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Comorbid depression or anxiety among migraine patients aged ten years or older living in Sweden in 2015 to 2023: A nationwide study

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Abstract

Background: Residential deprivation is a long-established risk factor for poor health outcomes including migraine, depression and anxiety that are significant public health problems in Sweden and globally. Yet the relationship between residential deprivation and patterns of comorbidity among these three conditions is less understood. We aimed to estimate the magnitude and determinants of comorbid depression or anxiety among migraine patients in Sweden including the relationship between residential deprivation and comorbidity prevalence.

Methods: A nationwide register-based cross-sectional study was conducted of persons aged ten years or older in Sweden in 2015–2023. Comorbid depression or anxiety was defined as any depression or anxiety diagnosis or treatment during the migraine-exposed period (from three months before until three months after the first and last recorded migraine exposure in the study period). Small-area deprivation was based on an Index for Multiple Deprivation in Sweden (IMDIS) applied to 5984 small geographic areas. Prevalence ratios (PR) estimated the association between comorbidity and small-area deprivation adjusted for other covariates (age, sex, area of residence, birthplace) using Poisson regression models with robust error variance. We compared sick leave utilization (over fourteen days) for any reason in the migraine-affected years among migraine patients with or without comorbidity.

Results: There were 372,926 migraine patients in the study, and 35.7% (n = 133,219) had comorbid depression or anxiety. There was higher comorbidity prevalence among migraine patients in the most versus the least deprived areas (PR: 1.18, 95% CI: 1.17–1.20). Although the data have limitations, we found that one-third (31.9%) of migraine patients took sick leave (over fourteen days) for any reason during the migraine-exposed years, which rose to 50.9% among migraine patients with comorbid depression or anxiety.

Conclusions: More than one-third of migraine patients had comorbid depression or anxiety with higher prevalence of comorbidity in the most deprived areas. Common comorbid depression or anxiety among migraine patients underscores the need to consider all three conditions in clinical encounters especially for residents of more deprived residential areas.

Keywords

migraine, depression, anxiety, residential deprivation, Sweden

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Introduction

Migraine, depression, and anxiety are considered highly disabling disorders that continue to be significant public health problems in Sweden and globally.[1,2] Each of these conditions not only impacts the person's health and well-being but may also result in income or productivity losses, sick leave and disruptions to social relationships.[3–5] Women and people with lower socio-economic status are disproportionately affected by migraine, depression and anxiety.[6,7]

Migraine, depression and anxiety also have a common comorbid presentation, which further worsens the affected person's health, well-being, and quality of life.[3–5] From a clinical perspective, comorbid presentation increases disease severity, worsens treatment outcomes, and further reduces the patient's overall quality of life and functioning.[8] The three conditions also share biological pathways and have known bidirectional relationships.[8,9]

Previous research on patterns and determinants of comorbid headache and psychiatric disorders have focused on individual-level risk factors such as age, sex and socio-economic status.[9–14] Yet the relationship between residential deprivation and comorbidity patterns among the three conditions is less understood, despite the well-established role of residential deprivation in contributing to poor health outcomes including for migraine, depression and anxiety.[15–20] Residential deprivation contributes to ill health through its links to stress, crime and violence, access to quality services, social cohesion, among other environmental factors.[15] It is therefore plausible that residential deprivation may exacerbate comorbidity across the three conditions although evidence of this outcome is limited.[21,22] One study from Scotland found that comorbid depression, anxiety and chronic migraine in the adult population was higher in more deprived areas,[21] but further evidence is limited including from Sweden and for younger age groups who may show different comorbidity patterns than adults.[21,22] To help fill this evidence gap, we aimed to examine the association between small-area deprivation and comorbid depression or anxiety among migraine patients aged ten years or older living in Sweden from 2015 to 2023.

Methods

Data sources

We conducted a register-based cross-sectional study based on multiple national and regional administrative registers that used the Swedish identification number unique to each resident to link individual information across data sources including: 1) the Total Population Register with data on population and household characteristics; 2) the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) with data on payments received from the Swedish Social Insurance Agency for certified sick leave taken from employment lasting more than fourteen days; 3) the National Prescribed Drug Register with data on prescription drugs dispensed at pharmacies; 4) the National Patient Register with data on the disorders and treatments managed through in-patient and specialized outpatient care; and 5) the Primary Healthcare Registers with data on the disorders and treatments managed through regional primary healthcare centers. All registers are mandatory and had national coverage across the study period except the primary healthcare registers that were available for 17 of 21 regions (89% of the Swedish population) from 2015 to 2017. The study received approval from the Ethical Review Authority in Sweden (2018/1339-31/5, 2018/2292-32, 2019-02185, 2021-00657, 2022-03111-02, 2023-07509-02, 2024-02816-02).

