Substance use in a Dutch migraine cohort compared with the general population

Hoek, T.C. van den; Verhagen, I.E.; Boer, I. de; Terwindt, G.M.

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RESEARCH SUBMISSIONS

Substance use in a Dutch migraine cohort compared with the general population

Thomas C. van den Hoek MD | Iris E. Verhagen MD | Irene de Boer MD | Gisela M. Terwindt MD, PhD

Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands

Correspondence
Gisela M. Terwindt, Department of Neurology, Leiden University Medical Center, P.O. 9600, 2300 WB, Leiden, the Netherlands.
Email: g.m.terwindt@lumc.nl

Abstract

Objective: To evaluate self-reported substance user profiles for individuals with migraine and compare these to the general population.

Background: There is increasing attention to lifestyle influences such as substance use as presumed migraine triggers.

Methods: Data on substance use were collected by survey in a large migraine cohort and from the biannual survey in the general Dutch population for substances. A representative cohort of Dutch patients with migraine ($n = 5176$) and the Dutch general population ($n = 8370$) was included. Patients with migraine were subdivided into episodic (EM) and chronic migraine (CM). Substance consumption was compared between the general population and patients with migraine, and between migraine subgroups after standardization for sex and level of education.

Results: Included patients with migraine were 83.4% female (4319/5176) and had a mean (standard deviation) age of 44.8 (11.3) years. Patients with migraine reported less illicit drug use (odds ratio [OR] 0.48, 95% confidence interval [CI] 0.42–0.55; $p < 0.001$), less current and lifetime smoking (OR 0.60, 95% CI 0.55–0.65; $p < 0.001$ and OR 0.75, 95% CI 0.71–0.79; $p < 0.001$), and less current alcohol consumption (OR 0.66, 95% CI 0.62–0.70; $p < 0.001$) compared with the general population. Prevalence of substance use was compared between CM and EM participants and showed higher illicit drug use (OR 1.73, 95% CI 1.11–2.69; $p = 0.011$), higher current smoking (OR 1.61, 95% CI 1.22–2.11; $p < 0.001$) but less alcohol use (OR 0.54, 95% CI 0.43–0.68; $p < 0.001$) for participants with CM compared with EM. No differences were found for a history of smoking (OR 1.18, 95% CI 0.92–1.50, $p = 0.19$).

Conclusions: Individuals with migraine are less likely to use illicit drugs, smoke, or drink alcohol compared with the general population. Patients with CM less often consume alcohol, while they more often use illicit drugs and smoke compared to those with EM.

Abbreviations: CI, confidence interval; EM, episodic migraine; CM, chronic migraine; ICHD-3, International Classification of Headache Diseases, third edition; MOH, medication overuse headache; OR, odds ratio; SD, standard deviation.

KEYWORDS
chronic migraine, epidemiologic research, episodic migraine, lifestyle, triggers

INTRODUCTION

Migraine is a common and debilitating brain disease characterized by headache attacks and additional neurological symptomatology, affecting ~15% of the population.[1] The pathophysiology of migraine is complex but over the past few decades, important steps have been taken to unravel this disorder. This has given rise to the concept of a dynamic internal migraine threshold that reflects the probability of experiencing a migraine attack based on various internal factors, such as the menstrual cycle. External factors like consuming alcohol, especially when the internal threshold is already lowered, could potentially contribute to surpassing this internal threshold and triggering an attack. Nonetheless, it is still unclear when and why migraine attacks start at particular moments. We hypothesized that the combination of a lowered internal threshold, caused by, for instance, genetic factors, combined with fluctuations in other internal and external factors leads to an increased risk of a migraine attack at certain time points. These fluctuating factors are known as triggers and may be sex dependent, such as the menstruation period, which is one of the most reported triggers in women but may also be associated with lifestyle.[2] Many patients with migraine may be interested in identifying and modifying lifestyle factors that are (presumed) triggers for migraine attacks.[3] In a previous study, we found that 25% of patients with migraine have stopped or never used alcohol because of presumed triggering effects.[4] This indicates that patients themselves apply lifestyle changes.[5]

In the present study, we evaluated data from the Leiden migraine cohort, a well-defined Dutch migraine cohort, for a variety of substances. For comparison, data on substance use from the Dutch general population were used (Statistics Netherlands 2016–2017).[6,7] We hypothesized that patients with migraine might avoid the use of substances such as alcohol, cigarettes, and illicit drugs due to patients' perceptions of presumed triggering effects.[4] We also evaluated whether differences in substance use could be observed between patients with the more severe subtype of migraine, so-called chronic migraine (CM), compared with those patients with the less frequent episodic subtype.

