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Profiling the real-world migraine patient: public health insights from sociodemographic, lifestyle, and clinical data in the Italian National Migraine Registry (I-GRAINE)

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Abstract

Background Although migraine attacks have been precisely characterized over the years – with significant advances in pathophysiology and treatment – the comprehensive identity of the migraine patient remains poorly defined. Real-world data capturing the full sociodemographic and clinical spectrum of individuals with migraine is still limited. The Italian National Migraine Registry (I-GRAINE) was established to address this gap by systematically collecting data on individuals with migraine across Italy's public healthcare system.

Methods I-GRAINE is an ongoing, nationwide, multicenter, prospective registry involving 43 publicly funded headache centers. Since 19/04/2021, patients diagnosed with episodic migraine (EM) or chronic migraine (CM) have been systematically enrolled. Data were collected through face-to-face interviews conducted by trained neurologists

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using a dedicated electronic platform. Information included sociodemographic and lifestyle factors, comorbidities, and detailed clinical characteristics. We aimed to define the patient profile, explore the broad clinical phenotype, and compare EM and CM subgroups.

Results As of 02/05/2025, 1,630 patients had been enrolled (81.7% EM, 18.3% CM), predominantly female (85.4%), mean age 45.7 years, normal BMI (23.2 kg/m^2), and high education level. Over 70% were physically inactive, and 32.2% reported sleep disturbances. Headache was typically unilateral (69.1%), pulsating (64.0%), and lasted > 24 h (57.1%). Frequently reported non-ICHD-3 symptoms included osmophobia (41.5%), allodynia (40.5%), dopaminergic symptoms (37.2%), cephalalgiaphobia (34.0%), and dizziness (16.9%). ≥ 1 comorbidity was present in 41.2% of patients.

Compared to those with EM, CM patients had higher BMI (24.0 vs. 23.0, $p < 0.001$), greater sleep disturbances (39.1% vs. 30.6%, $p = 0.006$), earlier onset (16.5 vs. 17.7 years, $p = 0.032$), more severe pain (NRS: 8.1 vs. 7.5, $p < 0.001$), and higher prevalence of medication overuse (58.3% vs. 14.5%, $p < 0.001$), dopaminergic symptoms (45.1% vs. 35.4%, $p = 0.002$), allodynia (47.5% vs. 38.9%, $p = 0.009$), and cephalalgiaphobia (41.4% vs. 32.3%, $p = 0.004$). Disability was also greater (MIDAS: 76.3 vs. 41.9; HIT-6: 64.3 vs. 61.2; *both* $p < 0.001$).

Conclusions The typical patient attending Italian headache centers is a 45-year-old, normal-weight, well-educated, employed woman, often physically inactive, affected by sleep disturbances, and experiencing an average of 9.8 migraine days/month. I-GRAINE identifies migraine symptoms that may represent endophenotypes and distinct patterns associated with CM, offering valuable real-world insights to inform personalized care, research, and health policy.

Keywords Migraine, Episodic migraine, Chronic migraine, Real-world data, Patient registry, Endophenotype

Introduction

Migraine is a highly prevalent and disabling neurological disorder, associated with a substantial individual, societal, and economic burden [1–3]. It is increasingly recognized as a time-dependent functional brain disease, with the potential to progress to more severe and chronic forms in a subset of patients [4–6]. This evolving framework has led to a shift in therapeutic paradigms, emphasizing timely intervention and the pursuit of clinically robust outcomes [7, 8].

Despite considerable advances in elucidating migraine pathophysiology – across neurochemical, neurophysiological, neuroimaging, and genetic/epigenetic domains – its management in clinical practice remains challenged by persistent under recognition, underestimation and undertreatment [9]. This discrepancy stems, in part, from a conceptual limitation. Although the International Classification of Headache Disorders has, for nearly four decades, enabled increasingly refined descriptions of migraine attacks, much less attention has been paid to the comprehensive profiling of the migraine patient [10–12]. This gap is particularly striking in the current therapeutic landscape, where both acute treatment and preventive strategies demand a patient-centered approach [13], integrating not only the clinical manifestations but also individuals' trajectories, treatment responsiveness, and healthcare system interactions.

Within this context, renewed attention to the clinical and experiential complexity of migraine sufferers is not a step backward, but a necessary step toward precision medicine. Disease-specific registries represent the optimal methodological framework to address this challenge, enabling systematic, longitudinal collection of real-world data encompassing both disease-related and patient-related dimensions [14–16].

The Italian Migraine Registry (I-GRAINE) [17] was established to address this unmet need. Originally conceived over a decade ago with an initial focus on chronic migraine (CM), it progressively evolved to encompass episodic migraine (EM), consolidating into a structured initiative aimed at bridging clinical and epidemiological gaps in migraine management [18–20].

As a prospective, multicenter, nationwide observational initiative, it adheres to accepted criteria for disease registries, including standardized patient inclusion, structured data acquisition, longitudinal follow-up, and defined clinical oversight. I-GRAINE was conceived not as a general data repository, but as a rigorous epidemiological platform aimed at capturing the evolving clinical and personal profiles of subjects with migraine in real-world settings. By integrating core migraine-specific variables with broader patient-related dimensions, this initiative aims at offering a unique opportunity to advance the characterization of migraine through the lens of real-life complexity and individualized care trajectories.

This paper outlines the profile of Italian migraine patients seeking care at headache centers, with a focus on their sociodemographic background, lifestyle habits, and clinical features.

Methods

Study design

I-GRAINE is an ongoing multicenter, longitudinal registry, launched on April 19, 2021, with the endorsement of the *Associazione Italiana per la Lotta contro le Cefalee* [21], the first Italian headache patients' association. All 141 Italian headache centers and outpatient clinics officially accredited by *Associazione Neurologica Italiana per la Ricerca sulle Cefalee* (ANIRCEF) and *Società Italiana per lo Studio delle Cefalee* (SISC) [22, 23] were invited via email to participate in the study. Of the 54 centers and clinics that accepted the invitation, 43 participants are currently active. All centers are affiliated with the Italian National Healthcare Service and are involved in the prospective collection of real-world clinical data on the course and management of both EM and CM [17].

San Raffaele University currently serves as the coordinating center of the registry, which was previously coordinated by the IRCCS San Raffaele Roma. The registry is governed by an Executive Committee comprising four board-certified neurologists with expertise in headache medicine, one epidemiologist, one pharmacologist, one clinical psychologist, two professional data managers, and one study nurse.