Study population

All persons registered in Sweden throughout the study period who had a personal identification number and primary address assigned to one of 5984 small geographical areas established by Statistics Sweden (DeSO) were identified (n = 8,728,980).[23] We excluded persons under ten years old on 31 December 2023 (n = 200,782) since migraine, depression and anxiety onset typically occurs in adolescence.[6] We further excluded persons without any migraine exposure (n = 8,148,827) and those under ten years old on the date of the first recorded migraine (n = 6445). The final study population included 372,926 migraine patients and each DeSO included between four and 153 participants (median: 68, IQR: 55-81) (Figure 1).

Migraine-exposed period

For each migraine patient, we defined a migraine-exposed period that started three months prior to the first recorded migraine date and ended three months after the last recorded migraine date during the study period. This was done such that each migraine-exposed person had a minimum exposure period of six months if there was only one date recorded for a migraine diagnosis or dispensed drug in the study period. The use of a migraine-exposed period to define comorbidity in our study that is based on data from healthcare and prescription registers is consistent with a disorder characterized by recurrent attacks in episodic or chronic form that frequently occur in the period between a medical visit or prescription fulfillment.[14]

Migraine exposure was defined as having a diagnosis in primary, specialist outpatient or inpatient care during the study period, or having been dispensed migraine drugs identified in the National Prescribed Drug Register. Online Supplementary Table S1 lists the diagnosis and prescription codes for migraine measurement based on the

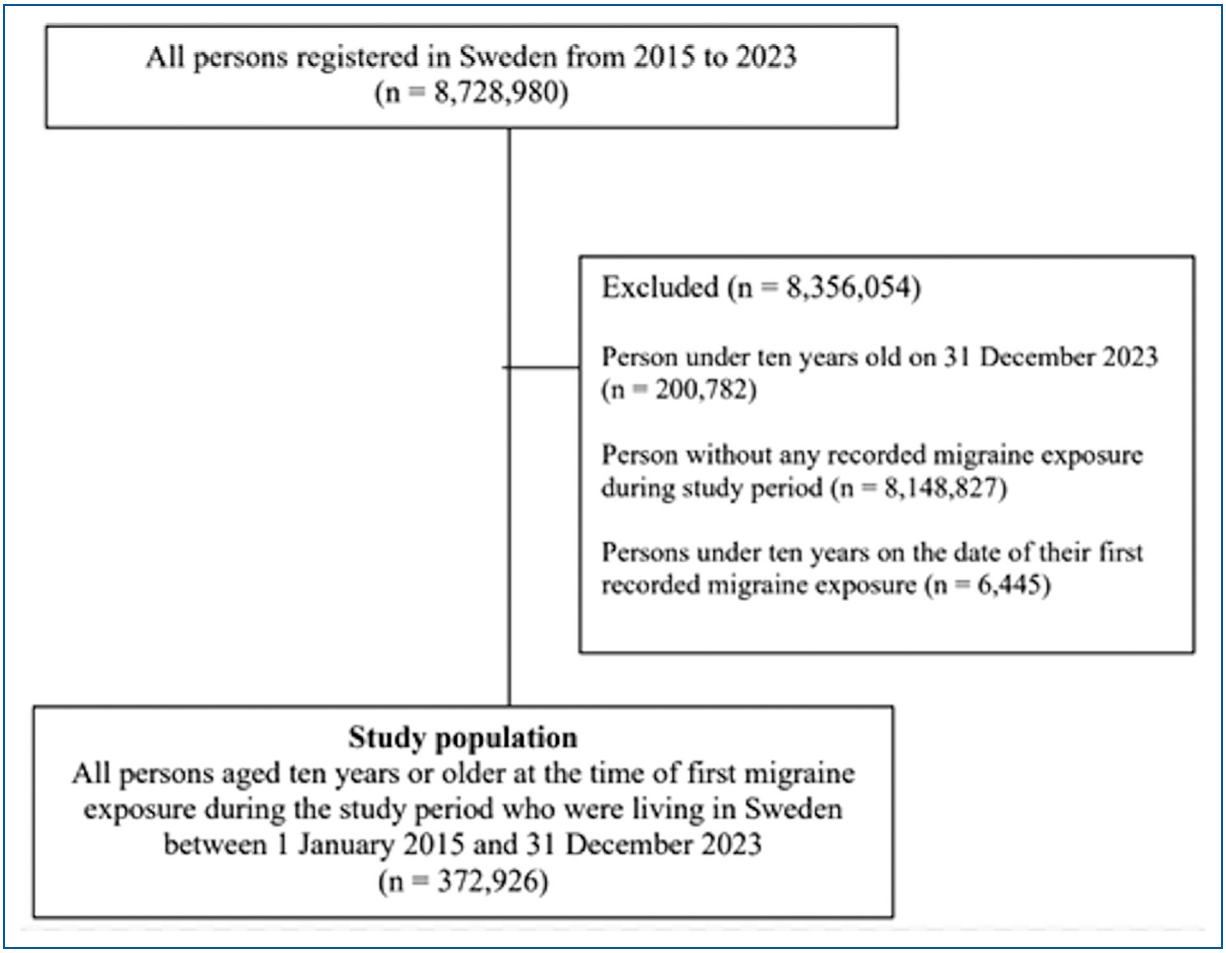

Figure 1. Flow diagram of inclusion criteria for the study population.