The objective of our study was to evaluate self-reported substance user profiles for individuals with migraine and compare these to the general population.

METHODS

Study design and population

This cross-sectional study was conducted as part of the ongoing migraine program at the Leiden Headache Center.[8] All data on substance use were collected by yes/no questions, see below for how data were collected in the different study cohorts.

Leiden Headache Cohort

Patients with migraine (aged 18–80 years) were previously recruited via nationwide public announcement, advertising in lay press, and our research website. They were considered eligible after a two-step inclusion process using validated questionnaires. In addition, patients were recruited from the outpatient clinic at the Leiden Headache Center between 2008 and 2020. All participants were invited to complete a validated, web-based screening E-questionnaire about migraine (sensitivity of 0.93 and specificity of 0.36 for migraine).[1,8] Patients who fulfilled the screening criteria for migraine received a validated web-based extended migraine E-questionnaire based on the International Classification of Headache Disorders criteria (ICHD-3 version) criteria.[1] The specificity of the extended migraine E-questionnaire was 0.95 and sensitivity was 0.45. These E-questionnaires are described in detail elsewhere.[8] We consider the cohort a well-defined web-based cohort, and representative of patients with migraine from the general population as only between 4% and 20% of individuals with migraine are included from our Leiden Headache Clinic. In addition to questions that were necessary to diagnose migraine accurately, the extended E-questionnaires also included items on demographic factors, aura and headache characteristics, and acute and prophylactic headache medication use.[9] Participants unable to use the web-based E-questionnaires were allowed to complete the questionnaires on paper. The Leiden Headache Cohort study was approved by the Leiden University Medical Center local Ethics Committee under the following Review Board code: NL41600.058.12/ P12.201. All patients provided written informed consent.

Patients with migraine were subdivided into CM or episodic migraine (EM). CM is defined according to the ICHD-3 criteria, that is, having ≥15 headache days/month, of which at least 8 days/month fulfill migraine criteria during the last 3 months.[1] Patients with CM were further subdivided based on whether they did or did not have medication overuse headache (MOH). MOH is defined as regular overuse for ≥3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache. For painkillers and non-steroidal anti-inflammatory drugs, overuse is defined as the intake of ≥15 days/month, for migraine-specific acute medication such as triptans alone or combinations of medications this is ≥10 days/month.[1]

Dutch general population

Data from the Dutch general population were retrieved from a health survey by Statistics Netherlands (Centraal Bureau voor Statistiek).[6,7] This survey is held biannually and monitors lifestyle

aspects including substance use for which 8370 randomly selected Dutch citizens above the age of 18 years are approached. The selected participants form a representative sample of the Dutch population. All data are available via their website and is publicly accessible. For this study, data from the year 2016–2017 was used because this was found to be representative of the data collected from the Leiden Headache Cohort.[10] As data on the level of education of the general population were only available from participants aged ≥25 years, we only included patients from the Leiden Headache Cohort aged ≥25 years. Data from the Dutch general population survey as provided by Statistics Netherlands were exempt from ethical approval according to Dutch law.

