Characterising Cluster Headache in Real-World OMOP-Standardised Health Databases across the EHDEN Network

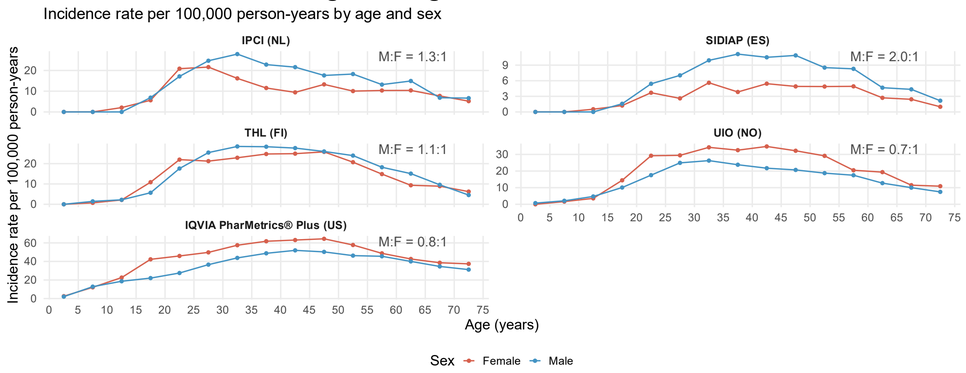
Cluster Headache in Five Databases Across Five Countries

Cluster headache (CH) is a rare but severely disabling primary headache disorder. Despite its burden, real-world evidence on CH across healthcare systems remains limited. We performed a retrospective observational study in collaboration with four data partners: **Integrated Primary Care Information (IPCI, the Netherlands)**, **Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP, Spain)**, **Terveyden ja hyvinvoinnin laitos (THL, Finland)** and **University of Oslo health registries (UiO, Norway),** and the database **IQVIA PharMetrics® Plus (USA)**, to characterize demographics, comorbidity profiles, and treatments among individuals with CH.

This was a **real-world evidence (RWE)** study conducted through the **European Health Data & Evidence Network (EHDEN) Foundation**, a federated research network built on the **OMOP Common Data Model**. EHDEN enables standardized, privacy-preserving analyses to be run locally across multiple healthcare databases, allowing robust cross-country comparisons while keeping patient-level data with the data partners.

Cluster Headache First Diagnosis: Age and Sex Distribution

Incidence rate per 100,000 person-years by age and sex



Cluster headache incidence and annual prevalence

	IPCI (NL)	SIDIAP (ES)	THL (FI)	UIO (NO)	IQVIA PharMetrics® Plus (US)
Incidence / 100k PY (95% CI)	11 (11–12)	5 (4–5)	15 (14–15)	18 (17–18)	42 (41–42)
Annual Prevalence / 100k (95% CI)	47 (35–62)	8 (4–16)	40 (29–54)	44 (33–59)	87 (71–107)

Databases

	IPCI	SIDIAP	THL	UiO	IQVIA PharMetrics® Plus
Country	The Netherlands	Spain	Finland	Norway	USA
N	1.24M	6.06M	6.62M	6.89M	318M*
CH patients	930	1670	6247	6350	69831
Years in analysis	2016–2023	2016–2023	2016–2023	2016–2023	2016–2023
Coverage	Nationwide	Catalonia	Nationwide	Nationwide	Commercially insured nationwide
Setting	Primary care + prescribed prescriptions	Primary care + prescriptions; some hospital data via discharge reports	Primary care + specialist outpatient + inpatient + prescriptions	Primary care + specialist outpatient + inpatient + dispensed prescriptions	Insurance claims + pharmacy claims/prescriptions
Reference	de Ridder et al., Int J Epidemiol, 2022	Recalde et al., Int J Epidemiol, 2022	Viippola et al., Int J Epidemiol, 2023	Litleskare et al., Int J Med Inform, 2024	IQVIA database fact sheet

* 318M lives available in IQVIA PharMetrics® Plus; may include duplicate individuals across health plans and over time.