Swedish adaptation of the International Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10-SE) and the Anatomical Therapeutic Chemical (ATC) classification system, respectively. Migraine diagnoses were derived from any inpatient admission or specialist outpatient visit during the study period, and any primary care visit in 17 of 21 regions from 2015 to 2017 when data were available. If the diagnosis date was missing (day and month), we imputed the date using the earliest prescription date in the same visit year with the assumption that the prescription date was the same as the primary care visit date. If there was no prescription in that year, the midpoint date in that same year was used to impute the diagnosis date.

Comorbid depression or anxiety measurement

Comorbid depression or anxiety was defined as having at least one depression or anxiety diagnosis or prescribed antidepressant during the migraine-exposed period. Depression or anxiety was defined as a diagnosis in primary, specialist outpatient or inpatient care, or a dispensed drug for depression or anxiety if no diagnosis was recorded during the study period. Online Supplementary Table S2 lists the ICD-10-SE and ATC codes that measured the outcome in these registers. We considered depression or anxiety jointly for the outcome since medications could not be easily separated for the two conditions. Depression or anxiety diagnoses were derived from any inpatient admission or specialist outpatient visit in the study period, and any primary care visit in 17 of 21 regions from 2015 to 2017 when data were available. If the diagnosis date was missing (day and month), we imputed the date using the earliest prescription date in the same visit year with the assumption that the prescription date was the same as the primary care visit date. If there was no prescription in that year, the midpoint date of the visit year was used to impute the diagnosis date.

Small-area deprivation

The level of deprivation for each of the 5984 DeSO areas in our study was estimated using an Index for Multiple Deprivation in Sweden (IMDIS), which has been described elsewhere.[24] IMDIS is a composite deprivation index that

includes 15 indicators to measure four domains: 1) income and capital; 2) education; 3) employment; 4) housing. The IMDIS value for each DeSO area was ranked from least to most deprived and categorized into quartiles using the 25th, 50th, and 75th percentiles (very low, low, high, and very high deprivation levels). Each study participant was assigned the deprivation level for the DeSO where they lived based on their address in the Total Population Register in the year of their first migraine exposure. We assumed the deprivation level of each DeSO in the year 2015 remained unchanged throughout the study period. Recent research from Stockholm indicated that nearly 80% of neighborhoods had stable housing and socio-economic characteristics between 1990 and 2015.[25]

Other covariates

Region and area of residence (urban, peri-urban, rural) as defined by Statistics Sweden was derived from the person's DeSO code for the address where they lived in the year of their first migraine exposure.[18] Other regression covariates included sex (male or female), birthplace (Sweden, Nordic outside Sweden, European Union (EU28) outside Nordic, Europe outside EU28, or another birthplace), and age at first migraine exposure (10 to 19 years; 20 to 29 years; 30 to 39 years; 40 to 49 years; 50 to 59 years; 60 years or more).

Statistical analyses

We calculated the median migraine-exposed period (in days) and frequency of comorbid depression or anxiety among persons with migraine in our study population. To examine comorbid determinants, we initially evaluated the extent of variation in the outcome across small geographic areas using a random-intercept model with a DeSO identifier as the random intercept. A small proportion of variance in the outcome was attributed to differences between DeSO areas (intra-class correlation (ICC) = 0.006) suggesting that a standard regression model was suitable to estimate coefficients with 95% confidence intervals (CI). We used Poisson regression models with robust error variance to estimate prevalence ratios (PR) for the association between comorbidity, small-area deprivation level and other covariates (age, sex, area of residence, birthplace). Since the outcome is common, we used prevalence ratios to better approximate relative risk.[26] We initially estimated crude PRs for the association between comorbidity and each covariate and subsequently adjusted for all covariates simultaneously in the final model. Wald tests were used to determine if there was an interaction between small-area deprivation and each covariate on the comorbid outcome. The level of statistical significance was set to 0.05. We analyzed data using Stata 18.1 (Stata Corp., College Station, TX).

Sensitivity analyses

Two sensitivity analyses were conducted for this study. In the first analysis, the definition of comorbid depression or anxiety was restricted to diagnoses only, e.g., prescribed drug was not included in the definition, since some antidepressants may be used to treat other conditions including chronic pain. In the second analysis, migraine, depression and anxiety were measured without primary healthcare data since these data were not available throughout the study period or for all regions.

Sick leave utilization

We conducted a descriptive analysis of certified sick leave use (over fourteen days) among migraine patients with or without comorbid depression or anxiety, including by region and personal characteristics. Sick leave use was defined as any payment received from the Swedish Social Insurance Agency for certified sick leave taken from employment that lasted more than fourteen days and was taken in the year(s) of the person's migraine-exposed period. The medical diagnosis motivating the sick leave was not recorded in our dataset nor were the exact sick leave dates beyond the year(s) the sick leave was taken by the person.