Statistics

Descriptives are reported as means ± standard deviations (SDs) or counts with percentages. Differences in means were compared between groups using an unpaired *t*-test for normally distributed continuous variables, and a chi-squared test for categorical data. To compare data from the migraine cohort with the Dutch general population, direct standardization was performed to correct for educational level and sex. Standardization was performed instead of including sex and educational level as covariates, as only summary data were available for the Dutch general population cohort. Prevalences are reported as percentages (%) and per age category (25–45, 45–65, and >65 years) for each substance. Secondarily, substance use was compared between patients with EM and CM (by standardization, to illustrate how these prevalences compare with the Dutch general population), as well as CM + MOH and CM – MOH patients using multinominal regression analyses adjusting for sex, age, and education level. The use of illicit drugs, smoking, and alcohol were compared between CM + MOH and CM – MOH to test the hypothesis that patients with CM who overuse medication are also more likely to use other substances as well. Odds ratios (ORs) were calculated on standardized data using chi-squared tests between the general population and patients with migraine and between patients with EM and CM. If no information was available on the number of monthly headache or migraine days or medication intake, the subject in question was excluded from these specific analyses. All data analyses were performed using the Statistical Package for the Social Sciences (SPSS®), version 25.0 (IBM Corp., Armonk, NY, USA), with statistical significance set at $p < 0.05$.

RESULTS

Patients with migraine and Dutch general population

A total of 5176 persons with migraine were included from the Leiden Migraine Cohort (Figure 1). Table 1 provides a full description of group characteristics. From the Dutch general population, a total of 8370 participants that provided data could be standardized to the migraine cohort.[10] Patients with migraine reported less illicit drug

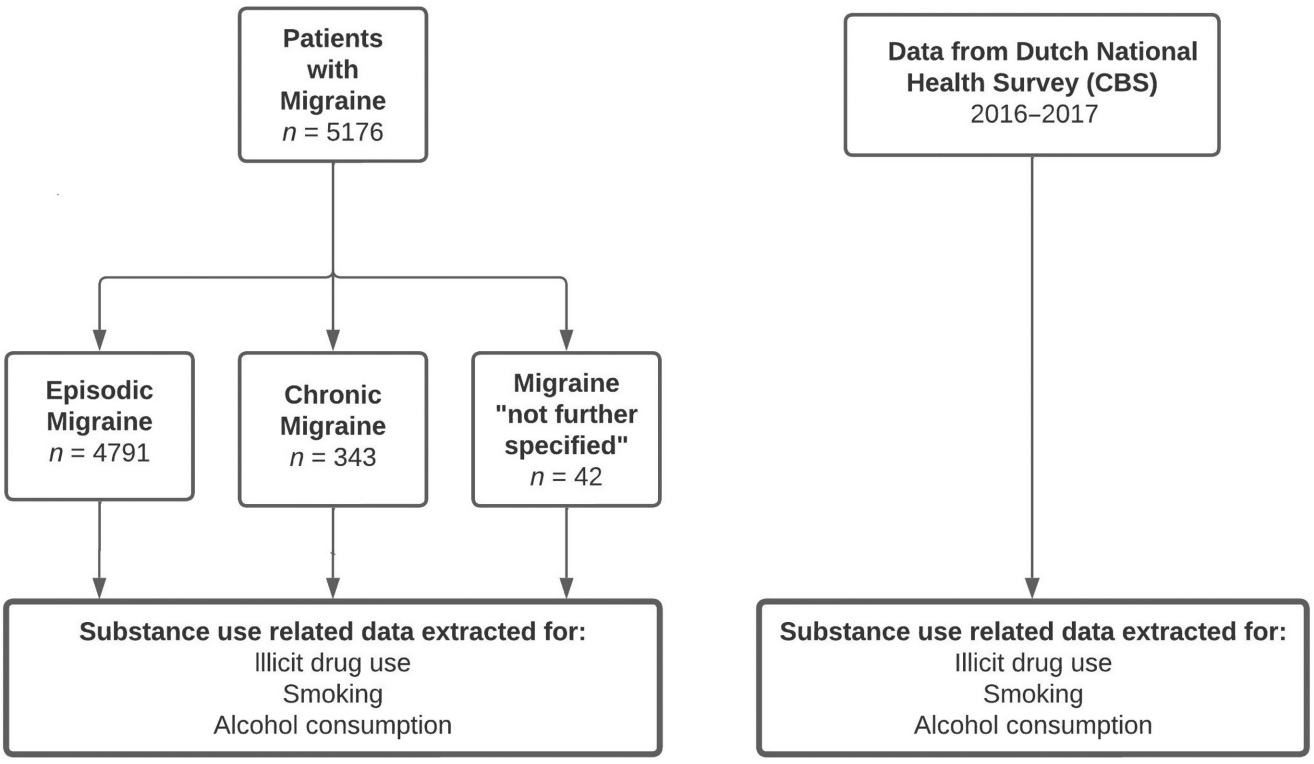

FIGURE 1 Flow chart of included patients from Leiden Headache Cohort and Dutch general population and types of collected substance data.

