighbouring countries.^{26,28} In the absence of systematic, cross-country research, some researchers have developed hypotheses about migraine as a maladaptive response to life in stressful environments, such as today's globalized, flexible, and complex societies.²⁹

Combining the clinical research of migraine as a neurological maladaptive stress response with the findings from the GBD-migraine study showing the high ranking of migraine in all Western societies as well as in developing countries suffering from conflict, I suggest a very preliminary hypothesis a relationship between society-wide stressors on the one hand and migraine YLD on the other hand.

Methods

This is an exploratory study for the reason that there is no systematic research available on the relationship between external stress factors and migraine at the cross-country level. Moreover, there are no publications about possible modifiable factors of migraine at the country level, and no publications about the relationship of external stress factors (as distinguished from personal stress factors) and migraine at the cross-country level. The only evidence available for a possible causal relationship between stress and migraine is from a few clinical studies and (national) health surveys. No cross-country studies on migraine and stress are available. Due to this gap in migraine epidemiology studies, the aim of the study is to explore the extent to which stress might turn out to be a possible modifiable factor for the prevalence and severity of migraine, at the cross-country level. The setting is a cross-country analysis with secondary data on migraine and stress for two country groups, each with their own set of pertinent stress variables.

The empirical analysis consists of a cross-section study with OLS regressions. Data was used for 153 developing countries, and as a comparison, a second analysis was carried out among 38 developed countries – OECD members and affiliates, of which four countries are classified as middle income countries by the World Bank classification for 2016–2017 (Russia, Turkey, Costa Rica and Mexico). A single country group would not be advisable on statistical and theoretical grounds. This is because poverty is ubiquitous in low- and middle-income countries and therefore not a relevant stress factor, whereas highly flexible and competitive labour markets in the context of globalization may involve stress factors in high-and middle-income countries. Moreover, since the GBD-migraine study did not find a significant effect of socio-economic status, it is statistically advisable to break up the population into two groups rather than to use the level of (socio-)economic development as a control variable in a combined analysis.

The cross-section method does not establish causality due to the lack of time variation. However, with migraine as the dependent variable, reverse causality is not likely at the country-level, contrary to a possible two-way relationship between migraine and stress at the individual level.

Migraine was measured as YLD rate per 100,000, for all ages and for 15–49 years old, respectively. The independent variables were deliberately chosen to be clearly exogenous, indeed, as external stress factors. Two estimations were done, with two country-groups: developed and developing countries, each with their own group-specific independent variables. The proxy variables for external stress for developed countries were selected to be labour market related whereas the proxies for the developing country group were selected to be related to more fundamental life insecurity.

For the developing country group, two proxy variables for external stress were used, related to war, conflict and insecurity. The first is the presence of high-intensity battle-related deaths (with a minimum of at least 1000 deaths in a year). The data for this binary variable ($BRD > 1000$) has been calculated from the data of battle-related deaths collected by the Uppsala Conflict Data Program.³⁰ The second proxy

variable for external stress is international migrants as share of the population in the receiving country. The data are available from the World Development Indicators of the World Bank.³¹ For the group of developed countries (OECD members and affiliates), the same two dependent variables were used for migraine. The independent variables, however, are two proxy variables for work-related stress. The first proxy variable is the unemployment rate, reflecting labour market insecurity, in particular in the context of labour market flexibilization. The second proxy variable is labour productivity, measured as output per worker. This variable signals work pressure but also tends to be positively related to wage rates.³² Together, the two labour market variables represent the carrot and the stick of flexible labour markets. Both variables are collected by the OECD.

Table 1 shows the descriptive statistics for both country groups. The summary makes clear that all variables used in the analysis are continuous variables (scale level of measurement) except for battle-related deaths because data was available for only 40 countries, including cases with less than ten deaths and including countries with military casualties abroad on UN peace keeping missions. Hence, the scale data was transformed to a binary variable with the value of 1 for at least 1000 battle related deaths and 0 otherwise. Finally, all data concern the year 2016 – the year to which the GBD data on migraine refer.

Table 1
Descriptive statistics

Developed countries	Average	Std dev	Min	Max	No
Migraine all ages	778	140	479	1075	38
Migraine 15–49 years	1063	212	675	1519	38
Labour productivity	81135	47089	22427	235385	38
Unemployment rate	7.39	4.10	2.98	23.54	38
Developing countries	Average	Std dev	Min	Max	No
Migraine all ages	623	139	301	1206	155
Migraine 15–49 years	881	170	475	1619	155
Battle Related Deaths > 25 (scale variable))	2157	7098	4	41340	40
Battle Related Deaths > 1000 (ordinal variable)	0.6	0.24	0	1	155
Migrants as share of population	8.4	14.95	0.07	88.4	153

Results

Two similar models are estimated, one for developed and the other for developing countries:

Model for developed countries

$$M = \alpha LP + \beta UR + \epsilon$$

In the OLS-estimation, the dependent variable, M, is measured as Years Lived with Disability (YLD) and obtained from the Global Burden of Disease project. In addition to migraine for all ages, the estimation was repeated for migraine in the age group 15–49, which is the age group that suffers most from the disease, and hence, this group has higher YLD-values. The independent variables are labour productivity (LP), which is measured as annual output per worker, and unemployment rate (UR), α and β are the respective parameters, while ϵ refers to the error term. The analysis is cross-section for OECD countries plus affiliate countries for which OECD collects data ($n = 38$).