Comorbidities First Year After Diagnosis

	IPCI (NL)		SIDIAP (ES)		THL (FI)		UIO (NO)		IQVIA PharMetrics® Plus (US)	
	Prev %	aRR	Prev %	aRR	Prev %	aRR	Prev %	aRR	Prev %	aRR
Allergic Rhinitis	2.2 (1.4–3.3)	0.8 (0.5–1.5)	1.3 (0.9–2.0)	1.3 (0.7–2.5)	1.4 (1.1–1.7)	1.4 (1.0–2.0)	16 (16–17)	1.3 (1.2–1.4)	14 (14–14)	1.8 (1.7–1.8)
Anxiety Disorder	5.9 (4.6–7.6)	1.3 (0.9–1.9)	5.6 (4.6–6.8)	1.7 (1.2–2.4)	10 (9.6–11)	1.5 (1.4–1.7)	12 (12–13)	1.3 (1.2–1.5)	27 (27–27)	1.8 (1.7–1.8)
Asthma	2.2 (1.4–3.3)	0.9 (0.5–1.6)	0.7 (0.4–1.2)	1.4 (0.6–3.4)	5.5 (5.0–6.1)	2.0 (1.7–2.5)	10 (9.4–11)	1.5 (1.4–1.7)	9.0 (8.8–9.3)	1.6 (1.6–1.7)
Atopic Dermatitis	8.1 (6.5–10.0)	0.9 (0.7–1.2)	4.2 (3.3–5.3)	1.3 (0.9–1.9)	6.0 (5.4–6.6)	1.2 (1.1–1.4)	7.8 (7.1–8.5)	1.2 (1.1–1.4)	13 (13–13)	1.3 (1.3–1.3)
Backache	5.4 (4.1–7.0)	1.2 (0.8–1.8)	7.3 (6.2–8.7)	1.1 (0.9–1.5)	13 (12–13)	1.6 (1.4–1.8)	11 (10–12)	1.3 (1.1–1.4)	21 (21–22)	1.7 (1.6–1.7)
Cardiac Arrhythmia	0.8 (0.4–1.5)	0.7 (0.3–2.0)	1.0 (0.6–1.6)	1.3 (0.6–2.7)	4.6 (4.1–5.2)	1.6 (1.3–1.9)	4.7 (4.2–5.2)	1.4 (1.2–1.7)	5.6 (5.4–5.8)	1.6 (1.5–1.7)
Cerebrovascular Disease	1.5 (0.9–2.5)	1.9 (0.8–4.7)	0.5 (0.3–1.0)	4.8 (1.0–23)	2.1 (1.8–2.5)	3.8 (2.6–5.5)	2.6 (2.2–3.0)	2.2 (1.7–2.9)	3.5 (3.4–3.6)	3.5 (3.3–3.9)
Drug Abuse	4.3 (3.2–5.8)	2.0 (1.2–3.3)	0.7 (0.4–1.2)	3.4 (1.0–11)	1.4 (1.1–1.7)	1.3 (0.9–1.7)	1.7 (1.4–2.0)	1.1 (0.9–1.5)	1.7 (1.6–1.8)	1.4 (1.3–1.6)
Fibromyalgia			0.4 (0.2–0.8)	3.6 (0.6–20)	1.1 (0.8–1.4)	5.3 (2.9–9.7)	0.7 (0.5–0.9)	3.5 (1.8–6.5)	3.0 (2.8–3.1)	3.3 (3.0–3.6)
Hypertensive Disease	6.1 (4.8–7.9)	1.1 (0.8–1.6)	2.6 (1.9–3.5)	2.1 (1.2–3.6)	8.6 (8.0–9.4)	1.4 (1.2–1.5)	17 (16–18)	1.4 (1.3–1.6)	30 (30–31)	1.3 (1.3–1.3)
Irritable Bowel Syndrome	0.6 (0.3–1.4)	0.9 (0.3–2.6)			1.2 (0.9–1.5)	2.0 (1.4–3.0)	1.9 (1.6–2.2)	2.1 (1.5–2.9)	3.3 (3.2–3.4)	2.6 (2.4–2.8)
Low Back Pain	3.2 (2.3–4.6)	1.1 (0.7–1.8)	6.2 (5.1–7.4)	1.1 (0.8–1.4)	10 (9.6–11)	1.6 (1.4–1.8)	6.7 (6.2–7.4)	1.2 (1.1–1.4)	17 (16–17)	1.6 (1.6–1.7)
Major Depressive Disorder	3.8 (2.7–5.2)	1.7 (1.0–2.8)	1.8 (1.3–2.6)	2.2 (1.2–4.2)	10 (9.3–11)	1.6 (1.4–1.8)	4.0 (3.5–4.5)	1.3 (1.1–1.5)	18 (17–18)	1.7 (1.7–1.8)
