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ARTICLE

Food and health

Sulfite concentration and the occurrence of headache in young adults: a prospective study

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Abstract

Background/Objectives Sulfites are additives commonly used in food and wine industries that are associated to adverse clinical effects such as headaches. The objective of this study is to investigate the possible association between sulfite concentration in wine and the occurrence of headaches in young adults.

Subjects/Methods Eighty volunteers, aged between 18 and 25 years, were evaluated. Sub-groups (with or without previous headaches related with wine) were created and volunteers were submitted to two wine tests (minimum and maximum sulfite concentration accordingly to weight). A questionnaire was handed out after the test regarding the presence or not of headaches, their main characteristics, as well as other symptoms associated.

Results Subjects that refer a previous headache history upon wine ingestion presented a risk 2266 greater of developing headaches after wine ingestion with a greater sulfite concentration. Those that refer constant headaches related to wine ingestion previous to the test present a risk of 6232 times more of developing headaches compared to those who refer sporadic headaches related to wine consumption.

Conclusions In our group of subjects, sulfite concentration in wine is related to the risk of developing headaches in individuals who are susceptible to wine induced headaches.

Introduction

Alcohol related headaches are described by the International Headache Society as having a pulsatile quality, with a bilateral location, aggravated by movement or physical activity, wine being its most important causal agent, more frequently red wine [1–6].

Several authors described the possible mechanisms by which alcohol could induce headaches [2–4, 7] referring specific culprits like histamine, tiramin, phenyletilamine and 5-HT, as well as sulfites. Sulfites were linked to wine headache previously [8] but as they are present in a large concentration in several foods like dried fruit and white wine, without an headache association, their contribution to wine headache is still disputable.

Sulfites (SO_2) are additives which prevent the deterioration of food compounds and inhibit various enzymatic and non-enzymatic reactions during the storage process [9]. In wine, these agents possess various technological functions, including antiseptic, antioxidant, dissolvent and clarification capacities [10–12], naturally occurring or laboratory associated [13]. SO_2 can be found in wine in a free form (SO_2 molecular, HSO_3^- e SO_3^{2-}) or combined with sugars, aldehydes, ketones, proteins and other compounds. The free form is the most studied and apparently the most responsible for adverse effects, such as headaches [11, 13]. The Food and Drug Administration (FDA) estimates that 1% of the American population is sensitive to sulfites and 5% of Asians have an increased risk of adverse reactions at the intake of SO_2 [10, 12].

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Sulfites have been linked to headache before, and some authors suggest that they could trigger headache through the release of histamine [14] but its presence in other foods without producing headaches, its major concentration in white wine than in red wine (while most authors claimed red wine to be the leading cause of headaches related to wine) reduced its role in headaches aetiology [2] with some authors claiming that sulfites only produced effects in susceptible persons [15, 16]. A suggested hypothesis was that SO_2 produced in the stomach after wine ingestion provoke a cholinergic reflex, which could explain the adverse reactions of diarrhoea, stomach ache or headache [17, 18]. Another hypothesis suggested that sulfites, through an immunological reaction mediated by Immunoglobulin E (IgE), induced degranulation of the mast cells, release of histamine and subsequent vasomotor response [2, 17]. Other authors refer that the adverse effects observed with wine seemed to be more related to specific drink components intolerance than to immunological mechanisms [19]. Prospective studies about the hypothetic contribution of these agents in the development of headaches are scarce.

The objective of our study was to evaluate the influence of sulfite concentration level in wine upon the development of headaches and other associated effects in a group of young adults. We hypothesized that subjects with a previous history of wine induced headaches will have a higher risk of headaches with a higher concentration of sulfites and that the risk of other effects associated with wine ingestion would be related with sulfite concentration.