Oversight of the registry's scientific validity and methodological consistency is ensured by a Scientific Committee composed of ten senior researchers in the field of headache disorders, selected to provide balanced geographic representation from Northern, Central, and Southern Italy.

I-GRAINE has been supported by the collaboration of two Contract Research Organizations – CD Pharma Group and CliREst – which have overseen both the start-up phase and subsequent project and data management activities. The digital infrastructure of the registry has been developed and is maintained by Data River, the designated technology partner.

Ethics committee

All patients enrolled signed written informed consent. The protocol of the study was approved by the Ethics Committee of the coordinating center, IRCCS San Raffaele Roma (16/int, 31/7/20) and shared by the Ethics Committees of the other centers [17, 24]. A Data Protection Impact Assessment (DPIA), developed by IRCCS San Raffaele Roma in collaboration with CD Pharma and Data River, was conducted in compliance with the EU GDPR (Regulation 679/2016) to evaluate and mitigate privacy risks associated to data registration and processing. Moreover, the study was submitted to the evaluations of the Italian Data Protection Authority (Garante della Privacy) who provided a series of indications that were accepted and implemented by the sponsor before the start of the study.

Study population and data collection

Adult patients diagnosed with EM or CM according to ICHD-3 criteria [12] have been enrolled in the registry after physical and neurological examination within each headache center, starting from 19 April 2021. All data included in this analysis were collected through May 2, 2025.

Participation in the registry was proposed on each outpatient visit day to the first patient at their first visit (*incident* patient) and to the first patient at their first control visit (*prevalent* patient), according to the systematic random method, until reaching ~ 10% of the annual migraine caseload per site. The determination of this percentage was based on the compatibility with the resources available at each center, considering both the clinical studies in progress and real-world evidence. Recruitment at each center was initiated after a site visit, conducted either in person or remotely. The registry includes a monthly virtual meeting involving all centers to review recruitment progress and discuss any critical issues. Two data managers regularly monitor participating centers by issuing targeted reports to address missing data and inconsistencies, querying centers as needed to resolve discrepancies and ensure data accuracy and completeness.

Patient data collected in each headache center were anonymized in accordance with current privacy policy requirements and sent to the coordinating center for statistical analysis.

Before the launch of the registry, a series of structured preliminary meetings were conducted by the Scientific Committee with the aim of establishing the core variables to be systematically collected. Through a consensus-driven process, the Committee defined the sociodemographic, lifestyle, clinical, and healthcare resource utilization domains to be assessed. All questionnaire items were jointly developed and approved during these meetings to ensure methodological consistency and content validity. Data collection was performed through face-to-face interviews conducted by trained neurologists, who entered the information into a dedicated Electronic Case Report Form (eCRF) via a secure, web-based platform. To ensure consistency across participating centers, all neurologists underwent specific training in the use of the platform and in the administration of the structured interview [17, 24]. The type of information collected from the patients is reported in Supplementary material (Table S1).

Clinical definitions

(i) *Comorbidities*: their presence was identified based on patient-reported medical history, review of available clinical documentation, or evidence of ongoing pharmacological treatment.

(ii) *Sleep disorders*: any chronic condition that impairs sleep and daytime functioning, negatively affecting overall health and well-being [25].

(iii) *Alcohol intake*: refers to moderate consumption, i.e. no more than one alcohol unit per day for women and no more than two alcohol units per day for men, as defined by the Italian National Institute of Health (Istituto Superiore di Sanità) corresponding to approximately 12 g of ethanol—the amount typically found in a can of beer (330 mL), a glass of wine (125 mL), or a shot of spirits (40 mL), based on standard alcohol content [26].

(iv) *Coffee intake*: refers to moderate consumption, defined as no more than 3 mg/kg of body weight per day – approximately equivalent to three Italian espressos – which represents the threshold below which no safety concerns have been identified in healthy adults [27].

(v) *Physical activity*: individual consistently participating in physical exercise or sporting activities [28].

(vi) *Unilateral cranial autonomic symptoms*: defined as the occurrence, during migraine attacks, of at least one unilateral symptom such as lacrimation, conjunctival injection, nasal congestion, ptosis, eyelid edema, miosis, or sweating on the forehead or face [29].

(vii) *Allodynia*: refers to ictal cutaneous allodynia, i.e., presence of pain in response to normally non-painful stimuli applied to the craniofacial region (e.g., wearing glasses or earrings, combing hair, etc.) during the attack [30].

(viii) *Dopaminergic symptoms*: presence during prodromes, headache stage or postdromes of at least one of the following symptoms: yawning, somnolence, nausea, vomiting, mood changes, fatigue or diuresis [31].

(ix) *Cephalalgiaphobia*: anticipatory anxiety characterized by fear of either the onset of a migraine attack or the escalation of a mild baseline headache into a full-blown attack [32, 33].

Statistical analysis

Descriptive statistics were computed using means and standard deviations for quantitative variables, and absolute frequencies (percentages) for categorical variables. Missing values were reported and statistical analyses were therefore performed using available data only (complete case analysis). Differences between patients with EM and those with CM were assessed using Pearson's chi-square tests for categorical variables and, given the large sample size (n = 1630), differences between EM (n = 1332) and CM (n = 298) patients were assessed using independent-samples t-tests for quantitative variables, without testing for normality. This choice is supported by the Central Limit Theorem, which ensures the robustness of the t-test even when the normality assumption is not strictly met in large samples. A p-value less than or equal to 0.05 was considered statistically significant. Therefore, we decided not to apply Bonferroni correction, which is more suitable for confirmatory studies with a limited number of a priori hypotheses, while in exploratory research an overly stringent correction like Bonferroni might stifle the identification of potentially important findings. All analyses were conducted using R (version 4.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Socio-demographic profile

As of 2 May 2025, a total of 1630 individuals with migraine had been included in the registry, of whom 81.7% (1332/1630) were classified as having EM and 18.3% (298/1630) as CM (Table 1).

Of the 43 centers that completed the study initiation visit, 34 were actively recruiting participants across 13 regions of Italy. Figure 1 qualitatively reports the distribution of patients across centers, while a breakdown of patient enrollment by center is included in Supplementary Table S2.