Menieres Disease					0.2 (0.1–0.4)	2.7 (0.9–7.6)	0.1 (0.1–0.2)	2.5 (0.6–10)	0.3 (0.3–0.4)	3.1 (2.4–4.0)
Migraine	6.9 (5.4–8.7)	7.6 (3.7–15)	7.0 (5.9–8.3)	16 (7.5–33)	24 (22–25)	13 (11–16)	47 (46–49)	11 (10.0–13)	28 (28–28)	7.2 (7.0–7.5)
Myocardial Infarction	1.0 (0.5–1.8)	1.4 (0.5–3.8)	0.4 (0.2–0.8)	4.1 (0.7–24)	0.4 (0.3–0.6)	1.1 (0.6–1.9)	0.6 (0.4–0.8)	0.9 (0.6–1.4)	1.2 (1.2–1.3)	1.5 (1.4–1.7)
Nicotine Use	3.1 (2.2–4.4)	2.3 (1.2–4.5)	1.6 (1.1–2.3)	2.7 (1.3–5.5)	0.4 (0.3–0.6)	1.6 (0.9–3.1)	0.1 (0.0–0.2)	0.9 (0.3–2.5)	8.5 (8.3–8.7)	1.8 (1.7–1.9)
Overweight And Obesity	1.0 (0.5–1.8)	1.4 (0.5–3.7)	1.8 (1.3–2.6)	1.2 (0.7–2.1)	2.8 (2.4–3.2)	1.7 (1.3–2.1)	3.9 (3.5–4.4)	1.4 (1.1–1.7)	13 (13–13)	1.4 (1.3–1.4)
PTSD	1.0 (0.5–1.8)	1.8 (0.6–5.5)			0.9 (0.7–1.2)	2.6 (1.6–4.2)	3.4 (3.0–3.9)	2.3 (1.8–2.9)	2.4 (2.3–2.5)	2.1 (1.9–2.3)
Panic Disorder	1.7 (1.1–2.8)	1.4 (0.7–3.1)			1.4 (1.2–1.8)	1.9 (1.4–2.7)	0.5 (0.3–0.7)	1.6 (0.9–2.9)	2.4 (2.3–2.5)	2.3 (2.1–2.5)
Peripheral Vascular Disease	2.3 (1.5–3.4)	1.2 (0.6–2.2)	0.5 (0.2–0.9)	1.5 (0.5–4.6)	2.7 (2.4–3.2)	1.2 (1.0–1.6)	2.1 (1.8–2.5)	1.0 (0.8–1.3)	8.3 (8.1–8.5)	1.4 (1.4–1.5)
Psoriasis	0.6 (0.3–1.4)	1.0 (0.3–3.3)			0.6 (0.5–0.9)	1.1 (0.7–1.7)	2.3 (2.0–2.7)	1.3 (1.0–1.6)	1.3 (1.2–1.4)	1.2 (1.1–1.3)
Sinusitis	4.6 (3.5–6.2)	2.6 (1.5–4.5)	4.3 (3.4–5.4)	4.4 (2.6–7.5)	5.7 (5.1–6.3)	2.1 (1.7–2.5)	5.6 (5.1–6.2)	2.3 (1.9–2.8)	20 (19–20)	2.0 (1.9–2.0)
Sleep Apnea	0.6 (0.3–1.4)	1.3 (0.4–4.3)	0.4 (0.2–0.9)	1.4 (0.4–4.5)	5.0 (4.5–5.6)	1.7 (1.4–2.1)	2.2 (1.8–2.6)	1.6 (1.2–2.1)	7.9 (7.7–8.1)	1.9 (1.8–2.0)
Sleep Disorder	3.9 (2.8–5.3)	1.6 (1.0–2.7)	1.9 (1.3–2.6)	1.5 (0.9–2.6)	10 (9.4–11)	1.7 (1.5–1.9)	10 (9.7–11)	1.8 (1.6–2.0)	19 (19–20)	2.0 (2.0–2.1)
Temporomandibular Joint Disorder					0.8 (0.6–1.0)	4.4 (2.3–8.5)	0.5 (0.3–0.7)	3.8 (1.8–8.4)	1.8 (1.7–1.9)	3.9 (3.5–4.4)
Trigeminal Neuralgia	0.8 (0.4–1.5)	27 (0.5–1341)	0.8 (0.5–1.4)	23 (1.8–307)	1.5 (1.2–1.9)	44 (11–171)	2.5 (2.2–2.9)	35 (14–88)	1.5 (1.4–1.6)	13 (10–16)

Prevalence: Wilson CI. aRR: weighted risk ratio vs an age/sex-matched general population at a random visit (Wald CI on log scale).

