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The association between migraine and dementia — a national register-based matched cohort study

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Objectives: Migraine and dementia, two major public health challenges, are associated, but more knowledge is needed to understand their relationship. Objectives of this study were to investigate 1) the association between non—self-reported measures of migraine and dementia, and whether dementia was associated with 2) migraine without aura (MO) and with aura (MA) in combination with migraine medication use, and 3) migraine severity operationalized as the number of migraine prescriptions.

Study design: Matched cohort study.

Methods: National register data were obtained from individuals born between 1934 and 1958. Migraine cases (aged 25—58 years) were identified by migraine diagnoses and redeemed migraine medication. Migraine cases were matched with non-cases (N = 340,850) and date of diagnosis or medication redemption was defined as index year. Dementia was identified by dementia diagnoses and redeemed dementia medication.

Results: We observed a 1.46 (95% CI: 1.26—1.69) times higher dementia rate in individuals with a migraine diagnosis and a 0.86 (95% CI: 0.76—0.97) times lower rate when using migraine medication. We found the highest dementia rate among individuals with MA, who also used migraine medication (HR = 2.23; 95% CI: 1.19—4.17), and the lowest rate among individuals with MO, who also used medication (HR = 1.25; 95% CI: 0.75—2.10). The number of migraine medication prescriptions was not associated with dementia.

Conclusions: Being registered with a migraine diagnosis was associated with a higher dementia rate, while use of prescribed migraine medication was not. The differences in the dementia rate among migraine cases identified via diagnoses versus medications warrants further investigation.

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Introduction

Migraine and dementia are prevalent neurological disorders and leading causes of disability. Several pathophysiological links between migraine and dementia are suggested, including white matter hyperintensities, increased cortisol levels, deficits in nerve growth factors or neurotrophins, changes in amyloid plaque formation, infarct-like lesions, inflammation, cardiovascular disease (CVD), and volumetric changes in white and grey matter. Still, the exact mechanisms are not well-established. Previous studies reported higher dementia risk in self-reported migraine or diagnosed migraine, and one study found no risk in self-reported migraine. A recent meta-analysis included all the mentioned studies on self-reported and diagnosed migraine, except one, and found a higher all-cause dementia risk.
In Danish national data, a 50% higher dementia rate was found among individuals registered with migraine diagnosis in a hospital setting. Hospital-based diagnoses may, however, only capture severe cases. In Denmark, most migraine cases are managed as outpatients and only 17% are registered in hospitals. In addition, international recommendations suggest that non-specialist healthcare providers in primary care could meet 90% of individuals’ needs when seeking headache treatment. Thus, most migraine cases are likely treated in primary care and cannot be identified through hospital-based registers. Instead, redeemed migraine medication data can be used to obtain an objective measure of migraine cases treated outside the hospital sector, e.g., in general practice or by neurologists working in primary care.

To add to the scientific evidence of the migraine—dementia association, the objectives of this study were to investigate 1) the association between migraine and dementia by using information on migraine diagnoses and extending these data with information on redeemed migraine medication to define migraine cases, and whether dementia was associated with 2) migraine without aura (MO) and with aura (MA) in combination with migraine medication use, and 3) migraine severity based on number of migraine medication prescriptions.

Methods

Study population and design

The starting point for this matched cohort study was all inhabitants in Denmark born 1934–1958 (n = 1,878,914). In this population, we identified individuals with migraine diagnoses from 1988 onwards, as this was the inception year of the International Classification of Headache Disorders. Specific migraine medication for acute migraine treatment became available in European countries from the 1990s, and information on redemption of prescribed acute migraine medication was included from 1995 when medication registration was initiated. As dementia is seldom in younger ages and validity of dementia diagnoses in younger patients is low, we considered individuals at dementia risk from age ≥60 years. Thus, from they turned 60 years, individuals were followed in registers until death, emigration, dementia, or end of follow-up in 2018, whichever occurred first (Fig. 1).