Results

Among the 372,926 patients diagnosed or treated for migraine in our analysis, a total of 133,219 (35.7%) had comorbid depression or anxiety according to the study definition. The median migraine-exposed period was 482 days (IQR: 182–2132 days). Comorbidity was higher among migraine patients living in the most versus the least deprived areas (37.6% vs 32.8%), women versus men (39.5% vs 24.5%), age group 40–49 years versus 20–29 years (43.1% vs 17.0%), and for those born within Europe (outside the European Union) compared to native-born Swedes (38.1% vs 35.9%) (Table 1).

Associations with comorbid depression or anxiety

All covariates were significantly associated with comorbid depression or anxiety among migraine patients after adjustment (Table 2). For small-area deprivation, compared to migraine patients in the least deprived areas, there was higher prevalence of comorbid depression or anxiety among migraine patients in very high (PR: 1.18, 95% CI: 1.17–1.20), high (PR: 1.14, 95% CI: 1.13–1.16) and low (PR: 1.09, 95% CI: 1.08–1.10) deprivation areas. Similarly, urban (PR: 1.03, 95% CI: 1.02–1.04) and peri-urban (PR: 1.03, 95% CI: 1.01–1.05) residents with migraine had increased comorbid prevalence than their rural counterparts. Women with migraine had 55% higher prevalence of

Table 1. Characteristics of migraine patients with or without comorbid depression or anxiety.

	Migraine patients	Migraine with comorbid depression or anxiety		Migraine-exposed period (days)	
	N	N	%	Median	IQR
Total	372 926	133 219	35.7	482	182–2 132
Small-area deprivation level					
Very low deprivation	98 849	32 391	32.8	506	182–2 240
Low deprivation	96 916	34 594	35.7	504	182–2 199
High deprivation	91 080	33 833	37.2	489	182–2 144
Very high deprivation	86 081	32 401	37.6	423	182–1 939
Area of residence					
Urban	287 216	102 740	35.8	465	182–2 099
Peri-urban	31 675	11 370	35.9	517	182–2 171
Rural	54 035	19 109	35.4	537	182–2 283
Age at first migraine					
10 to 19 years	43 495	7 405	17.0	212	182–812
20 to 29 years	63 735	21 153	33.2	228	182–1 320
30 to 39 years	74 772	29 504	39.5	399	182–1 922
40 to 49 years	81 260	35 043	43.1	1 017	182–2 788
50 to 59 years	60 754	24 582	40.5	1 093	182–2 925
60 or more years	48 910	15 532	31.8	485	182–2 358
Sex					
Male	93 017	22 780	24.5	250	182–1 513
Female	279 909	110 439	39.5	578	182–2 309
Birthplace					
Sweden	307 234	110 153	35.9	506	182–2 201
Nordic not Sweden	6 913	2 573	37.2	722	182–2 580
EU28 not Nordic	10 365	3 628	35.0	408	182–1 981
Europe not EU28	10 810	4 118	38.1	328	182–1 816
Other birthplace	37 604	12 747	33.9	328	182–1 664

comorbid depression or anxiety than men (PR: 1.55, 95% CI: 1.53–1.56). Compared to migraine patients born outside Europe, there was higher comorbidity prevalence for all other groups including native-born Swedes (PR: 1.20, 95% CI: 1.18–1.22). Migraine patients in each older age group had higher prevalence of comorbid depression or anxiety than patients under 20 years.

Stratification by small-area deprivation

We found significant interaction terms for small-area deprivation level with age ($p < 0.001$), sex ($p < 0.001$), birthplace ($p < 0.001$) and area of residence ($p < 0.001$) on the comorbidity outcome. Specifically, the prevalence ratio of comorbid depression or anxiety among migraine patients associated with urban versus rural residence in the most deprived areas was 1.07 (95% CI: 1.03–1.11) while there was an opposite association in the least deprived areas (PR: 0.95, 95% CI: 0.92–0.98) (Table 3). There was also higher comorbidity prevalence for women versus men in the least deprived areas (PR: 1.62, 95% CI: 1.58–1.66) compared to the most deprived areas (PR: 1.48, 95% CI: 1.45–1.52). Similarly, in the most deprived areas, the prevalence of comorbid depression or anxiety among migraine patients associated with being a native-born Swede versus born outside Europe was 1.36 (95% CI: 1.33–1.39) while there was a non-significant association in least deprived areas (PR: 1.02, 95% CI: 0.98–1.05).

Sensitivity analysis

In the sensitivity analysis excluding primary healthcare data, 121,599 (32.6%) of migraine patients had comorbid depression or anxiety. There was no significant difference in adjusted coefficients compared to the main analysis (Online Supplementary Table S3). In the sensitivity analysis excluding prescribed drugs without a concurrent diagnosis, 57,839 (15.5%) of migraine patients had comorbid depression or anxiety. Compared to the main analysis, we found stronger relative associations between the comorbid outcome and small-area deprivation level, area of residence, and sex, while there was a weaker relative association between comorbidity and age at first migraine exposure (Online Supplementary Table S4).