The majority of patients were female (85.4%, 1391/1630), with a mean age of 45.7 ± 12.9 years. The mean body mass index (BMI) of the cohort was 23.2 ± 3.8 kg/m^2. According to WHO classification [28], 70.3% (1120/1593) of the individuals reported a normal weight. Most of the included individuals were either married or cohabiting (58.8%, 956/1626), typically had one or two children (50.2%, 799/1592), were employed (70.8%, 1130/1596), and had a high level of education (> 13 years in 49.0% of cases) (772/1577).

Among female participants, the mean age at menarche was 12.5 ± 1.4 years. Contraceptive use was reported by 14.5% (200/1380), primarily in the form of oral contraceptive pills (78.4%, 152/194), while 38.5% (430/1118) were postmenopausal, with a mean age at menopause of 49.1 ± 4.5 years. Approximately one-fourth of participants were either smokers (15.9%, 258/1618) or former smokers (6.7%, 108/1618). Moderate alcohol and coffee intake were reported by 5.9% (95/1617) and 5.5% (89/1609) of patients, respectively. Regular physical activity was practiced by 25.8% (415/1610) of individuals. One-third of patients (32.2%, 519/1612) reported sleep disturbances (Table 1, Fig. 2).

Comorbidities

At least one comorbidity was reported by 42.8% of patients. The most frequent comorbidities reported were psychiatric disorders (12.9%, 211/1630), endocrinological conditions (12.1%, 197/1630), gastrointestinal disorders

Table 1 Sociodemographic characteristics of individuals with episodic and chronic migraine enrolled in the I-GRAINE Registry. Categorical variables are expressed by absolute frequency (%) and continuous by mean (standard deviation = SD)

	All	Episodic migraine	Chronic migraine	p value	N
Patients	1630	1332 (81.7%)	298 (18.3%)		
Female	1391 (85.4%)	1135 (85.3%)	256 (85.9%)	0.851	1629
Age	45.7 (12.9)	45.2 (13.0)	47.7 (12.5)	0.002	1616
Marital status					1626
Married/living common law	956 (58.8%)	759 (57.2%)	197 (66.1%)		
Single	533 (32.8%)	453 (34.1%)	80 (26.8%)		
Separated/divorced	88 (5.4%)	71 (5.3%)	17 (5.7%)		
Widower	15 (0.9%)	13 (1.0%)	2 (0.7%)		
Education (years)				0.389	1577
< 8	184 (11.7%)	143 (11.1%)	41 (14.0%)		
9 – 13	621 (39.4%)	509 (39.6%)	112 (38.2%)		
> 13	772 (49.0%)	632 (49.2%)	140 (47.8%)		
Employment status				0.002	1596
Employed	1130 (70.8%)	929 (71.4%)	201 (68.4%)		
Retired	76 (4.8%)	63 (4.8%)	13 (4.4%)		
Unemployed	120 (7.5%)	98 (7.5%)	22 (7.5%)		
Housework	144 (9.0%)	100 (7.7%)	44 (15.0%)		
Student	126 (7.9%)	112 (8.6%)	14 (4.8%)		
Number of children				0.029	1592
0	702 (44.1%)	594 (45.7%)	108 (37.1%)		
1–2	799 (50.2%)	635 (48.8%)	164 (56.4%)		
> 2	91 (5.7%)	72 (5.5%)	19 (6.5%)		
BMI	23.2 (3.8)	23.0 (3.6)	24.0 (4.4)	< 0.001	1593
Underweight [I]	89 (5.6%)	78 (6.0%)	11 (3.8%)	0.003	1593
Normal weight [II]	1120 (70.3%)	930 (71.4%)	190 (65.5%)		
Overweight [III]	297 (18.6%)	235 (18.0%)	62 (21.4%)		
Obese [IV]	87 (5.5%)	60 (4.6%)	27 (9.3%)		
Menarche age	12.5 (1.4)	12.5 (1.4)	12.4 (1.4)	0.280	1293
Contraceptives	200 (14.5%)	183 (16.3%)	17 (6.6%)	< 0.001	1380
Pill	152 (78.4%)	139 (78.5%)	13 (76.5%)	0.914	194
Intrauterine device	26 (13.4%)	23 (13.0%)	3 (17.6%)		
Patch/Ring	16 (8.3%)	15 (8.5%)	1 (5.9%)		
Menopause	430 (38.5%)	332 (37.3%)	98 (43.2%)	0.119	1118
Physiological	370 (86.7%)	285 (86.4%)	85 (87.6%)	0.879	427
Surgical	57 (13.3%)	45 (13.6%)	12 (12.4%)		
Menopause age	49.1 (4.5)	49.1 (4.6)	49.1 (4.2)	0.954	412
Current smokers	258 (15.9%)	201 (15.2%)	57 (19.3%)	0.068	1618
Years of smoking	16.6 (11.0)	16.3 (10.9)	17.8 (11.4)	0.333	340
Cigarette/day (n)	10.3 (7.4)	10.2 (7.5)	11.0 (6.9)	0.382	349
Previous smokers	108 (6.7%)	95 (7.2%)	13 (4.4%)		
Alcohol intake	95 (5.9%)	83 (6.3%)	12 (4.0%)	0.177	1617
Coffee intake	89 (5.5%)	70 (5.3%)	19 (6.4%)	0.549	1609
Physical activity	415 (25.8%)	352 (26.8%)	63 (21.2%)	0.055	1610
Sleep disorders	519 (32.2%)	403 (30.6%)	116 (39.1%)	0.006	1612