Methods

Participants

This study took place with the participation of 80 volunteers, medical students from the Faculty of Health Sciences (FCS) UBI - Covilhã, Portugal, aged between 18 and 25 years and selected on the basis of established inclusion criteria as follows:

- Inclusion criteria:

  Age [18–25] years;
  Weight [50–60] kg, females;
  Weight [70–80] kg, males;

- Exclusion criteria

  Menstrual period for females; pregnancy;
  History of other primary headaches (cluster, tension type, paroxysmal hemicrania)
  History of secondary headaches (tumors, trauma, dementia, stroke, hydrocephalus)
  Gastro intestinal distress (vomiting, diarrhea, pain] and/or other gastro intestinal pathology)
  Hypo and hyperthermia; respiratory infections; nefro-urological pathology
  Medication (gastric inhibitors, gastro intestinal motility modifiers, nervous system stimulators and inhibitors)

A questionnaire adapted from a headache questionnaire validated for the Portuguese population [20] was applied to all volunteers concerning previous headache characterization and a subgroup of 51 subjects with previous headaches related to wine ingestion was detected. A second questionnaire, on side effects developing in the 24 h after each test, was also applied.

Wine testing procedure

We followed a double-blind wine testing procedure. Volunteers were divided according to their sex and were randomly allocated to a first test with wine with either high or low sulphite concentrations. Subsequently, volunteers underwent a cross-over procedure for a second wine test, one week after the first test. Thus, each volunteer wine had two wine tests at two different stages, with high or low sulphite content, but was not aware of which concentration he/she was being exposed at either test.

Wine used in the tests had previously been controlled in laboratory: a sulphurous solution with 6% of SO_2 in white wine with <5 g/L sugar content, not exceeding the legal maximum specified by law of 200 mg/L of SO_2 in the bottles used [10, 11, 13, 21]. White wine was used since it has the most easily manipulated sulfite.

The following amounts of a 6% SO_2 solution were added to the original white wine, for the 2nd test wine:

- For the female test: 1.35 ml of 6% SO_2 solution;
- For the male test: 2.3 ml of 6% SO_2 solution.

Therefore, three types of bottles with different SO_2 contents - total (T) and free (F) SO_2 were obtained:

- 56 mg/L (T) e 19 mg/L (F) in the 1st test for both genders (initially, the bottle contained 60 mg/L (T) and 22 mg/L (F) of SO_2);
- 139.2 mg/L (T) and 80 mg/L (F) in the 2nd test for females;
- 192.4 mg/L (T) and 140.8 mg/L (F)in the 2nd test for males.

Table 1 Amounts of total and free SO_2 (mg) ingested by the individuals in each test

	1st test		2nd test	
	Total SO_2	Free SO_2	Total SO_2	Free SO_2
Men (70–80) kg	13.7	4.7	47.1	34.5
Women (50–60) kg	13.7	4.7	34.1	19.6

Sulfite concentration in the wine - total and free - was determined by the OIV Test Method: Method OIV-MA-AS323-04A- Titrimetric Method.

Wine was stored and served in 0.75 L glass bottles at a temperature of 8 °C. Both tests took place in the morning on an empty stomach; each subject drank 245 ml of wine in each test.

Table 1 shows the respective amounts of total and free SO_2 ingested by each individual in each of the two tests. In the first test, the quantity of total SO_2 ingested was very low (approximately 13.7 mg), value obtained an hour after having opened the bottles before the test, in order to lower SO_2 content, which is released in a volatile form. In the second test, the amount of total SO_2 reflects a maximum daily intake recommended by the World Health Organization (WHO), according to the minimum weight established by convenience for each gender (70 kg for males and 50 kg for females). Male subjects and female subjects ingested 47.1 mg and 34.1 mg of total SO_2, respectively, in the second test.

Throughout the investigation, subjects had no idea of the amounts of sulfites they were exposed to. Wine components remained constant in both tests. For the purpose of the investigation, SO_2 expressed throughout the study encompasses the different forms of sulfites in which this component can be present in wine.

At the end of each test, subjects were given a questionnaire and a numerical pain scale to take with them. This questionnaire was related specifically to both wine tests held. The numerical pain scale was applied to evaluate headache intensity and variability in the next 24 h, both were completed and returned to the investigator the following day.