TABLE 1 Baseline characteristics Dutch migraine population.

Characteristic	Migraine (total) ($n=5176$)	Migraine "not further specified" ($n=42$)	EM ($n=4791$)	CM ($n=343$)	CM + MOH ($n=198$)	CM – MOH ($n=145$)
Male, *n* (%)	857 (16.6)	5 (11.9)	794 (16.6)	58 (16.9)	34 (17.2)	24 (16.6)
Age, years, mean (SD)	44.8 (11.3)	43.6 (10.3)	44.8 (11.3)	44.8 (11.9)	45.5 (11.4)	43.8 (12.6)
Body mass index, kg/m^2, mean (SD)	24.7 (4.2)	24.3 (3.7)	24.7 (4.2)	25.1 (4.5)	25.7 (4.8)	24.3 (3.9)
Education, *n* (%)						
Low	806 (15.6)	8 (19.0)	721 (15.0)	77 (22.4)	53 (26.8)	24 (16.6)
Middle	1635 (31.6)	11 (26.2)	1498 (31.3)	126 (36.7)	75 (37.9)	51 (35.2)
High	2735 (52.8)	23 (54.8)	2572 (53.7)	140 (40.8)	70 (35.4)	70 (48.3)
Migraine days, mean (SD)	6.6 (6.1)	–	6.1 (5.7)	14.1 (6.1)	14.8 (6.2)	13.1 (5.9)
Headache days, mean (SD)	5.9 (7.4)	–	4.7 (6.0)	22.0 (5.7)	21.9 (5.6)	22.1 (5.8)

Abbreviations: CM, chronic migraine; MOH, medication overuse headache; SD, standard deviation.