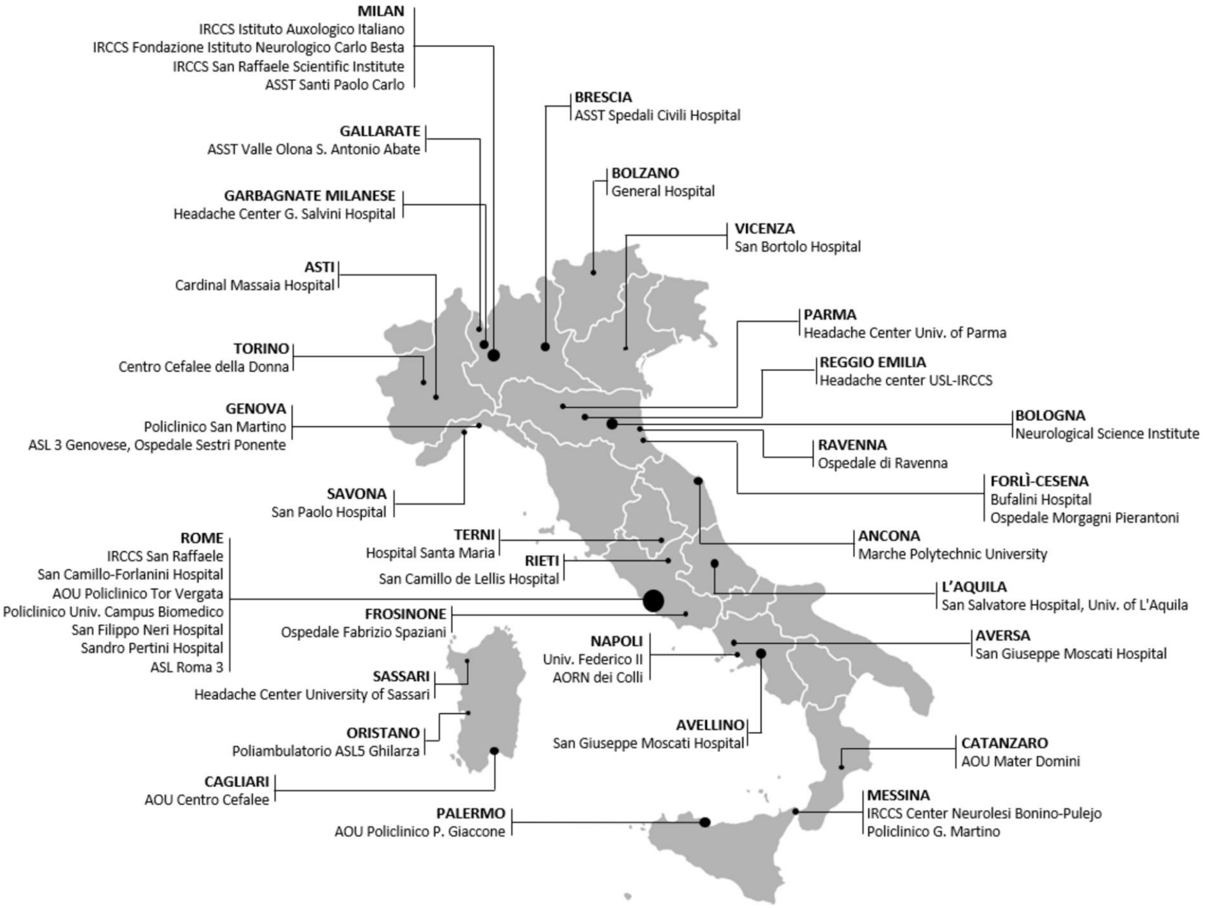
Abbreviation: *BMI* body mass index

[I] BMI < 18.5

[II] 18.5 ≤ BMI ≤ 24.9

[III] 25 ≤ BMI ≤ 29.9

[IV] BMI ≥ 30



AOU: Azienda Ospedaliera Universitaria (University Hospital); ASL: Azienda Sanitaria Locale (Local Health Unit); ASST: Azienda Socio-Sanitaria Territoriale (Territorial Healthcare Agency); IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico (Scientific Institute for Research, Hospitalization and Healthcare); USL: Unità Sanitaria Locale (Local Health Unit).

Fig. 1 Map of the distribution of the 43 Italian Headache centers involved in the I-GRAINE Registry

(5.8%, 94/1630), and hypertension (5.2%, 85/1630) (Table 2).

Anxiety and depression were the most frequently reported psychiatric disorders, affecting 5.6% (92/1630) and 6.0% (98/1630) of the population, respectively.

Migraine clinical features

EM was diagnosed in 1332/1630 patients (81.7%), while 298/1630 patients (18.3%) met criteria for CM. Migraine with aura was reported by 8.1% (132/1630) of the sample. The mean age at migraine onset was 17.5 ± 8.7 years, with an initial mean attack frequency of 6.4 ± 5.9 days per month (Table 3). At the time of enrollment in the I-GRAINE study, the overall mean migraine frequency was 9.8 ± 8.0 days per month. The transition of EM patients to CM occurred at a mean age of 37.0 ± 12.1 years across the cohort.

Medication overuse was reported in 22.6% (356/1578) of patients. Most patients reported unilateral pain (69.1%), with a pulsating quality present in 64.0% of patients. In 57.1% of cases, attacks lasted longer than 24 h. The mean pain intensity, assessed using the Numerical Rating Scale (NRS), was 7.6 ± 1.7. The mean scores on the Migraine Disability Assessment (MIDAS) and the Headache Impact Test (HIT-6) were 48.5 and 61.8, respectively.

The most common accompanying symptoms, as defined by the diagnostic criteria of the ICHD-3 [12], were photophobia, reported by 88.6% (1421/1603) of individuals, of moderate or severe intensity in 83.2% of cases, phonophobia (85.1%, 1355/1593; moderate or severe in 83.1%), nausea (78.6%, 1251/1592; moderate or severe in 77.8%), and vomiting (36.0%, 558/1548; moderate or severe in 72.6%). Additional symptoms not currently included in the ICHD-3 diagnostic criteria were also observed: osmophobia (41.5%, 643/1549), ictal cutaneous allodynia (40.5%, 625/1543), dopaminergic symptoms (37.2%, 592/1590), cephalalgiaphobia (34.0%, 513/1511), unilateral cranial autonomic symptoms (28.4%, 450/1586), and dizziness (16.9%, 254/1501) (Fig. 3).

Fig. 2 Socio-demographic profile of the most representative patient in the I-GRAINE Registry

Sociodemographic and clinical differences between patients with EM and CM

Patients with CM differed significantly from those with EM across a range of sociodemographic, lifestyle, and clinical characteristics. Specifically, individuals with CM were older than those with EM (47.4 vs. 45.2 years; $p = 0.002$) and were more often engaged in housework (15.0% vs. 7.7%; $p = 0.002$). Individuals with CM had more children on average (individuals with more than 2 children: 6.5% vs. 5.5%; $p = 0.029$), a higher mean BMI (24.0 vs. 23.0; $p < 0.001$), a higher prevalence of obesity (9.3% vs. 4.6%, $p = 0.003$), and were less likely to use hormonal contraceptives (6.6% vs. 16.3%; $p < 0.001$). CM was associated with a higher prevalence of sleep disturbances (39.1% vs. 30.6%; $p = 0.006$). Fewer CM patients engaged in regular physical activity but the difference did not reach statistical significance (21.2% vs. 26.8%; $p = 0.055$). A non-significant trend was also noted toward a higher proportion of current smokers among CM patients (19.3% vs. 15.2%; $p = 0.068$) (Table 1).