Table 2. Association between small-area deprivation and other covariates on comorbid depression or anxiety among migraine patients.

	Crude				Adjusted			
	Prevalence ratio	95% CI		p-value	Prevalence ratio	95% CI		p-value
Small-area deprivation								
Very low deprivation	1.00				1.00			
Low deprivation	1.09	1.08	1.10	<0.001	1.09	1.08	1.10	<0.001
High deprivation	1.13	1.12	1.15	<0.001	1.14	1.13	1.16	<0.001
Very high deprivation	1.15	1.13	1.16	<0.001	1.18	1.17	1.20	<0.001
Area of residence								
Urban	1.01	1.00	1.02	0.071	1.03	1.02	1.04	<0.001
Peri-urban	1.02	1.00	1.03	0.116	1.03	1.01	1.05	0.001
Rural	1.00				1.00			
Age at first migraine								
10 to 19 years	1.00				1.00			
20 to 29 years	1.95	1.90	2.00	<0.001	1.84	1.79	1.88	<0.001
30 to 39 years	2.32	2.27	2.37	<0.001	2.24	2.19	2.29	<0.001
40 to 49 years	2.53	2.48	2.59	<0.001	2.45	2.40	2.50	<0.001
50 to 59 years	2.38	2.32	2.43	<0.001	2.31	2.25	2.36	<0.001
60 or more years	1.87	1.82	1.91	<0.001	1.81	1.77	1.86	<0.001
Sex								
Female	1.61	1.59	1.63	<0.001	1.55	1.53	1.56	<0.001
Male	1.00				1.00			
Birthplace								
Sweden	1.06	1.04	1.07	<0.001	1.20	1.18	1.22	<0.001
Nordic not Sweden	1.10	1.06	1.14	<0.001	1.16	1.12	1.19	<0.001
EU28 not Nordic	1.03	1.00	1.06	0.035	1.08	1.04	1.11	<0.001
Europe not EU28	1.12	1.09	1.16	<0.001	1.09	1.06	1.12	<0.001
Other birthplace	1.00				1.00			

Table 3. Association between risk factors and comorbid depression or anxiety among migraine patients stratified by small-area deprivation.

	Very low deprivation				Low deprivation				High deprivation				Very high deprivation			
	Adjusted				Adjusted				Adjusted				Adjusted			
	PR	95% CI		p-value	PR	95% CI		p-value	PR	95% CI		p-value	PR	95% CI		p-value
Area of residence																
Urban	0.95	0.92	0.98	0.004	1.00	0.98	1.02	0.831	1.08	1.05	1.10	<0.001	1.07	1.03	1.11	<0.001
Peri-urban	0.97	0.93	1.02	0.249	1.00	0.97	1.04	0.997	1.08	1.05	1.12	<0.001	1.01	0.97	1.06	0.543
Rural	1.00				1.00				1.00				1.00			
Age at first migraine																
10 to 19 years	1.00				1.00				1.00				1.00			
20 to 29 years	1.89	1.80	1.97	<0.001	1.85	1.76	1.93	<0.001	1.78	1.70	1.87	<0.001	1.88	1.79	1.97	<0.001
30 to 39 years	2.18	2.09	2.28	<0.001	2.27	2.17	2.38	<0.001	2.18	2.08	2.27	<0.001	2.35	2.24	2.47	<0.001
40 to 49 years	2.37	2.28	2.47	<0.001	2.43	2.32	2.54	<0.001	2.37	2.27	2.48	<0.001	2.68	2.55	2.81	<0.001
50 to 59 years	2.18	2.09	2.28	<0.001	2.25	2.15	2.36	<0.001	2.21	2.11	2.31	<0.001	2.66	2.54	2.80	<0.001
60 or more years	1.77	1.69	1.86	<0.001	1.77	1.68	1.86	<0.001	1.75	1.66	1.83	<0.001	2.00	1.90	2.11	<0.001
Sex																
Female	1.62	1.58	1.66	<0.001	1.56	1.52	1.60	<0.001	1.52	1.49	1.56	<0.001	1.48	1.45	1.52	<0.001
Male	1.00				1.00				1.00				1.00			
Birthplace																
Sweden	1.02	0.98	1.05	0.423	1.07	1.03	1.10	0.001	1.17	1.13	1.20	<0.001	1.36	1.33	1.39	<0.001
Nordic not Sweden	0.96	0.84	1.04	0.349	1.05	0.97	1.12	0.208	1.18	1.11	1.26	<0.001	1.22	1.14	1.29	<0.001
EU28 not Nordic	0.97	0.91	1.03	0.332	1.01	0.94	1.07	0.835	1.03	0.97	1.10	0.319	1.12	1.06	1.17	<0.001
Europe not EU28	1.00	0.93	1.08	0.951	1.00	0.93	1.07	0.928	1.08	1.02	1.14	0.010	1.15	1.10	1.19	<0.001
Other birthplace	1.00				1.00				1.00				1.00			