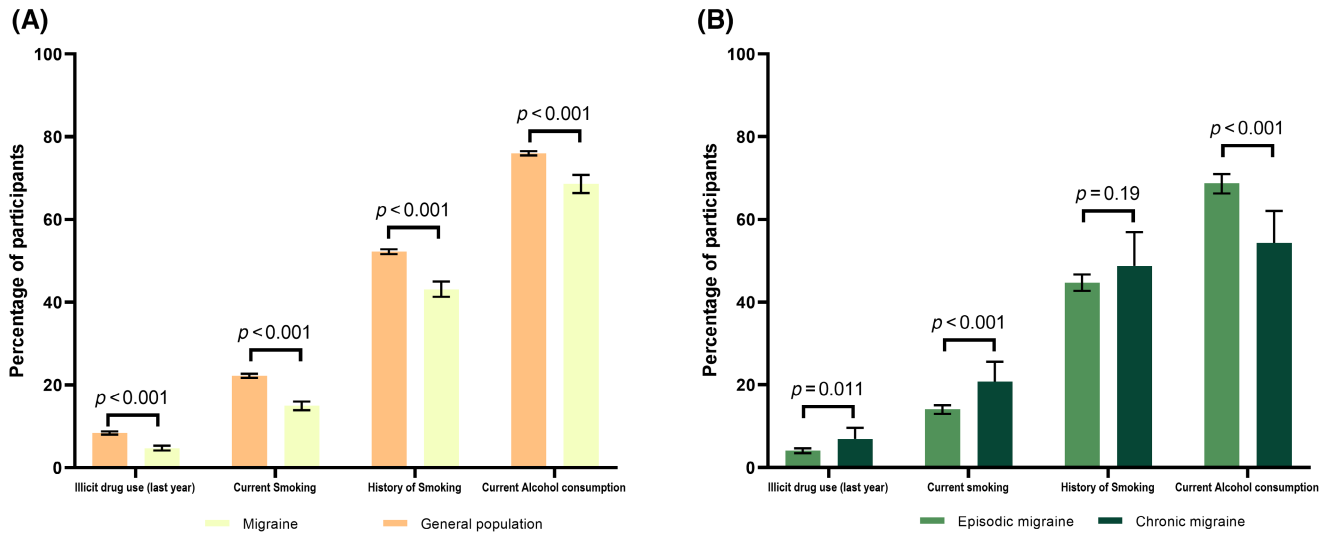

FIGURE 2 Prevalence (percentage of population ± standard error) per group for substance use (illicit drug use, history of smoking, current smoking, and current alcohol consumption). Prevalence of substance use for patients with migraine and Dutch general population (A) and prevalence of substance use for patients with episodic migraine and patients with chronic migraine (B). All prevalence numbers shown have been standardized for sex and education. Comparisons shown are the result of chi-square test on standardized counts. All data were present for all participants except for the variable history of smoking (missing data for $n=606$ for migraine, $n=540$ for episodic migraine and $n=62$ for chronic migraine).

use (OR 0.48, 95% confidence interval [CI] 0.42–0.55; $p<0.001$), lower current smoking prevalence (OR 0.60, 95% CI 0.55–0.65; $p<0.001$), lower rates for history of smoking (OR 0.75, 95% CI 0.71–0.79; $p<0.001$) and were less often consumers of alcohol (OR 0.66, 95% CI 0.62–0.70; $p<0.001$) compared to the Dutch general population (Figure 2A). In Figure 3A–D, the prevalence of substance use per age category is shown for patients with EM, patients with CM, and the general population showing an overall decline in prevalence of substance use with age in all groups.

Episodic migraine and CM

A total of 5134 patients with migraine were categorized into EM ($n=4791$, 93.3%) or CM ($n=343$, 6.7%); for other participants, the subtype could not be established (Figure 1). Prevalence of substance use was compared between patients with CM and EM and showed higher illicit drug use (OR 1.73, 95% CI 1.11–2.69; $p=0.011$), higher current smoking (OR 1.61, 95% CI 1.22–2.11; $p<0.001$) but less alcohol use (OR 0.54, 95% CI 0.43–0.68; $p<0.001$) in patients with CM compared to those with EM (Figure 4). No differences were found for history of smoking (OR 1.18, 95% CI 0.92–1.50; $p=0.19$). For prevalence per migraine subgroup for substance use see Figure 2B.

Medication overuse headache

A total of 198 (57.7%) patients with CM fulfilled the criteria for MOH.[1] After comparing baseline characteristics, it was found that patients