The prevalence of comorbidities was largely comparable between patients with CM and those with EM (Table 2).

The clinical phenotype of CM was characterized by greater disease severity. Patients reported an earlier onset of EM (16.5 vs. 17.7 years; $p = 0.032$), more frequent bilateral pain localization (40.2% vs. 28.8%; $p < 0.001$), a higher prevalence of pressing/tightening pain quality (31.1% vs. 26.3%; p = 0.029), longer attack duration – as indicated by a lower proportion of attacks lasting less than 24 h (39.4% vs. 43.7%; $p = 0.001$) – and higher average pain intensity (NRS: 8.1 vs. 7.5; $p < 0.001$).

The burden of associated symptoms was also greater in CM. Nausea, vomiting, and dizziness were also more intense in patients with CM, as indicated by a higher frequency of moderate/severe forms (84.5% vs. 76.3%, $p = 0.029$; 85.8% vs. 69.4%, $p = 0.003$; 82.8% vs. 54.9%, $p < 0.001$, respectively). CM patients had a markedly higher prevalence of medication overuse (58.3% vs. 14.5%; $p < 0.001$), ictal cutaneous allodynia (47.5% vs. 38.9%; p = 0.009), cephalalgiaphobia (41.4% vs. 32.3%; $p = 0.004$), and dopaminergic symptoms (45.1% vs. 35.4%; $p = 0.002$).

Among patients exhibiting unilateral cranial autonomic symptoms, miosis was significantly more frequent in those with CM (25.6% vs. 7.6%; $p < 0.001$), as well as ear fullness (28.7% vs. 17.8%; $p = 0.037$). Functional disability and headache-related impact were also greater in CM, as reflected by significantly higher scores on both the MIDAS (76.3 vs. 41.9; $p < 0.001$) and HIT-6 (64.3 vs. 61.2; $p < 0.001$) scales.

Table 2 Comorbidities in individuals with episodic and chronic migraine expressed by absolute frequency (%) enrolled in the I-GRAINE Registry

	All patients	Episodic migraine	Chronic migraine	p value	N
≥ 1 comorbidity	697 (42.8%)	556 (41.8%)	141 (47.3%)		
Psychiatric	211 (12.9%)	173 (13.0%)	38 (12.8%)	0.989	1630
Depression	98 (6.0%)	77 (5.8%)	21 (7.1%)	0.486	1630
Anxiety	92 (5.6%)	79 (5.9%)	13 (4.4%)	0.357	1630
Other	24 (1.5%)	20 (1.5%)	4 (1.3%)	1.000	1630
Endocrinologic	197 (12.1%)	158 (11.9%)	39 (13.1%)	0.625	1630
Gastrointestinal	94 (5.8%)	76 (5.7%)	18 (6.0%)	0.924	1630
Hypertension	85 (5.2%)	68 (5.1%)	17 (5.7%)	0.782	1630
Neurologic	73 (4.5%)	57 (4.3%)	16 (5.4%)	0.505	1630
Gynecologic	63 (3.9%)	47 (3.5%)	16 (5.4%)	0.186	1630
Cardiovascular	53 (3.3%)	43 (3.2%)	10 (3.4%)	1.000	1630
Immunologic	50 (3.1%)	41 (3.1%)	9 (3.0%)	1.000	1630
Neoplastic	40 (2.5%)	29 (2.2%)	11 (3.7%)	0.187	1630
Orthopedic	29 (1.8%)	21 (1.6%)	8 (2.7%)	0.287	1630
Ophthalmologic	27 (1.7%)	23 (1.7%)	4 (1.3%)	0.804	1630
Rheumatologic	25 (1.5%)	17 (1.3%)	8 (2.7%)	0.111	1630
Dermatologic	22 (1.4%)	20 (1.5%)	2 (0.7%)	0.404	1630
Otorhinolaryngological	22 (1.4%)	18 (1.4%)	4 (1.3%)	1.000	1630
Hematologic	18 (1.1%)	16 (1.2%)	2 (0.7%)	0.554	1630
Urological	18 (1.1%)	13 (1.0%)	5 (1.7%)	0.352	1630
Other	16 (1.0%)	16 (1.2%)	–	0.055	1630
Pneumological	2 (0.1%)	1 (0.1%)	1 (0.3%)	0.332	1630

Discussion

The I-GRAINE registry represents a pioneering, nationwide effort to systematically collect real-world clinical data on migraine patients in Italy. By integrating prospectively gathered information from headache centers and outpatient clinics, it provides a high-quality, ecologically valid dataset that overcomes limitations of cross-sectional studies and randomized trials, offering a clinically grounded, population-level perspective. This registry enables both detailed phenotyping and broader epidemiological insights, informing clinical care and health policy. Compared to the initial I-GRAINE report [17], this expanded analysis provides a characterization of a much larger and more heterogeneous cohort, allowing for a more accurate comparison between EM and CM across sociodemographic, lifestyle, and clinical domains.

Three key findings emerge. First, data from I-GRAINE registry delineate the typical profile of patients accessing specialist care: predominantly adult, professionally active women with higher education, stable relationships and typically one/two children. The low prevalence of hypertension in our cohort, largely composed of normal-weight (70.3%) or underweight (5.6%) individuals, is not unexpected considering the well-documented hypotensive tendency observed in migraine patients. Despite a generally healthy BMI and limited alcohol or caffeine intake, over 70% reported physical inactivity, and one-third reported sleep disturbances. Although these patterns may partially reflect the burden of migraine, they also constitute potentially modifiable risk factors that may influence disease trajectory, chronification, and treatment responsiveness [5, 25, 34]. Their systematic assessment is therefore of both prognostic and therapeutic relevance.