Treatment Use First Year After Diagnosis

	IPCI (NL)		SIDIAP (ES)		THL (FI)		UIO (NO)		IQVIA PharMetrics® Plus (US)	
	Prev %	aRR	Prev %	aRR	Prev %	aRR	Prev %	aRR	Prev %	aRR
Amitriptyline/Nortriptyline	5.9 (4.6–7.6)	3.7 (2.1–6.4)	11 (9.5–13)	8.5 (5.5–13)	15 (14–15)	5.2 (4.5–6.1)	9.8 (9.1–11)	6.2 (5.1–7.7)	5.7 (5.5–5.8)	5.8 (5.3–6.2)
Antidepressants	14 (12–16)	2.0 (1.5–2.6)	26 (24–29)	2.5 (2.1–2.9)	30 (29–31)	2.1 (1.9–2.2)	19 (18–20)	2.4 (2.2–2.7)	24 (24–24)	1.7 (1.7–1.8)
Antiemetics	3.3 (2.4–4.7)	1.5 (0.9–2.6)	5.4 (4.5–6.6)	1.5 (1.1–2.0)	9.2 (8.5–10.0)	4.7 (3.9–5.7)	7.0 (6.4–7.6)	3.3 (2.8–4.0)	26 (26–26)	2.3 (2.2–2.3)
Anxiolytics	12 (10–15)	2.1 (1.6–2.9)	29 (27–31)	1.9 (1.7–2.2)	14 (13–15)	2.1 (1.9–2.3)	9.1 (8.4–9.8)	2.1 (1.8–2.4)	14 (14–14)	1.9 (1.9–2.0)
Beta Blockers	9.6 (7.8–12)	1.3 (1.0–1.8)	7.8 (6.6–9.2)	1.7 (1.3–2.2)	20 (19–21)	2.0 (1.8–2.2)	9.5 (8.8–10)	1.9 (1.7–2.2)	9.8 (9.5–10.0)	1.8 (1.7–1.8)
Corticosteroids Oral	6.6 (5.1–8.3)	2.1 (1.3–3.2)	13 (12–15)	4.1 (3.1–5.5)	27 (26–28)	6.3 (5.5–7.1)			23 (23–23)	2.0 (1.9–2.0)
Cyclobenzaprine			2.7 (2.0–3.6)	1.3 (0.8–2.0)					7.2 (7.0–7.4)	2.0 (1.9–2.1)
Flunarizine Oral			3.1 (2.3–4.0)	21 (5.8–75)						
Indomethacin	4.5 (3.4–6.0)	80 (5.3–1226)	5.3 (4.4–6.5)	17 (7.1–42)	4.5 (4.0–5.0)	38 (18–80)	11 (9.9–11)	353 (85–1460)	2.0 (1.9–2.1)	5.8 (5.1–6.6)
Lamotrigine			1.0 (0.6–1.6)	4.8 (1.5–16)	2.0 (1.6–2.3)	3.2 (2.2–4.6)	2.4 (2.0–2.8)	3.5 (2.5–4.8)	1.4 (1.3–1.5)	2.0 (1.8–2.3)
Lidocaine Injection	1.0 (0.5–1.8)	1.5 (0.5–4.1)	0.3 (0.1–0.7)	4.3 (0.6–32)					3.3 (3.2–3.5)	1.7 (1.6–1.8)
Lithium	0.8 (0.4–1.5)	4.3 (0.8–23)	2.3 (1.7–3.1)	14 (4.1–48)	1.0 (0.8–1.3)	4.8 (2.7–8.7)	0.5 (0.3–0.7)	3.1 (1.5–6.3)	0.4 (0.4–0.5)	2.7 (2.2–3.4)
NSAIDs	34 (31–37)	1.8 (1.5–2.1)	69 (67–71)	1.6 (1.5–1.7)	71 (70–72)	1.6 (1.5–1.6)	62 (61–63)	1.7 (1.6–1.8)	33 (33–33)	2.0 (2.0–2.0)
Ondansetron			0.4 (0.2–0.9)	1.8 (0.5–6.2)	1.3 (1.1–1.7)	2.8 (1.8–4.2)	1.2 (1.0–1.5)	2.7 (1.8–4.2)	19 (18–19)	2.0 (1.9–2.1)
Opiates/Opioids*	18 (15–20)	1.9 (1.5–2.4)	16 (15–18)	1.7 (1.4–2.1)	23 (22–24)	2.0 (1.9–2.2)	26 (25–27)	2.3 (2.1–2.5)	21 (21–21)	1.7 (1.7–1.8)
Topiramate	0.6 (0.3–1.4)	5.7 (0.7–45)	11 (9.5–12)	23 (11–46)	7.1 (6.5–7.8)	86 (36–206)	5.3 (4.8–5.9)	32 (17–60)	7.3 (7.1–7.5)	8.3 (7.6–9.0)
Triptans All	53 (50–57)	35 (21–58)	59 (57–61)	59 (37–96)	67 (66–68)	29 (25–35)	46 (45–47)	15 (13–18)	20 (20–21)	13 (12–13)
Triptans Injection	24 (22–27)	203 (31–1309)	8.0 (6.8–9.4)	639 (8.8–46382)					2.6 (2.5–2.8)	47 (34–64)
Triptans Nasal	19 (16–21)	159 (24–1040)	9.7 (8.4–11)	471 (17–13345)	43 (42–44)	119 (78–179)			2.5 (2.4–2.6)	53 (37–74)
Triptans Oral	19 (17–22)	14 (7.9–24)	42 (40–45)	44 (27–72)	23 (22–24)	13 (11–15)			17 (16–17)	11 (10–12)
Valproate	0.5 (0.2–1.3)	1.9 (0.4–8.2)	2.0 (1.5–2.8)	4.3 (2.0–9.4)	2.8 (2.4–3.2)	4.9 (3.4–6.9)	0.8 (0.6–1.1)	3.0 (1.7–5.1)	1.4 (1.3–1.4)	6.9 (5.8–8.3)
Verapamil	17 (15–20)	53 (17–164)	27 (25–29)	370 (62–2216)	28 (27–29)	240 (116–496)	9.4 (8.7–10)	69 (35–136)	6.3 (6.2–6.5)	26 (22–30)