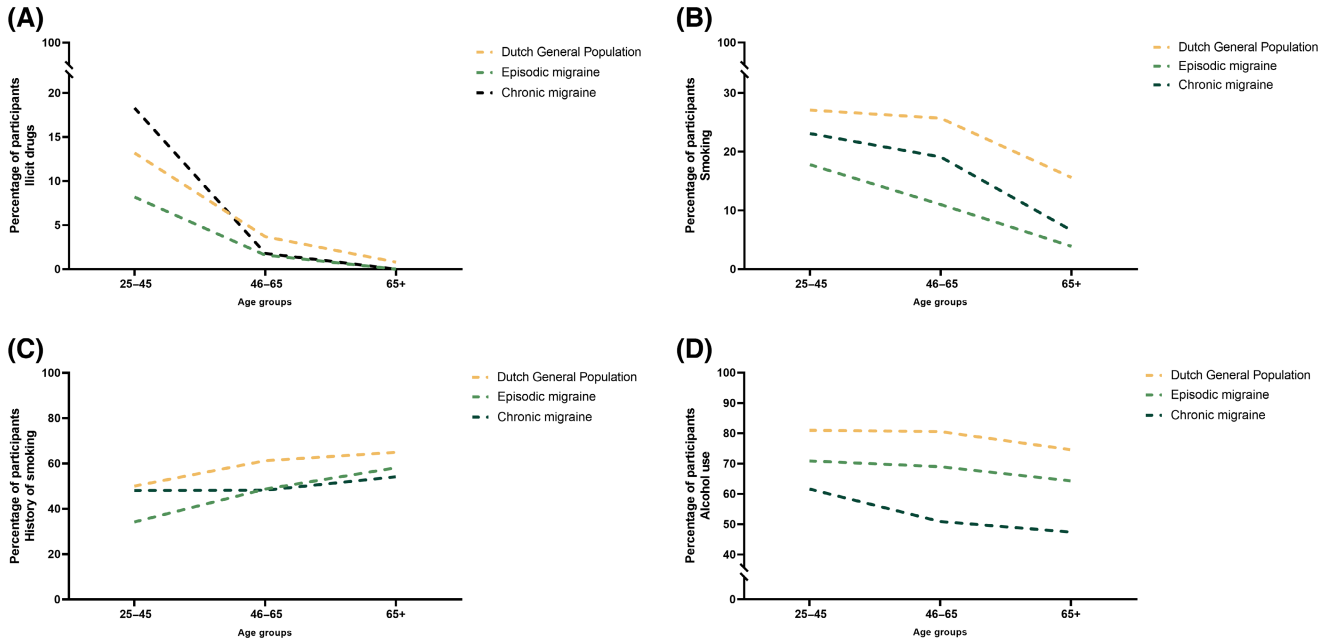

FIGURE 3 Prevalence numbers (percentage of population ± standard error) for substance use: illicit drug use (A), history of smoking (B), current smoking (C) and current alcohol consumption (D) per age group (25–45, 45–65, >65 years) for the Dutch general population, chronic and episodic migraine. All prevalence numbers shown have been standardized for sex and education level. All data were present for all participants except for the variable history of smoking (missing data for $n = 540$ for episodic migraine and $n = 62$ for chronic migraine).

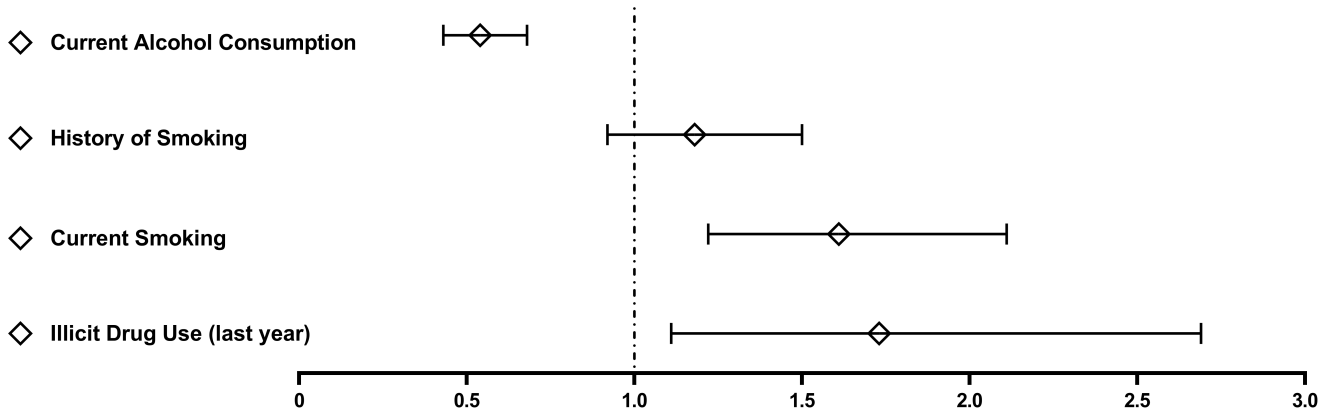

FIGURE 4 Odds ratios for substance use in chronic migraine standardized for sex and education level (episodic migraine as reference group).