All volunteers resumed to a balanced diet and almost equal for all, approximately 30 min after the end of each test. Volunteers' follow-up was maintained for 24 h.

Data analysis

Statistical analysis of the data collected was carried out through IBM SPSS version 21 program. For the statistical data analysis we resorted to some descriptive techniques and to the independency tests of Chi-square, test exact from Fisher and Wilcoxon for paired samples. A logistic regression model was adjusted to the condition of "headache" in both tests [minimum and maximum of sulfites], using generalized estimating equations (GEE).

All the hypotheses tests were considered significant whenever the respective test value did not exceed the 5% level of significance and the confidence intervals were considered at 95%.

Results

Eighty volunteers participated in this study, 40 (50%) female and 40 (50%) male. For the convenience of this research, and to minimise variability in body weight and body composition, male subjects were grouped in the 70–80 kg weight range and female subjects into the 50–60 kilogram weight range. Ages varied between 18 and 25 years.

Eleven subjects had a previous diagnosis of migraine. Twenty four subjects had a previous diagnosis of headaches for other causes not included in the exclusion criteria.

A sub group of 51 subjects (30 male; 21 female) with previous headaches related to wine consumption was disclosed. In this group most male (87%) and female (95%) subjects referred headaches as being equal between the various episodes of wine consumption, bilateral and with a pulsating nature. Both white and red wine would produce headache They occurred sporadically to wine consumption (53% in men, 10% in women), while some were constant after wine consumption (27% in men, compared to 43% in women). Half of our subjects would have taken medication for pain, without medical prescription, only one subject has seek medical advice for headache related with wine consumption.

Analysis of the experimental procedure.

After the 1st test (minimum sulfite concentration)

Sixty seven subjects did not have any headache. Thirteen individuals (16%) came up with headaches after the ingestion of wine:

a. headache had a medium intensity of 4,23 in the pain scale and occurred mostly in the first three hours after ingestion (61%), mainly with pulsating characteristics (77%), of a bilateral character (92%) and without interfering with activity (77%).
b. Of this sub-group of 13 subjects, 8 subjects referred a background of headaches from wine in the past;
c. headache location was mainly frontal (76.9%) with 15.3% of subjects reporting temporal location of pain and 7% reporting orbital pain
d. Mean duration of pain was 2.12 h

e. Visual aura was present in 38.46%
f. Other main side effects, in descending order, were: yawning and drowsiness (59%); thirst or an excessive appetite (25%); nausea (23%); blurred vision (19%).

Five of these subjects never had any headache related to wine consumption.

After the 2nd test (maximum sulfite concentration)

Sixty subjects did not complain about headaches after the second test. Twenty individuals (25%) came up with headaches after the test:

a. headaches referred had a medium intensity of 4 in the pain scale and occurred mainly in the first three hours after the test (85%), mainly with pulsating characteristics (60%), of a bilateral character (85%) and without interfering with activity (75%).
b. of this subgroup of 20 individuals, 14 subjects referred a background of headaches related to wine consumption in the past.
c. headache location was mainly frontal (70%) with 30% of subjects reporting temporal location of pain.
d. mean duration of pain was 1.71 h
e. visual aura was present in 20%
f. main side effects, in descending order of frequency, were: yawning and drowsiness (66%), thirst or an exaggerated appetite (23%); nausea (21%); weakness (19%).

Six of these subjects never had any wine related headache.

Evaluation of both groups

Subjects with no previous headaches related with wine consumption

For the total number of subjects with no previous headaches related to wine consumption ($n = 29$) the following results were found:

In the first test (minimum sulfite concentration) 5 subjects came out with an headache after wine consumption.

In the second test (maximum sulfite concentration) 6 subjects come out with an headache related with wine consumption.