Of 1,878,914 individuals, we excluded individuals who died (n = 153,101), emigrated (n = 26,734), had dementia before age 60 years (n = 9,577), or missed data on country of birth (n = 365) or education (n = 127,997). Among all individuals eligible for inclusion, we sex- and age-matched one individual with migraine to five individuals without migraine. The included individuals were aged 28–58 years, when registered with migraine. Date of first migraine diagnosis or redemption of migraine medication was defined as index year for all six individuals in each matched set. After running the matching procedure, the population consisted of 396,765 individuals, yet, data were still missing on educational level (n = 6,891) and marital status (n = 49,024), because some information was not available for all years and individuals with missing information at this step were therefore deleted. The final study population consisted of 340,850 individuals.

All data were obtained with approval from Statistics Denmark and the Danish Health Data Authority.

Migraine

Migraine was defined as being registered for the first time with a 1) migraine diagnosis without any registered redeemed migraine medication prescription for acute migraine treatment, 2) redeemed migraine medication prescription for acute migraine treatment without a registered migraine diagnosis, or 3) migraine diagnosis and redeemed migraine medication prescription for acute migraine treatment registered at any time (Table 1). Migraine diagnoses were obtained from the Danish National Patient Register (NPR) and Danish Psychiatric Central Research Register (PCR), which include hospital-based diagnoses based on the 8th and 10th revision of the International Classification of Diseases (ICD). The first registered migraine diagnosis included a diagnosis of either: hemicrania ophthalmoplegica (ICD-8: 346.00), hemicrania alia definita (ICD-8: 346.08), hemicrania (ICD-8: 346.09), migraine (ICD-10: G43.0), MO (ICD-10: G43.0), MA (ICD-10: G43.1), status migrainosus (ICD-10: G43.2), complicated migraine (ICD-10: G43.3), other migraine (ICD-10: G43.8), or unspecified migraine (ICD-10: G43.9). Information on migraine medication was based on Anatomical Therapeutic Chemical (ATC) codes obtained from the Danish National Prescription Registry (DNPR) and included the first redeemed medication of either Triptans (ATC: N02CC) or Ergotamine (ATC: N02CA).

Dementia

We defined all-cause dementia as the first registration with a dementia diagnosis or first redeemed antidementia medication. Dementia diagnoses were obtained from the NPR, PCR, and

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Fig. 1. Study design illustrated by six examples of individuals belonging to different birth cohorts.
Table 1
Operationalization of the three different migraine exposures.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Migraine operationalization</th>
<th>Migraine variable categorization</th>
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| To investigate differences in dementia risk among individuals identified with migraine either by a registered migraine diagnosis, by a redeemed migraine medication, or both | Migraine cases based on either: first ever registered migraine diagnosis without a registered migraine medication prescription, first ever redemption of migraine medication without a migraine diagnosis, or registrations of both a migraine diagnosis and migraine medication at any time | 1) No migraine (reference)  
2) Any migraine diagnosis  
3) Any migraine medication  
4) Any migraine diagnosis and migraine medication |
| To investigate whether there were differences in dementia risk among individuals with MO and MA in combination with migraine medication | Migraine cases were defined by two variables:  
1) first ever registration with migraine without aura (MO) and any registered migraine medication afterwards, or first ever registration with MO without any registered migraine medication afterwards;  
2) first ever registration with migraine with aura (MA) and any registered migraine medication afterwards, or first ever registration with MA without any registered migraine medication afterwards. Individuals registered with both MA and MO were categorized as MA | 1) No migraine (reference)  
2) MO with migraine medication  
3) MO without migraine medication  
4) MA with migraine medication  
5) MA without migraine medication |
| To investigate whether the risk of dementia increased with migraine severity | Migraine severity was defined as the total number of redeemed prescriptions of migraine medication used for acute migraine treatment before the age of 59 | 1) 1 prescription (reference)  
2) 2 prescriptions  
3) 3 prescriptions  
4) ≥4 prescriptions |

Danish Register of Causes of Death (DAR) based on ICD codes of: unspecified dementia, Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia, and Lewy body dementia (Supplementary material). Based on ATC codes from the DNPR, data on first redeemed prescriptions of antidiementia medication included the cholinesterase-inhibitors Donepezil (ATC: N06DA02), Rivastigmine (ATC: N06DA03), and Galantamine (ATC: N06DA04), and the glutamate-receptor antagonist Memantine (ATC: N06DX01).