with CM + MOH were comparable in age (mean [SD] 45.5 [11.4] vs. 43.8 [12.6] years, $p < 0.001$), had no different sex distribution (male gender: 17.2% vs. 16.6%, $p = 0.19$), but had a higher body mass index (mean [SD] 25.7 [4.8] vs. 24.3 [3.9] kg/m^2, $p = 0.005$). Patients with CM + MOH had more monthly migraine days (mean [SD] 14.8 [6.2] vs. 13.1 [5.9] migraine days/month, $p = 0.009$) compared with patients with CM – MOH. After adjustment for age, sex, and education, no differences between CM + MOH and CM – MOH were found for illicit drug use (OR 2.50, 95% CI 0.86–7.27; $p = 0.093$), smoking (OR 1.37, 95% CI 0.75–2.50; $p = 0.31$), history of smoking (OR 1.11, 95% CI 0.68–1.81; $p = 0.67$), or alcohol use (OR 0.83, 95% CI 0.53–1.30; $p = 0.42$).

DISCUSSION

Among patients with migraine, there are fewer illicit drug users, fewer smokers, and fewer consumers of alcohol compared to the Dutch general population. Additionally, patients with CM were less often consumers of alcohol, while they were more often illicit drug users and more often smokers compared to patients with EM.

Our observations support previous studies reporting about presumed migraine-triggering effects of alcohol.[4,11] In a previous study of our group, one third of patients with migraine reported alcoholic beverages as a trigger of their migraine attacks.[4] In addition, in that

study >25% of patients with migraine had stopped consuming or never consumed alcoholic beverages and did so because of presumed trigger effects. Wine, especially red wine (77.8% of participants), was recognized as the most common trigger among alcoholic beverages; however, red wine consistently led to an attack in only 8.8% of participants. Time of onset was rapid (<3 h) in one third of patients and almost 90% had an onset of <10 h independent of beverage type.[4] In the present study, we found that indeed patients with migraine consume alcoholic beverages less often compared to the general population, and this is even more so for those patients who experience the more severe migraine subtype, CM. This likely indicates that if patients with migraine experience this high-frequency subtype, presumed triggers such as alcohol are avoided more actively. The low consistency of provocation that we found in our earlier study suggests that alcoholic beverages acting as a singular trigger are insufficient to cause a migraine attack. Whether an attack occurs at a certain time point upon alcohol consumption in an individual patient likely depends on an internal (fluctuating) trigger threshold, that is defined by at least genetic factors and sex-hormonal changes.[4,12,13]

We demonstrated a lower prevalence of illicit drug use in patients with migraine. In line with lower alcohol consumption, this might be explained by presumed triggering effects. Because of the lack of data on the types of illicit drugs used, we could not investigate if this was the case for all illicit drugs. This makes interpretation harder because different classes of illicit drugs have different effects on the central and peripheral nervous systems, thus potentially resulting in different triggering or even protective mechanisms. Popular media frequently reports about patients with migraine experimenting with alternative treatments involving illicit drugs. In this respect, cannabis and cannabidiol (a psychoactive substance present in cannabis but lacking hallucinogenic capabilities) enriched products, such as oils, are of particular interest.[14] During the last few years, cannabidiol-containing products have gained widespread popularity for a variety of medical conditions and are widely available in drug stores and pharmacies as over-the-counter food supplements.[15] Though cannabis use among patients with migraine is gaining popularity in the United States,[16] at this moment no exact numbers have been published for the number of patients with migraine using cannabis as an alternative and/or additional treatment in Europe, or specifically the Netherlands. Further studies must be done specifying the exact type of illicit drug used in patients with migraine as it may well be that patients with migraine use illicit drugs such as cannabis (or related products) for treatment purposes.