Sick leave utilization

While sick leave utilization data in our analysis has important limitations, we found that 31.9% of the 372,926 migraine patients took certified sick leave (over fourteen days) for any reason during the years of their migraine-exposed period. Among the subset of migraine patients with comorbid depression or anxiety, 50.9% took sick leave for any reason in the exposed years (Table 4). Among all migraine patients, a higher proportion took sick leave (over fourteen days) if they lived in the most versus least deprived areas (32.2% versus 29.3%), lived in rural versus urban areas (34.0% vs 31.3%), were female (35.1% vs 22.1%), or were 50–59 years versus 20–29 years (41.0% vs 33.2%). The proportion of migraine patients taking sick leave (over fourteen days) for any reason during the migraine-exposed years varied between 30.0% in Stockholm and 30.4% in Skåne to 34.3% in three regions (Södermanland, Örebro, and Västerbotten).

Discussion

Principle findings

In this nationwide register-based cross-sectional study, over one-third of migraine patients aged ten years or older had comorbid depression or anxiety with higher prevalence of comorbidity among patients living in more deprived areas, females, and older age groups. Findings suggest that comorbid depression or anxiety in migraine patients is common in our study population and reinforces the importance of considering all three conditions in clinical encounters, particularly in deprived residential areas where comorbidity occurrence is more frequent.

Comparisons with other studies

Numerous studies have reported increased rates of depression or anxiety among migraine patients although the magnitude of the comorbid occurrence has differed across analyses depending on the study context, population, data sources or measurement methods.[9,13,27] Across several population-based surveys, between approximately one-fifth and one-half of migraine patients reported comorbid depression, anxiety or other mental health condition,[5,10,12,27,28] including one study from Västerbotten (Sweden) where one-fifth of migraine patients reported any psychiatric disorder.[13] A recent analysis of Japanese insurance claims data showed that 10% of migraine patients had comorbid depression or anxiety,[4] which is a lower estimate that may be partly due to the focus on insured persons who sought care and received a diagnosis. In our study using health and prescription registers, one-third of migraine patients aged ten years or older had comorbid depression or anxiety, which is broadly consistent with prior estimates.

We further showed that the risk of comorbid depression or anxiety among migraine patients is higher among people living in more deprived areas, as well as for women, urban residents, older persons, and migraine patients born within Europe. Previous research has shown similar population patterns for comorbid depression or anxiety among migraine patients,[11,12,29] although our analysis is one of the first to examine this relationship by small-area deprivation.[21,22,30] One prior study from Scotland showed that migraine patients in more deprived areas had an increased risk of combined mental and physical conditions, including pain and depression.[22] This finding builds on other studies showing higher multimorbidity rates among residents of areas with greater deprivation.[21,30]

We also conducted stratified analyses by small-area deprivation level to examine variations in the associations of other factors on comorbid depression or anxiety among migraine patients. In this analysis, there was higher comorbidity prevalence among urban residents and older age groups in the most deprived versus the least deprived areas, while the opposite occurred for women. It could be that urban or older migraine patients in the most deprived areas are at higher risk of comorbid depression or anxiety than their counterparts in the least deprived areas potentially due to structural conditions of deprived areas (e.g., stress levels or worse healthcare accessibility).[15] Indeed, worse accessibility to specialized healthcare for migraine and mental health disorders in rural areas of Sweden is well-documented,[1,31] which could lead to further underdiagnosis especially in deprived and remote rural areas. In contrast, for women compared to men, higher comorbidity prevalence remained across deprivation levels but was reduced in the most deprived areas compared to other deprivation levels. The complicated inter-relationship between gender and occupation or socio-economic status on health outcomes has been reported in other research and should be further explored in relation to residential deprivation and comorbidity patterns for migraine, depression and anxiety.[32,33] These hypotheses merit further investigation to understand reasons for varying effects of risk factors for comorbid depression or anxiety in migraine patients across deprivation areas in our study.

Finally, we conducted a descriptive analysis of sick leave utilization for migraine patients with or without comorbidity based on available data. In our study nearly one-third of migraine patients took certified sick leave (over fourteen days) for any reason during the years of their migraine-exposed period, and this proportion rose to over half for migraine patients with comorbid depression or anxiety. Importantly, there are data limitations to consider in the interpretation of results. First, the diagnosis motivating the long-term sick leave is unknown and could be unrelated to migraine, depression, or anxiety (e.g., injury) leading to overestimation. At the same time, shorter sick leave periods are not captured in our dataset that are more common for

Table 4. Sick leave utilization (over fourteen days) for any reason in the affected years among migraine patients with or without comorbid depression or anxiety.