Model for developing countries

$$M = \alpha BRD + \beta MIG + \epsilon$$

In the OLS-estimation, the dependent variable, M, is again measured as Years Lived with Disability (YLD) for all ages and for the age group 15–49 years and obtained from the Global Burden of Disease project. The independent variables are Battle Related Deaths over 1000 (BRD), measured as a binary variable with the value of 1 for at least 1000 deaths per year and 0 otherwise, and the share of migrants in the population (MIG). α and β are the respective parameters, while ϵ refers to the error term. The analysis is cross-section for all developing countries for which data is available ($n = 153$).

For developed countries, Table 2 shows the results. All parameters are statistically significant ($p < 0.01$) with the sign in the expected direction. When output per worker increases with 1000 US dollar per year, migraine increases with one YLD for all ages and two YLD for the age bracket of 15–49 years. When the unemployment rate increases with 1 percentage point (for example, from 6 to 7 percent), migraine increases with 19 YLD for all ages and 29 YLD for the age group of 15–49 years.

Table 2
Results for developed countries

	Migraine all ages	Migraine 15–49 years
Labour productivity	0.001*** (3.624)	0.002*** (4.690)
Unemployment rate	19.235*** (4.569)	28.841*** (4.838)
Constant	527.889*** (10.930)	652.628*** (9.544)
R ²	0.685	0.735
N	38	38
F-statistic	15.462***	20.584***

Notes: t-values between brackets; * = p < 0.1; ** = p < 0.05; *** = p < 0.01.

For developed countries, Table 3 shows the results. Three of the four parameters of the independent variables are statistically significant ($p < 0.01$ for two and $p < 0.05$ for one variable). The parameter for battle related deaths is not statistically significant for migraine for all ages. The interpretation of the parameters is as follows. When the number battle-related deaths increase from less than 1000 to more than 1000, migraine increases by 66 YLD for all ages and 192 YLD for the age group 15–49 years. When the share of migrants in the population increases by 1 percentage point (for example, from three to four percent), migraine increases by 2.8 YLD for all ages and 1.6 YLD for those between 15 and 49 years old.

Table 3
Results for developing countries

	Migraine all ages	Migraine 15–49 years
BRD > 1000	66.436 (1.454)	192.598*** (3.419)
Migrants	2.837** (3.933)	1.586* (1.783)
Constant	596.776*** (46.968)	859.652*** (54.872)
R ²	0.100	0.085
N	153	153
F-statistic	8.351***	6.950***

Notes: t-values between brackets; * = p < 0.1; ** = p < 0.05; *** = p < 0.01

Discussion

In clinical research as well as in national health surveys, migraine and stress appear to be related. Moreover, recent research suggests that not only personal-level stress factors are involved but also that external stress factors may play an important role in the prevalence and severity of migraine. The availability of cross-country data from the Global Burden of Disease study 2016 allows for an exploratory cross-country analysis of potential external stressors and migraine YLD. The results of this exploratory analysis suggest that, while for developed countries work stress factors show to be related to migraine, for developing countries civic unrest and conflict factors show to be correlated with migraine.

The limitations of the study relate to the lack of detailed stress-indicators. It would be helpful, for example, if there would be representative national survey data available on types of stress and the severity of the stress experienced by people.

Conclusion

This is the first cross-country study into potential society-level modifiable factors for migraine. The findings are preliminary and further research is necessary. Future cross-country research may, for example, include other proxy variables for stress or may use time-series data from earlier GBD-studies and perform panel-data analysis. The high ranking of migraine as a debilitating chronic disease worldwide and the fact that there exists no effective treatment, calls for a wide variety of research, including cross-country analyses. The current study illustrates that such a public health approach may

provide useful insights for much-needed research hypotheses for the search for causes and modifiable factors for migraine.

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials:

The data are available in the public domain, from OECD, World Bank, and University of Uppsala. The dataset used and analysed during the current study is available from the author on request.

Competing interests:

The author declares that she has no competing interests.

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Authors' contributions:

All the work was done for the full 100 percent by the author herself.

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Authors' information (optional):

The author is a migraine patient herself and member of the Rotterdam Global Health Initiative.

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