The number of current smokers was observed to be lower among patients with migraine. Though the number of smokers in the general population has been declining in the last few years,[17] the proportion of smokers among patients with migraine was much lower than expected. Interestingly, the number of female smokers among the general population was increasing until a few years ago.[18] Contrarily, this trend was not found among female patients with migraine, with an especially lower prevalence among younger female patients. One clarification for this could be an increasing awareness among young female patients with migraine about elevated cerebrovascular and cardiovascular risks in migraine, especially for young women with migraine.[19–23] In this respect, patients with migraine may take safety measures by implementing lifestyle adjustments to reduce cerebrovascular and cardiovascular risk. Contrarily, patients with CM have higher odds of lifetime smoking and illicit drug use compared to the EM subgroup. Future investigations are necessary to determine whether substance use contributes towards chronification, is a consequence of the high attack frequency, or is caused by the higher comorbidity of depressive and anxiety symptomatology among patients with CM.[24–27] While interesting, it is important to realize that in both patients with EM and patients with CM, the lifetime smoking and illicit drug use prevalence were lower compared with the general population. Interestingly, we found no differences between patients with CM with and without MOH. Collectively, this indicates that patients with migraine who overuse acute medications are not more likely to use substances than patients who do not.

This study comes with the limitation of a cross-sectional study design. For this reason, no causal relations can be identified for the differences in substance use. Another limitation of this study is that only use and not amount of consumption was studied. The next step would be to determine if there are differences in the amount of consumption, e.g., number of alcoholic units per week. Additional studies are warranted to provide more insights into the relationship between the consumption of substances and the triggering or prevention of migraine in more detail. Although we were not able to exclude potential patients with migraine from the reference/general population, excluding those cases likely would have amplified substance use differences beyond what is presented here. Also, by standardization for sex and education, we may not have ruled out all differences between the migraine cohort and the general Dutch population and this may need to be addressed in future (prospective) studies, although the presented results in this paper provide an accurate direction of substance use among patients with migraine compared to the general population. Data in the general population for educational level is available from those aged ≥25 years. The explanation is that from 25 years, an accurate determination of education level is possible because it usually is definitive around that age. Education is an important determinant factor in substance use and thus essential for an accurate comparison between the two populations. Therefore, we included only participants aged ≥25 years for comparison. Additionally, we were unable to add a history of major depression as a covariate in the analysis because the information for the general population was lacking. We acknowledge that depression is an important factor in substance use and major depression is common in the general population[28] and three times more likely in those with migraine.[29] For those with a history of major depression, 25% meet the criteria for a substance use disorder.[30] Finally, as a strength, we were able to compare substance use to the Dutch general population within a well-defined Dutch migraine cohort that is representative of persons with migraine from the general population and based

on self-reported substance use from E-questionnaires. Our cohort is not a cohort collected at a headache clinic but is a good representation of patients with migraine from the general population, which is shown by the fact that only 6.7% of patients had a CM diagnosis.

We conclude that patients with migraine have a lower alcohol consumption, use less illicit drugs, and smoke less compared to the general population. For alcohol and illicit drug use, this may be explained by presumed trigger effects. Less smoking may be explained by an awareness of the elevated risk of cerebrovascular and cardiovascular diseases for young (female) patients with migraine.

AUTHOR CONTRIBUTIONS

Study concept and design: Thomas C. van den Hoek, Gisela M. Terwindt. *Acquisition of data*: Thomas C. van den Hoek, Irene de Boer, Iris E. Verhagen. *Analysis and interpretation of data*: Thomas C. van den Hoek, Iris E. Verhagen, Irene de Boer, Gisela M. Terwindt. *Drafting of the manuscript*: Thomas C. van den Hoek. *Revising it for intellectual content*: Thomas C. van den Hoek, Irene de Boer, Gisela M. Terwindt, Iris E. Verhagen. *Final approval of the completed manuscript*: Gisela M. Terwindt, Irene de Boer, Iris E. Verhagen, Thomas C. van den Hoek.

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CONFLICT OF INTEREST STATEMENT

Thomas C. van den Hoek reports no conflict of interest. **Iris E. Verhagen** and **Gisela M. Terwindt** report independent support from the Dutch Research Council (849200007) and the Dutch Brain Foundation (HA2017.01.05). **Irene de Boer** reports independent support from the Dutch Heart Foundation [2020T065 I.B.] and the International Retinal Research Foundation (IRRF). **Gisela M. Terwindt** reports consultancy or industry support from Abbie/Allergan, Lilly, Lundbeck, Novartis, Teva, and independent support from the IRRF and Dioraphte.

ORCID

Iris E. Verhagen https://orcid.org/0000-0002-9509-7233

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