Subjects with previous headaches related with wine

For the total number of individuals who reported previous headaches with wine ingestion ($n = 51$), the following results were found:

Headaches arose mainly with both types of wine (small and high sulfite concentration, both in men (70%) and in women (76%).

eight individuals [16%] came down with headaches in the first experimental test; 43 [84%] individuals had no headaches in the 1st test.
fourteen individuals (27%) came down with a headache in the 2nd experimental test; 37 (73%) individuals had no headaches in the 2nd test.

For this subgroup a logistic model, using generalised estimation equations (GEE) [22, 23] was adjusted to the headache condition resulting from ingestion depending on the quantity of sulfites (minimum and maximum, that is, first and second tests, respectively) and the frequency of the pain usually felt (constant or not constant). The classes "not feel pain after wine ingestion", "minimum sulfites ingested (first test)" and "inconstant pain" were used as a reference, respectively, for the adjusted variable and for the two factors in study (see Table 2).

Consequently, for the population with previous headaches related with wine consumption, it is possible to say that:
the odds ratio of having headaches after wine ingestion with maximum sulfite concentration is $e^{0,818} \approx 2{,}266$ times greater, when compared to those who have

Table 2 Logistic regression model, using GEE, to the headache condition

Characteristics	Headache		OR Yes/No (95%CI)	P [a]
	Yes	No		
Sulfites (*N* (%))				
Min	8 (15.7)	43 (84.3)	1	0.049
Max	14 (27.5)	37 (72.5)	2.266 (1.002; 5.125)	
Pain (*N* (%))				
Sulfites Min: Inconstant	2 (6.1)	31 (93.9)		
Constant	6 (33.3)	12 (66.7)		
Sulfites Max: Inconstant	5 (15.2)	28 (84.8)	1	
Constant	9 (50.0)	9 (50.0)	6.232 (1.886; 20.590)	0.003

[a] Wald test

Model intercept = −2.592 ($p < 0.001$); Link function: logit;

ROC analysis for min. sulfites: AUC = 0.735 (95%CI: (0.544; 0.927), $p = 0.036$); sensibility = 75.0% and specificity = 72.1% (probability cutoff = 0.194)

ROC analysis for max. sulfites: AUC = 0.700 (95%CI: (0.532; 0.868), $p = 0.029$); sensibility = 64.3% and specificity = 75.7% (probability cutoff = 0.330)

Min minimum, *Max* maximum, *OR* = odds ratio, *CI* confidence interval, *ROC* receiver operating characteristic, *AUC* area under curve

headaches after wine ingestion with minimum sulfite concentration;
the odds ratio of having headaches when ingesting wine with maximum sulfite concentration is $e^{1,83} \approx 6,232$ times greater for those who usually report a frequency of constant pain with wine consumption, when compared to those who report periodic or sporadic pain.

For the second test [maximum sulfite concentration], this model correctly classifies 75.7% of the individuals who did not have headaches and 64.3% of the individuals who had headaches. Consequently, the model only correctly classifies 73% of the individuals who usually have a headache [0.5 was used as a cut-off amount]. The logistic model only presents an acceptable discrimination (ROC area approximately equal to 0.7, with a confident interval of 95% for the true area given by (0.532; 0.868) (13).

We used Wilcoxon paired samples test to evaluate the relationship between increased sulfite concentration and increased headache. However, we did not find any difference between headache responses to minimum and maximum sulfite concentration (p value = 0.257).

Discussion

We have carried out, as far as we know, the first prospective study in a controlled environment of sulfite effect as headache triggers. In our population of healthy adults, increased sulfite concentration increased headaches in a subgroup of subjects with a previous history of headaches related to wine consumption. This effect was more pronounced in subjects that had a constant response of headaches to wine consumption when compared with those with an irregular response. Other headaches not related with wine did not increase, and gender was not an issue in this case.

Wine seems to be responsible for many of the adverse reactions presented by its consumers. In fact, intolerance to wine is greater than expected when compared to other foods, and a variety of symptoms, such as erythema, pruritus, diarrhoea, rhinorrhoea, tachycardia and epigastric pain, among others, can emerge after its consumption. Headaches can also be caused by wine, via different mechanisms and believed to be due to various components present in this drink [17].