Covariates

We adjusted for covariates associated with migraine, dementia, and/or treatment-seeking behaviour, and other headache disorders and morbidities. We obtained this information one year before index year for all individuals to ensure that confounder information was obtained before migraine diagnosis or medication redemption. We obtained information on 1) sociodemographic factors: birthdate, sex, country of origin (Denmark/Western countries/Non-Western countries), marital status (unmarried/married), and highest attained educational level (low educational level: primary school; medium educational: upper secondary education, business high school, and vocational education and training; high educational level: short-term further education, middle-range education, bachelor's degree, extended education, and research degree); 2) headache diagnoses: cephalalgia, other headache syndromes, cluster headache syndrome, vascular headache, tension-type headache, chronic post-traumatic headache, drug-induced headache, and other specified headache syndromes; 3) diagnoses of previous head injuries; 4) psychiatric diagnoses: schizophrenia, schizotypal and delusional disorders, mood affective disorders, psychoses, neuroses, and transient situational disturbances from NPR and PCR; and 5) morbidities registered in NPR and PCR potentially associated with migraine and dementia by using morbidities defined in the Charlson Comorbidity Index (CCI), myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, renal disease, cancer, metastatic cancer, severe liver disease, and human immunodeficiency virus (Supplementary material).

Statistical analyses

We analysed the distribution of covariates among individuals with and without migraine (Table 2). The association between migraine and dementia was investigated using a Cox regression model and estimated hazard ratios (HRs) of dementia with time since age 60 years as time scale (Table 3). As the probability of exposure misclassification may differ between birth cohorts, and we included individuals born from a wide range of years, all analyses were stratified on birth cohort to ensure comparisons were made among individuals with the same exposure misclassification probability. We adjusted for confounding in two steps: Model 1 included sex; Model 2 included sex, country of origin, marital status, educational level, headache, head injuries, psychiatric morbidities, and CCI. In sensitivity analyses, we postponed start of follow-up 5, 10, 15, and 20 years after index year to reduce reverse causation, i.e., that migraine reflected prodromal dementia. We also investigated the associations of dementia with MO with or without migraine medication and MA with or without migraine medication (Table 3). Finally, we investigated dementia risk related to migraine severity operationalized as total number of redeemed migraine medication prescriptions (Table 4).

We tested the hazard proportionality by using a Cox model including covariates of Model 2 and tested significance of a time-dependent interaction between time and covariates. For all analyses, we used SAS Enterprise Guide version 7.11 and a 5% significance level. Data underlying this article cannot by law be shared publicly, but accessed by employees at Danish research institutions after application to Statistics Denmark.

Results

We identified 59,436 (17%) migraine cases aged 28–58 years in a national sample of 1,878,914 individuals. Of these, 8,800 individuals were identified based on migraine diagnoses, 45,342 on use of redeemed migraine medication, and 5,294 had a migraine diagnosis and redeemed migraine medication at the same registration date (Table 2). Among migraine cases, 537 had dementia at a median age of 67 years, and among individuals without migraine, 2,345 individuals had dementia at a median age of 67 years. Most
dementia cases were registered in national hospital patient data (92%), followed by prescription data (7%), and mortality data (1%). Migraine cases with a hospital-based diagnosis had a dementia rate of 1.46 (95% CI: 1.26–1.69). Migraine cases identified based on their use of medication had a dementia rate of 0.86 (95% CI: 0.76–0.97). Individuals with a concurrent migraine diagnosis and use of migraine medication had a statistically non-significant dementia rate of 1.28 (95% CI: 0.95–1.72).