Second, the registry provides a comprehensive clinical characterization that extends beyond current ICHD-3 criteria [12]. Migraine onset averaged 17.5 years, with a disease duration of about 20 years. At evaluation in the I-GRAINE study, patients reported an average attack frequency of 9.8 days per month. Chronification occurred, on average, nearly 2 decades after onset, highlighting the slow and multifactorial nature of disease progression [4]. The prevalence of migraine with aura was 8.1%, closely matching that observed in our previous IRON study (7.8%) [20]. This apparently lower figure compared with earlier reports likely reflects a more accurate estimate, as the registry's detailed and analytical classification minimizes overestimation due to the misinterpretation of short-lasting, nonspecific visual phenomena or prodromal symptoms. Pain was unilateral and pulsating in two-thirds of cases – consistent with patterns observed in responders to trigeminal-targeted therapies [35] – and lasted more than 24 h in over half of the sample, suggesting suboptimal or delayed acute treatment [35]. Notably, several symptoms not captured by ICHD-3 criteria [12] were frequently reported, including osmophobia (41.5%), ictal cutaneous allodynia (40.5%), dopaminergic symptoms (37.2%), cephalalgiaphobia (34.0%), unilateral cranial autonomic symptoms (28.4%), and dizziness (16.9%). These may represent clinically relevant endophenotypes, potentially informing individualized therapy and future revisions of diagnostic criteria.

Third, the data underscores the distinctiveness of individuals with CM compared to those with EM. CM patients were slightly older, with higher BMI, and were less likely to engage in physical activity or use hormonal contraceptives. Sleep disturbances were more prevalent, indicating a broader systemic vulnerability. CM was also associated with earlier disease onset, bilateral pain and more intense and prolonged attacks, suggesting increased attack severity, reduced response to acute treatment, or both. Moreover, symptoms such as nausea, vomiting, dizziness, cutaneous allodynia, cephalalgiaphobia, dopaminergic symptoms, and unilateral cranial autonomic signs – particularly miosis – were more frequent and/or more severe, pointing to enhanced peripheral and central sensitization [29]. Functional disability was markedly

Table 3 Migraine characteristics in individuals with episodic and chronic migraine enrolled in the I-GRAINE Registry. Categorical variables are expressed by absolute frequency (%) and continuous by mean (standard deviation = SD)

	All	**Episodic migraine**	**Chronic migraine**	**p value**	**N**
Patients	1630	1332 (81.7%)	298 (18.3%)		
Age	45.7 (12.9)	45.2 (13.0)	47.7 (12.5)	0.002	1616
Type of migraine					1630
Migraine without aura	1200 (73.6%)	1200 (90.1%)	–		
Migraine with aura	132 (8.1%)	132 (9.9%)	–		
Chronic migraine	298 (18.3%)	–	298 (100%)		
Medication overuse	356 (22.6%)	187 (14.5%)	169 (58.3%)	< 0.001	1578
Age at migraine onset	17.5 (8.7)	17.7 (8.9)	16.5 (7.9)	0.032	1611
Age at chronification	–	–	37.0 (12.1)		
Frequency at migraine onset	6.4 (5.9)	6.3 (5.8)	6.7 (6.2)	0.377	1550
Frequency at first headache center consultation	11.6 (7.5)	10.6 (7.1)	15.8 (7.7)	< 0.001	1558
Frequency at enrollment (days/month)	9.8 (8.0)	8.3 (7.0)	16.3 (9.0)	< 0.001	1616
Pain location					
Unilateral, side-locked	471 (26.6%)	398 (27.4%)	73 (22.6%)	0.075	1630
Unilateral, alternating side	754 (42.5%)	634 (43.7%)	120 (37.2%)	0.026	1630
Bilateral	548 (30.9%)	418 (28.8%)	130 (40.2%)	< 0.001	1630
Attack duration				0.001	1610
< 24 h	691 (42.9%)	573 (43.7%)	117 (39.4%)		
24–47 h	528 (32.8%)	442 (33.7%)	86 (29.0%)		
48–72 h	296 (18.4%)	233 (17.7%)	63 (21.2%)		
> 72 h	95 (5.9%)	64 (4.9%)	31 (10.4%)		
Pain intensity (NRS)	7.6 (1.7)	7.5 (1.8)	8.1 (1.4)	< 0.001	1564
Pain quality					
Pulsating	1243 (64.0%)	1013 (64.2%)	230 (63.4%)	0.734	1630
Pressing/Tightening	528 (27.2%)	415 (26.3%)	113 (31.1%)	0.029	1630
Burning	30 (1.5%)	27 (1.7%)	3 (0.8%)	0.344	1630
Other	141 (7.3%)	124 (7.9%)	17 (4.7%)	0.059	1630
Associated symptoms (based on the ICHD-3 criteria, [12])					
Photophobia	1421 (88.6%)	1159 (88.6%)	262 (88.8%)	1.000	1603
Mild	235 (16.8%)	197 (17.3%)	38 (14.7%)	0.601	1395
Moderate	820 (58.8%)	664 (58.4%)	156 (60.5%)		
Severe	340 (24.4%)	276 (24.3%)	64 (24.8%)		
Phonophobia	1355 (85.1%)	1096 (84.4%)	259 (88.1%)	0.127	1593
Mild	226 (17.0%)	192 (17.9%)	34 (13.3%)	0.193	1331
Moderate	790 (59.4%)	634 (59.0%)	156 (60.9%)		
Severe	315 (23.7%)	249 (23.2%)	66 (25.8%)		
Nausea	1251 (78.6%)	1027 (79.0%)	224 (76.7%)	0.434	1592
Mild	273 (22.2%)	239 (23.7%)	34 (15.5%)	0.029	1230
Moderate	705 (57.3%)	569 (56.3%)	136 (61.8%)		
Severe	252 (20.5%)	202 (20.0%)	50 (22.7%)		
Vomiting	558 (36.0%)	450 (35.7%)	108 (37.4%)	0.651	1548
Mild	149 (27.4%)	134 (30.6%)	15 (14.2%)	0.003	544
Moderate	264 (48.5%)	203 (46.3%)	61 (57.5%)		
Severe	131 (24.1%)	101 (23.1%)	30 (28.3%)		
Other associated symptoms (not currently listed in the ICHD-3, [12])					
Osmophobia	643 (41.5%)	525 (41.7%)	118 (40.8%)	0.846	1549
Allodynia	625 (40.5%)	490 (38.9%)	135 (47.5%)	0.009	1543
Dopaminergic symptoms	592 (37.2%)	459 (35.4%)	133 (45.1%)	0.002	1590
Cephalalgiaphobia	513 (34.0%)	397 (32.3%)	116 (41.4%)	0.004	1511
Unilateral autonomic symptom	450 (28.4%)	359 (27.8%)	91 (31.0%)	0.310	1586
Lacrimation	262 (62.8%)	208 (63.2%)	54 (61.4%)	0.844	417
Ptosis	229 (55.2%)	182 (55.7%)	47 (53.4%)	0.798	415