In spite of the classification of the International Headache Society, in which headaches related to alcohol are a form of secondary headache [24], there is some controversy about the relationship between alcohol and headaches, and also about wine constituents that can provoke headaches. Several authors trying to assess wine inducing headaches concluded that most studies were retrospective and did not allow to assess the real role of wine as a trigger in headache [1, 25]. Simultaneously it was suggested that tannins and phenolic flavonoid components of red wine were the most important factors in inducing headaches by wine [1]. Other authors found no evidence of an association between migraine or tension type headache and alcohol consumption [25–27]. However two large population- based studies reported a relationship alcohol/headache with contradictory results, one referring to a decrease of migraine prevalence among high alcohol consumers [28] the other associating headache with an occasional large consume of alcohol [29].

In our study, headaches after the use of sulfite in high concentration in wine were moderate, with a pulsatile quality and associated mostly with photo and phonofobia. Alcohol has been reported to trigger the principal types of primary headaches and no differences seem to exist between headaches produced by wine [30] or other secondary types of migraine or tension type headache [2]. Headaches reported by our subjects were migraine type, and similar to previous episodes described by the subjects related to wine consumption. The similarity of these clinical aspects suggest a similar mechanism among this laboratory experiment and wine headaches related by our subjects suggesting a specific mechanism of headache induced by sulfites, in a specific type of population.

Skypala et al. mentioned that food additives and naturally occurring ‘food chemicals’ have long been reported as having the potential to provoke symptoms in those who are more sensitive to their effects [31]. Our results suggest an effect of sulfites on headache in a specific group of subjects, since the increase of sulfite concentration in wine increased the number of headaches related by our subjects. This occurred mostly in persons previously reporting headaches related to wine, suggesting a specific type of subjects susceptible to sulfite concentration as already referred by some authors [1]. It is arguable that components other than sulfites may be involved in the process, but the unchanged laboratory conditions in our experiment, and the standard diet pursuit by the subjects before and after the experiment, as well as the results obtained for different sulfite concentrations allow us to advocate that sulfites may have an important role in the headaches reported. Thus, wine ingestion with the maximum of sulfites has a risk of $e^{0,818} \approx 2.266$ times more of inducing headache when compared to wine ingestion with a minimum of sulfites, leaving sulfites as a probable cause of headaches in this study [considering the controlled experimental protocol previously described].

As not all subjects with a previous story of headache with wine presented an increase in headaches after an increase in sulfite concentration we suggest that, more than a single process, headaches related to wine consumption may have several triggers- not only sulfites, but also histamine, tyramine, flavonoids and serotonin. This could

explain the red wine effect [with less sulfites than white wine], and also the discrepancy between sulfite concentration and headache related with wine when considering sulfites independently [2, 15].

Subjects that experienced headaches were a percentage of the group that previously referred headaches related to wine consumption. In the literature the percentage of subjects with headache related to alcohol consumption is not very high, varying between 20 and 34% of subjects with an occasional response to wine [2] but alcohol is a constant trigger only in 10% of the cases [16, 32]. Prospective studies on alcohol as migraine trigger are few [33] and give evidence of the limited effect of wine in the precipitation of migraine [28, 32]. Our group of responders is also small, but consistent.

To our knowledge, this is the first prospective study in a controlled environment of sulfite effect as headache triggers. Our logistic model allows us to predict the ratio of increasing headaches in a population susceptible to wine related headaches, after sulfite presentation and concentration increase. The results suggest an important role of sulfites in the headaches related with wine in a specific population.