	All migraine patients			Migraine patients with comorbid depression or anxiety			Migraine patients without comorbid depression or anxiety		
	Total	Sick leave use		Total	Sick leave use		Total	Sick leave use	
	N	N	%	N	N	%	N	N	%
Total	372 926	118 903	31.9	133 219	67 850	50.9	239 707	51 053	21.3
Small-area deprivation									
Very low deprivation	98 849	28 915	29.3	32 391	16 299	50.3	66 458	12 616	19.0
Low deprivation	96 916	31 481	32.5	34 594	18 136	52.4	62 322	13 345	21.4
High deprivation	91 080	30 796	33.8	33 833	17 626	52.1	57 247	13 170	23.0
Very high deprivation	86 081	27 711	32.2	32 401	15 789	48.7	53 680	11 922	22.2
Area of residence									
Urban	287 216	89 912	31.3	102 740	51 665	50.3	184 476	38 247	20.7
Peri-urban	31 675	10 628	33.6	11 370	6 014	52.9	20 305	4 614	22.7
Rural	54 035	18 363	34.0	19 109	10 171	53.2	34 926	8 192	23.5
Age at first migraine									
10 to 19 years	43 495	1 451	3.3	7 405	815	11.0	36 090	636	1.8
20 to 29 years	63 735	21 151	33.2	21 153	11 007	52.0	42 582	10 144	23.8
30 to 39 years	74 772	31 125	41.6	29 504	18 076	61.3	45 268	13 049	28.8
40 to 49 years	81 260	34 150	42.0	35 043	21 163	60.4	46 217	12 987	28.1
50 to 59 years	60 754	24 926	41.0	24 582	13 911	56.6	36 172	11 015	30.5
60 years or older	48 910	6 100	12.5	15 532	2 878	18.5	33 378	3 222	9.7
Sex									
Male	93 017	20 568	22.1	22 780	9 726	42.7	70 237	10 842	15.4
Female	279 909	98 335	35.1	110 439	58 124	52.6	169 470	40 211	23.7
Birthplace									
Sweden	307 234	98 422	32.0	110 153	56 786	51.6	197 081	41 636	21.1
Nordic not Sweden	6 913	2 082	30.1	2 573	1 172	45.5	4 340	910	21.0
EU28 not Nordic	10 365	3 195	30.8	3 628	1 727	47.6	6 737	1 468	21.8
Europe not EU28	10 810	3 903	36.1	4 118	2 197	53.4	6 692	1 706	25.5
Other birthplace	37 604	11 301	30.1	12 747	5 968	46.8	24 857	5 333	21.5
Region of residence									
Stockholm	91 073	27 316	30.0	32 149	16 011	49.8	58 924	11 305	19.2
Uppsala	14 659	4 845	33.1	5 365	2 728	50.8	9 294	2 117	22.8
Södermanland	9 900	3 400	34.3	3 371	1 782	52.9	6 529	1 618	24.8
Östergötland	16 218	5 087	31.4	5 748	2 875	50.0	10 470	2 212	21.1
Jönkoping	13 012	4 362	33.5	4 688	2 476	52.8	8 324	1 886	22.7
Kronoberg	7 410	2 433	32.8	2 479	1 280	51.6	4 931	1 153	23.4
Kalmar	8502	2 620	30.8	2 871	1 402	48.8	5 631	1 218	21.6
Gotland	2 316	735	31.7	843	403	47.8	1 473	332	22.5
Blekinge	5 432	1 774	32.7	1 949	1 028	52.7	3 483	746	21.4
Skåne	48976	14 872	30.4	17 877	8 652	48.4	31 099	6 220	20.0
Halland	11 703	3 794	32.4	3 832	1 968	51.4	7 871	1 826	23.2
Västra götaland	62750	20 814	33.2	23 123	12 004	51.9	39 627	8 810	22.2
Värmland	9114	2 858	31.4	3 392	1 686	49.7	5 722	1 172	20.5
Örebro	10190	3 493	34.3	3 628	1 945	53.6	6 562	1 548	23.6
Västmanland	10376	3 394	32.7	3 762	1 922	51.1	6 614	1 472	22.3
Dalarna	10189	3 456	33.9	3 568	1 983	55.6	6 621	1 473	22.2
Gävleborg	9754	3 310	33.9	3 573	1 894	53.0	6 181	1 416	22.9
Västernorrland	9287	2 962	31.9	3 289	1 720	52.3	5 998	1 242	20.7
Jämtland	4446	1 474	33.2	1 566	833	53.2	2 880	641	22.3
Västerbotten	9431	3 238	34.3	3 355	1 765	52.6	6 076	1 473	24.2
Norrbotten	8188	2 666	32.6	2 811	1 493	53.1	5 377	1 173	21.8

migraine patients who typically experience acute migraine attacks. We therefore may additionally underestimate short-term work and productivity losses in our cohort given this issue.[4] Nevertheless, in this exploratory analysis of certified sick leave utilization (over fourteen days) for any reason in the migraine-exposed years, we described variations in

utilization within Sweden by region and personal characteristics based on data available and as potentially additional evidence of associated income or productivity losses.[34,35]