Prevalence: Wilson CI. aRR: weighted risk ratio vs an age/sex-matched general population at a random visit (Wald CI on log scale).
* Excluding anti-tussives.

Methodology

Individuals with cluster headache (CH) were found using standardized SNOMED CT concept sets, with the first recorded CH diagnosis defined as the index date and requiring at least one year of observation before and after index.

Demographics, incidence, prevalence, comorbidities, and treatment use were characterized using SNOMED CT for diagnoses, ATC for drug classes, and RxNorm for medication ingredients and route of administration.

A background population—restricted to individuals with at least one recorded healthcare visit—was assigned a visit-anchored index date requiring at least one year or observation before and after, and weighted by age, sex, and calendar period to enable comparison with the CH cohort.

Analyses were executed at each data partner in a federated framework, using a standardized analytic pipeline to ensure consistency and reproducibility across databases.

Conclusion

This large multi-country real-world study identified 85,028 individuals with cluster headache (CH) across five databases and confirmed that CH remains a rare disorder, with annual prevalence below 50 per 100,,000 in all European databases and 87 per 100,000 in IQVIA PharMetrics® Plus.

Cluster headache has traditionally been seen as a male-predominant disorder, although the male-to-female ratio has fallen from over 6:1 to around 2:1 over the past six decades [1][2]. This study reflects that trend, and both improved recognition in women and possible misclassification with conditions such as migraine with autonomic features may contribute to it.

Across all datasets, individuals with CH had a substantial comorbidity burden, including higher rates of cerebrovascular disease, hypertension, cardiac arrhythmias, mental and behavioural disorders, and migraine than the background population. Recorded use of guideline-recommended treatments was sometimes low and variable across healthcare systems.

Overall, the study shows the value of OMOP-standardized, federated real-world evidence generation through EHDEN for rare disease research.

[1] Kim SA et al., *Cephalalgia*, 2023 [2] San-Juan D et al., *Frontiers in Pain Research*, 2024.

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