In accordance with the results obtained, it can be concluded that the increase of sulfite concentration in wine is associated with the occurrence of headaches and other specific symptoms in subjects that have a higher susceptibility. However, our study had some limitations. Firstly, due to sample size limitations and possible subjective biases to this type of investigation, it is not possible to specify the intensity of the headaches reported. Another important restriction of this study was the difficulty in obtaining information about the subject, essentially due to the scarcity of bibliographical sources available. In reality, few or no controlled studies were performed in this topic with these parameters. Another limitation is that we used an adapted questionnaire, resulting from a prior and general questionnaire on headaches, which was not specifically designed and validated to analyse sulfite-induced headaches. However, the fact that the questionnaire was validated to assess headaches, was also validated in its Portuguese version, and had simple questions, allowed its application in the population we studied, with no identifiable problems. A final limitation of our study was the fact that we did not perform serum sulfite determinations in each individual, before and after drinking test wines. However, even with that limitation, our study is novel in its methodology and results, and can be compared with other studies which did not perform blood sulfite concentration determinations [5, 14].

Wine consumption is increasing in the younger generation in Portugal and this was one of the reasons for our volunteer selection. However, our results cannot be directly applied to other age groups, namely elderly individuals. In fact, the latter group has significant variability in metabolic pathways, due to their age, but also to multimorbility and polimedications, which may also change such pathways, indirectly affecting sulphite metabolism. Future work should address this specific population.

Headaches are a burden to the individual and to the society, producing lower quality of life, and several economic and social costs. The presence of sulfites in the environment makes it important to evaluate susceptibility to them and explain their possible effects in individuals, with headaches being one of such effects. Currently, there is a strong attempt by health organisations worldwide to significantly reduce the use of sulfites in wine and other food, thereby making the planning of new research projects in this field essential.

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Compliance with ethical standards

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

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. This project was validated by the Faculty of Health Sciences UBI Ethics Committee, Portugal. All the participants signed an informed consent.

References

1. Krymchantowski AV, Jevoux CC. Wine and headache. Headache. 2014;54:67–75.
2. Panconesi A. Alcohol and migraine: trigger factor, consumption, mechanisms: a review. J. Headache Pain. 2008;9:19–27.
3. Peatfield RC, Glover V, Littlewood JT, Sandler M, Clifford Rose F. The prevalence of diet-induced headache. Cephalalgia. 1984;4:179–83.
4. Peatfield RC, Fletcher G, Rhodes K, Gardiner IM, de Belleroche J. Pharmacological analysis of red wine-induced migrainous headaches. J Headache Pain. 2003;4:18–23.
5. Littlewood JT, Gibb C, Glover V, Sandler M, Davies PTG, Clifford Rose F. Red wine as a cause of migraine. Lancet. 1988;1:558–9.
6. Maxwell CR, Spangenberg RJ, Hoek JB, Silberstein SD, Oshinsky ML. Acetate causes alcohol hangover headache in rats. PLoS ONE. 2010;31:e15963 https://doi.org/10.1371/journal.pone.0015963
7. Pradalier A, Weinman S, Launay JM, Baron JF, Dry J. Total IgE, specific IgE and prick-tests against foods in common migraine – a prospective study. Cephalalgia. 1983;3:231–4.
8. Gorman-McAdams M. Sulfites in wine. The myths, the facts, and the truth. 2009. http://www.thekitchn.com/sulfites-in-wine-necessary-or-100878, (Accessed on 28 Dec 2013).