Methodological limitations

The main strength of this study is the linkage of multiple administrative registers, including primary healthcare data, to enable research on a national level. At the same time, there are several limitations to consider when interpreting results. First, the reliance on healthcare registers to capture people affected by migraine, depression or anxiety will undercount cases at a population level due to healthcare gaps for these patients in Sweden. In addition, a large proportion of cases were ascertained from prescription registers alone. We included only migraine drugs that did not have multiple indications, and the registers did not include over-the-counter drugs used in migraine, such as NSAIDs. In contrast, antidepressants may be prescribed for unrelated conditions, e.g., chronic pain, which could overestimate the rate of comorbidity with depression or anxiety found in our study. We aimed to address this issue in sensitivity analyses using diagnosed cases only. Nevertheless, depression or anxiety identification in the main analysis relied heavily on prescription data (35.7% vs 15.5%) that could misclassify individuals and thus overestimate comorbidity prevalence. It could also result in biased associations if people with migraine taking antidepressants for other conditions are systematically different from those diagnosed with depression or anxiety. Moreover, primary care registers were available for only 17 of 21 regions (89% of the Swedish population) in the years 2015 to 2017 further contributing to this underestimation that could bias associations if conditions are differentially diagnosed at primary versus specialist care for specific regions and population groups (e.g., adolescents versus older adults), or if milder cases commonly diagnosed in primary care visits are less likely to lead to comorbid depression or anxiety. Second, the analysis of sick leave use for migraine patients captured only sick leave taken for at least fourteen days that was certified and reimbursed by national authorities, which underestimates work and productivity losses in migraine patients who commonly require shorter sick leave periods.[14] Moreover, the diagnosis motivating sick leave was not recorded in our dataset, and the work absence may be unrelated to these conditions making it difficult to attribute the loss of workdays or productivity to migraine, depression or anxiety. Third, observational studies are prone to residual confounding that makes causal inferences difficult. Fourth, small-area deprivation has measurement challenges including defining areas or indicators, and composite indices could obscure differences in areas even within the same deprivation level. Fifth, small-area deprivation level for each DeSO was measured in 2015 and the quartile grouping was assumed to remain unchanged throughout the study period. This assumption could result in exposure misclassification given changes in neighborhood characteristics over time. A recent study showed stability in the housing and socio-economic characteristics of over 80% of Stockholm neighborhoods between 1990 and 2015.[25] Although this research does not cover all of Sweden or the most recent period from 2015 onwards, it does suggest that the vast majority of the nearly 6000 small geographic areas in our analysis could likely be classified into the same deprivation quartile over the study period. Finally, estimates were not adjusted for individual-level socio-economic characteristics (e.g., income or education) although the small-area deprivation measure assigns the area-level value to each individual residing in the area. While this could increase risks of ecological fallacy, interpretations of results have focused on associations between comorbid depression or anxiety and small-area deprivation levels.

Conclusions

Our nationwide register-based cross-sectional study showed that approximately one-third of migraine patients aged ten years or older in Sweden had comorbid depression or anxiety, with higher comorbidity prevalence among women, older age groups, and people with migraine living in more deprived areas. Common comorbid depression or anxiety in migraine patients reinforces the importance of considering all three conditions, especially in more deprived areas where comorbidity occurrence is more prevalent.

Article highlights

- 35.7% of migraine patients in Sweden in 2015–2017 had comorbid depression or anxiety.
- Prevalence of comorbidity was higher among migraine patients in the most versus least deprived areas (PR: 1.18, 95% CI: 1.17–1.20).
- Although data have limitations, 31.9% of migraine patients took sick leave (over fourteen days) for any reason during their migraine-exposed years, which rose to 50.9% for migraineurs with comorbid depression or anxiety.

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Ethical considerations

Ethical approvals for this study were received from the Swedish Ethical Review Authority (DNR: 2018/1339-31/5, 2018/2292-32, 2019-02185, 2021-00657 and 2022-03111-02, 2023-07509-02.2018/1339-31/5, 2018/2292-32, 2019-02185, 2021-00657, 2022-03111-02, 2023-07509-02, 2024-02816-02).

Author contributions

Concept and design: E.W.J., A.N.S., E.E.A., S.G. Additional input on design: all authors. Data acquisition, processing, and analysis: E.W.J., A.N.S., , M.M., E.E.A. Data interpretation: all authors. Statistical analysis: E.W.J., A.N.S., M.M., E.E.A. Drafting of the manuscript: E.W.J., A.N.S., E.E.A. Critical revision of the manuscript for important intellectual content: all authors. Accessed and verified the data and had responsibility for the integrity of the data and accuracy of the data analysis: E.W.J., A.N.S., M.M., E.E.A. Read and approved the final manuscript and had final responsibility for the decision to submit for publication: all authors.

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Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/. J.H. and S.G. are employees and stock owners at Pfizer. M.L. has received honoraria from Abbvie, Lundbeck, Novartis, Pfizer, TEVA, and holds a patent related to a biofeedback intervention for migraine prophylaxis, Coinventor. No other competing interests have been declared.

Data availability statement

Due to ethical restrictions, the individual level data used in this study are not publicly available. However, the data supporting the findings of this study can be obtained from Statistics Sweden (www.scb.se) and the Swedish National Board of Health and Welfare (www.socialstyrelsen.se).

Supplemental material

Supplemental material for this article is available online.

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