Table 3 (continued)

	All	Episodic migraine	Chronic migraine	p value	N
Nasal congestion	146 (36.0%)	116 (36.4%)	30 (34.9%)	0.899	405
Eyelid edema	123 (30.8%)	91 (29.0%)	32 (37.2%)	0.182	400
Conjunctival injection	117 (28.8%)	89 (27.9%)	28 (32.2%)	0.517	406
Rhinorrea	95 (23.8%)	69 (22.0%)	26 (30.2%)	0.147	400
Ear fullness	81 (20.2%)	56 (17.8%)	25 (28.7%)	0.037	401
Flushing	61 (15.4%)	44 (14.2%)	17 (19.5%)	0.298	396
Sweating	54 (13.6%)	41 (13.2%)	13 (15.1%)	0.784	396
Miosis	44 (11.5%)	23 (7.6%)	21 (25.6%)	< 0.001	384
Dizziness	254 (16.9%)	196 (16.2%)	58 (20.1%)	0.133	1501
Mild	97 (38.6%)	87 (45.1%)	10 (17.2%)	< 0.001	251
Moderate	111 (44.2%)	82 (42.5%)	29 (50.0%)		
Severe	43 (17.1%)	24 (12.4%)	19 (32.8%)		
MIDAS	48.5 (48.2)	41.9 (41.4)	76.3 (62.9)	< 0.001	1455
HIT-6	61.8 (8.8)	61.2 (8.8)	64.3 (8.2)	< 0.001	1432

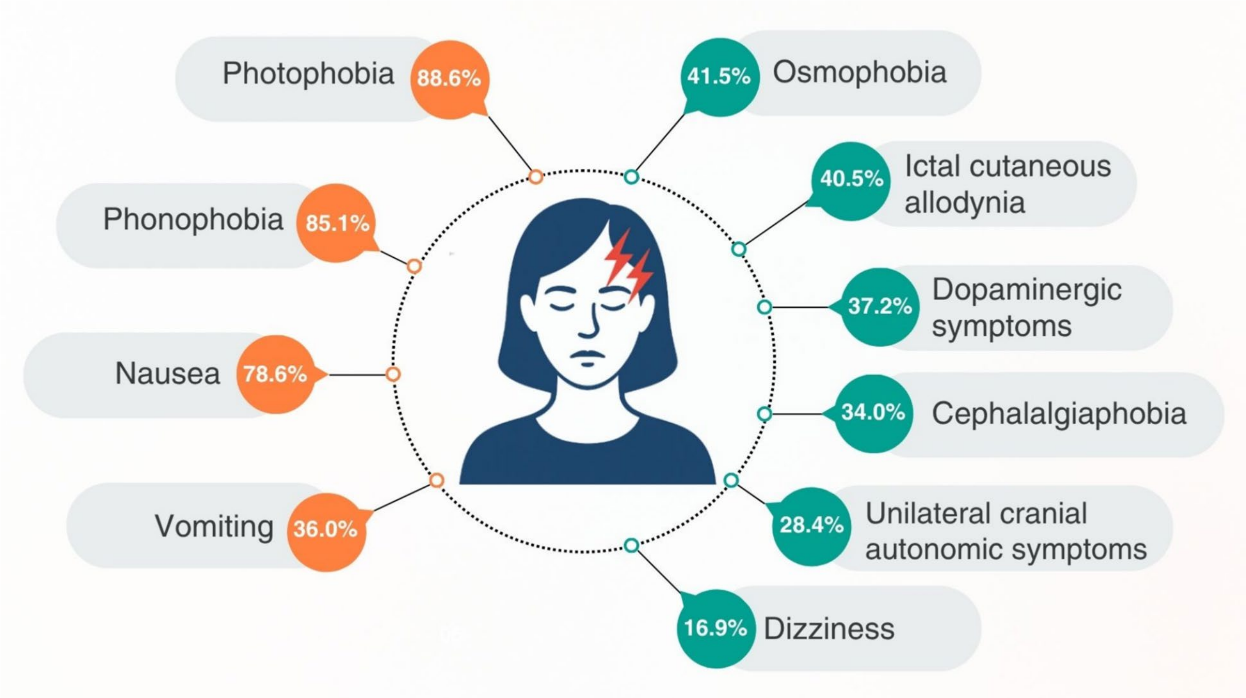


Fig. 3 Migraine accompanying symptoms emerging from the I-GRAINE Registry. On the left, the most common accompanying symptoms, as defined by the diagnostic criteria of the ICHD-3 [12]; on the right, the accompanying symptoms not currently included in the ICHD-3 criteria [12]

greater in CM, as reflected by elevated MIDAS and HIT-6 scores. Nearly 60% of CM patients met criteria for medication overuse, underscoring its dual role as both a driver and a consequence of disease progression [36].

The relatively low proportion of CM cases in our cohort likely reflects the heterogeneous nature of participating centers, some of which were first-level clinics where fewer complex cases are managed. This contrasts with other international registries, which draw predominantly from tertiary centers and thereby report higher proportions of CM and greater attack frequencies (e.g., 14.4 ± 8.5 and 19.1 ± 9.2 days/month in the German and U.S. registries, respectively, versus 9.8 ± 8.0 in I-GRAINE) [37, 38]. Rather than representing a limitation, this case-mix reduces the selection bias typically associated with specialized settings and enhances the external validity of our findings to a broader clinical context.

The inclusion of first-level healthcare centers may also contribute to the relatively low prevalence of psychiatric comorbidities in the I-GRAINE registry compared to tertiary center reports [37, 39, 40], potentially due to both the lower CM proportion and the lack of standardized specific screening tools to assess anxiety or depression among individuals with migraine [41]. Nonetheless, the high prevalence of sleep disturbances – often associated with psychiatric conditions – may hide subsyndromal or undiagnosed psychiatric symptoms [42].