9. Favero D, Ribeiro C, de Aquino A. Sulfites: Importance in the food industry and possible harm to the population. Food security and nutrition. 2011;18:11–20.
10. Pozo-Bayon MA, Monagas M, Bartolome B, Moreno-Arribas MV. Wine features related to safety and consumer health: an integrated perspective. Crit Rev Food Sci Nutr. 2012; 52:31–54.
11. World Health Organization, Food and Agriculture Organization of the United Nations. Safety evaluation of certain food additives. Genéve: World Health Organization Press, 2009. http://whqlibdoc.who.int/publications/2009/9789241660600_eng.pdf, (Accessed on 14 Sept 2012).
12. Jackowetz N, Li E, Mira, de Orduña R. Sulphur Dioxide Content of Wines: the Role of Winemaking and Carbonyl Compounds. Appellation Cornell. 2011;7:1–7.
13. Chichester CO, Mrak EM, Schweigert BS Advances in Food Research. Orlando: A. Press; 1986. (pgs 2, 7, 22, 31).
14. Dahl R, Henriksen JM, Harving H. Red wine asthma: a controlled challenge study. J Allergy Clin Immunol. 1986;78:1126–9.
15. Zaeem Z, Zhou L, Dilli E. Headaches: a Review of the Role of Dietary Factors Curr Neurol Neurosci Rep. 2016;16:101. https://doi.org/10.1007/s11910-016-0702-1
16. Kelman L. The triggers or precipitants of the acute migraine attack. Cephalalgia. 2007;27:394–402.
17. Aun MV, Mafra C, Philippi JC, Kalil J, Agondi RC, Motta AA. Additives in food. Brazilian magazine on Alergies and Immunopathology. 2011;34:177–86.
18. Yang WH, Purchase ECR. Adverse reactions to sulfites. CMAJ. 1985;133:865–80.
19. Vally H, Thompson PJ. Allergic and asthmatic reactions to alcoholic drinks. Addict Biol. 2003;8:3–11.
20. Pereira Monteiro JM. Headaches: epidemiological and clinical study of na urban population. Porto: PhD Thesis in Medical Sciences, specialized in Internal Medicine, presented to the Institute of Biomedical Sciences of the Abel Salazar University; 1995.
21. EUR-Lex Access to the European Union Law. Regulation [CE] n.° 606/2009 of the 10th July 2009 commission which establishes the Regulation of the execution rules of the Council with regards to the categories of wine products, to the oenological practices and restrictions which apply to them [2009]. http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:193:0001:0059:pt:PDF (Accessed on 20 Sept 2012).
22. Kleinbaum, DG Klein, M. Logistic Regression, A Self-Learning Text, 3rd edn. Springer Science + Business Media, 2010.
23. Hosmer D, Lemeshow S. Applied Logistic Regression, 2nd edn. John Wiley & Sons, 2000.
24. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edn. [beta version]. Cephalalgia. 2013;33:728.
25. Davis-Martin RE, Polk AN, Smitherman TA. Alcohol Use as a Comorbidity and Precipitant of Primary Headache: Review and Meta-analysis. Curr Pain Headache Rep. 2017;21:42. https://doi.org/10.1007/s11916-017-0642-8
26. Winter AC, Hoffmann W, Meisinger C, Evers S, Vennemann M, Pfaffenrath V, et al. Association between lifestyle factors and headache. J Headache Pain. 2011;12:147–55. https://doi.org/10.1007/s10194-010-0286-0
27. Boardman HF, Thomas E, Millson DS, Croft PR. Psychological, sleep, lifestyle, and comorbid associations with headache. Headache. 2005;45:657–69.
28. Aamodt AH, Stovner LJ, Hagen K, Brathen G, Zwart J. Headache prevalence related to smoking and alcohol use. The Head-HUNT Study. Eur J Neurol. 2006;13:1233–8.
29. Molarius A, Tegelberg A, Ohrvik J. Socio-economic factors, lifestyle, and headache disorders—a population-based study in Sweden. Headache. 2008;48:1426–37.
30. Takeshima T, Ishizaki K, Fukuhara Y, Ijiri T, Kusumi M, Wakutani Y, et al. Population-based door-to-door survey of migraine in Japan: the Daisen study. Headache. 2004;44:8–19.
31. Skypala IJ, Williams M, Reeves L, Meyer R, Venter. C. Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. Clin Transl Allergy. 2015;5:34. https://doi.org/10.1186/s13601-015-0078-3.
32. Wober C, Holzhammer J, Zeitlhofer J, Wessely P, Wober-Bingol C. [2006] Trigger factors of migraine and tension-type headache: experience and knowledge of the patients. J Headache Pain. 2006;7:188–95.
33. Chabriat H, Danchot J, Michel P, Joire JE, Henry P. Precipitating factors of headache. A prospective study in a national control-matched survey in migraineurs and nonmigraineurs. Headache. 1999;39:335–8.