Overall, the patient profile emerging from the I-GRAINE registry is broadly consistent with that reported by other international registries, particularly regarding females' predominance (82.2% in the German registry and 86.7% in the U.S. registry) and the high educational level of individuals with migraine. The mean age in the Italian cohort (45.7 ± 12.9 years) falls between that of the German (39.6 ± 12.9 years) and U.S. (48.6 ± 13.9 years) registries [37, 38]. However, differences among the I-GRAINE, German, and U.S. registries must be acknowledged. The U.S. registry integrates electronic health records, neuroimaging, and biorepository data, offering a broader perspective. In contrast, both I-GRAINE and the German registry focus on standardized clinical phenotyping, without collecting imaging or biological samples. The German registry includes 16 centers (10 private) and 1351 patients, and the US registry includes 8 centers with fewer than 1000 patients, and both registries mainly collect patient data from auto-filled web-based questionnaires [37, 38]. To the best of our knowledge, I-GRAINE includes the largest number of patients (n = 1630) and of participating centers (n = 43) worldwide, all of which are publicly funded and conduct direct, in-person patient assessments, ensuring both data uniformity and high diagnostic reliability.

This study has several limitations. First, data reporting bias is inherent to registry-based research, particularly when relying on patient self-report and physician-entered information. Certain conditions, such as comorbidities, may be underreported or underdiagnosed due to differences in diagnostic sensitivity, clinical expertise, or structural limitations of the registry. Despite shared protocols and specific training, inter-center heterogeneity remains a possible source of variability in clinical practice, resource availability, and patient case mix. Moreover, unlike some international registries, I-GRAINE does not include biological samples or advanced instrumental assessments (e.g., neuroimaging, genetics), limiting translational opportunities and biomarker exploration. In addition, the registry does not collect data on income level. Finally, although representative of Italian public headache care, the findings may not be fully generalizable to countries with different healthcare systems, referral models, or sociodemographic characteristics.

Nonetheless, I-GRAINE has notable strengths. It is grounded in a robust methodological framework, with systematic, prospective enrollment of patients from 43 accredited headache centers distributed across 13 regions and covering all levels of care within the Italian National Health Service. Ethical standards are ensured through centralized and local approvals, informed consent, and full GDPR compliance under the supervision of the Italian Data Protection Authority. Data collection is performed through a dedicated, centralized electronic platform, designed to standardize input across sites and minimize entry errors, thereby enhancing both the quality and reliability of the data collected.

To sum up, the I-GRAINE registry offers a comprehensive real-world characterization of individuals with migraine in Italy, integrating sociodemographic, lifestyle, and clinical dimensions. It responds to the growing need for systematic profiling of migraine patients in an era increasingly driven by personalized and mechanism-based therapeutic strategies. As such, I-GRAINE stands as a strategic resource not only for clinical and research purposes but also for informing health policy, particularly given the current limited availability of large-scale data. Ongoing analyses will explore acute and preventive treatment patterns, as well as the utilization of healthcare and social resources, with results to be reported in forthcoming publications.

Conclusion

The I-GRAINE registry represents the largest real-world dataset on migraine care conducted to date within a public healthcare system. Designed to systematically characterize patients seeking specialist treatment, the registry outlines the profile of the typical Italian migraine patient: a 45-year-old, normal-weight, well-educated, employed woman, often physically inactive and affected by sleep disturbances, reporting an average migraine frequency of approximately 10 days per month. I-GRAINE also captures several common migraine-associated symptoms not currently encompassed by the ICHD-3 diagnostic criteria, opening new perspectives for identifying potential endophenotypes. Further, the registry documents distinct sociodemographic and clinical differences between individuals with EM and those with CM, including variations in BMI, sleep disturbances, pain features, and attack severity. By integrating sociodemographic, lifestyle, and clinical variables, this comprehensive dataset provides robust real-world evidence to support personalized care strategies, inform public health policy, and guide targeted future research.

Abbreviations

ANIRCEF	Associazione Neurologica Italiana per la Ricerca sulle Cefalee
BMI	Body Mass Index
CM	Chronic Migraine
DPIA	Data Protection Impact Assessment
eCRF	Electronic Case Report Form
EM	Episodic Migraine
GDPR	General Data Protection Regulation
HIT-6	Headache Impact Test
ICHD-3	International Classification of Headache Disorders, 3rd Edition
I-GRAINE	Italian National Migraine Registry
MIDAS	Migraine Disability Assessment
NRS	Numerical Rating Scale
SISC	Società Italiana per lo Studio delle Cefalee
WHO	World Health Organization

Supplementary Information

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Supplementary material 1.

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Authors' contributions

PB, S. Cevoli, PT, CT conceived the study; G. Fiorentini, C. Camarda, M. Autunno, F. Pistoia, CA, FdO, GE, A. Carnevale, S. Caproni, AD, AC, RDS, MZ, SR, BC, MF, SQ, MR, A. Coppola, RG, MB, GV, RR, M. Albanese, FV, LG, FF, ADS, M. Aguggia, MLBDP, CF, RT, MS, FG, PQ, F. Perini, P. Solla, VF, LF, GS, EI, C. Colosimo, SM, LDC, F. Cortese, P. Scatena, DC, NB, GQ, AG, S. Cazzulo, FT, MG, TE, ST, BO, FB, PAB, CT, I-GRAINE Study Group curated the data; SB, AP, SP analyzed the data. PB, S. Cevoli, PT, CT drafted the manuscript. All authors edited and reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

The protocol of the study was approved by the Ethics Committee of the coordinating center, IRCCS San Raffaele Roma (16/int, 31/7/20) and shared by the Ethics Committees of the other centers.

Competing interests

Piero Barbanti received travel grants, honoraria for advisory boards, speaker panels or clinical investigation studies from Abbvie, Alder, Allergan, Amgen, Angelini, Assosalute, Bayer, Biohaven, ElectroCore, Eli-Lilly, Fondazione Ricerca e Salute, GSK, Lundbeck, Lusofarmaco, 1MED, MSD, New Penta, Noema Pharma, Novartis, Organon, Orion Pharma, Pfizer, Stx-Med, Teva, Viatris, Visufarma, Zambon and serves as President with Italian Association of Headache Sufferers. Francesca Pistoia received travel grants, honoraria for advisory boards from Allergan/Abbvie, Lilly, Lundbeck, Organon, Pfizer, Novartis, and Teva. Cinzia Aurilia received travel grants from Eli-Lilly, FB-Health, Lusofarmaco and Teva, honoraria from Novartis, Eli-Lilly and Teva. Florindo d'Onofrio received travel grant, honoraria as a speaker or for partecipating in advisory boards from Novartis, Teva, Neopharmed Gentili, Qbgroup srl, K link srl and Eli-Lilly. 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