Among individuals with MO and redeemed migraine medication, the dementia rate was 1.25 (95% CI: 0.75–2.10) and 1.35 (95% CI: 0.93–1.94) when not having redeemed migraine medication. Individuals with MA and redeemed migraine medication had a dementia rate of 2.23 (95% CI: 1.19–4.17) and a rate of 1.64 (95% CI: 1.09–2.46) when not having redeemed migraine medication (Table 3).

We did not find a convincing dose–response relationship between number of redeemed migraine medication prescriptions and dementia rate (Table 4). Our sensitivity analyses showed that the direction and rate of dementia was unchanged among individuals registered with migraine diagnoses, migraine medication, or both with a time interval of 5–20 years between migraine registration and start of follow-up. Furthermore, the proportional hazards assumption could not be rejected meaning that the overall
dementia rate for migraine cases did not vary significantly with time after age 60 years.

Discussion

Main results

In this national register-based matched cohort study, we found 1) a higher dementia rate among individuals with a hospital-based migraine diagnosis (no redeemed medication prescriptions) and a lower dementia rate among individuals only registered as having redeemed prescribed migraine medication (no hospital-based diagnosis); 2) a higher dementia rate in individuals with MA with and without medication use; and 3) no association between number of redeemed migraine medication prescriptions and dementia rate. Adjusting for confounding or including longer time intervals between registration of migraine and dementia did not change direction and magnitude of the observed associations.

Comparison with previous research

To the best of our knowledge, this is the first study including migraine cases based on both hospital diagnoses and redeemed medication to obtain register-based information about severe and less severe migraine cases. Our results are in accordance with previous studies finding a higher dementia risk in self-reported migraine and diagnosed migraine. In the previous study using Danish data, an association was observed between hospital-based migraine diagnoses and dementia risk, and in the present study, we extend these findings by adding information about migraine medication redemption. Our results are supported by several pathological mechanisms suggesting a link between migraine and dementia, most markedly for MA. A recent meta-analysis of nine (two case–control and seven cohort) studies reported a 33% higher dementia risk in individuals with migraine. Earlier studies showed a three to four times higher risk of all-cause and vascular dementia specifically in individuals with self-reported migraine. One explanation of the higher effect sizes in self-reports (compared with our findings) could be differential recall of migraine history, particularly if individuals at a mean age of 75 years already had memory issues at the time of data collection. Some studies collected information on both migraine and dementia when participants were above age 60 years, which increase the reverse causation risk and confounding due to CVD leading to an overestimation of the migraine–dementia association. Other studies reported comparable or lower dementia risks in diagnosed migraine. However, if severe tension-type headache is misclassified as migraine, this may influence the observed association, as tension-type headache is also associated with dementia. Furthermore, too short follow-up time may yield an underestimation of dementia incidence, as it often develops over decades. This may explain why some studies did not report a higher risk of cognitive decline or dementia in self-reported migraine.

One explanation for the higher dementia rate in those registered only with a migraine diagnosis, but a lower rate in those only registered with migraine medications could be that those using medications may reflect a patient group with well-managed and/or less severe migraine. Also, those only with migraine diagnoses may be patients with contraindications for migraine treatment, e.g., CVD. Thus, these patients may have an increased dementia risk because of other reasons. Another explanation is that individuals redeeming medication only 1–2 times may not represent actual migraine cases. Because migraine can remit over time, using only one and first registration of either diagnosis or medication may not necessarily reflect recurring migraine attacks.

Apart from reflecting a potential effect of migraine itself (due to increasing severity), one could also speculate whether a higher dementia risk in individuals with several prescriptions could reflect adverse migraine side-effects. Current evidence does not suggest a significant association between the most frequently used migraine medication, triptans, CVD events, and dementia, whereas some studies found that the migraine medication, Ergotamine, is associated with ischemic complications. Nevertheless, despite that cardiovascular and cerebrovascular mechanisms play a role in dementia aetiology, our data did not provide any substantial support for the hypothesis of a higher dementia risk in individuals with more redeemed prescriptions. Non-steroidal anti-inflammatory drugs (NSAID) are also used for migraine treatment, but evidence regarding its association with dementia shows mixed results. We did not have available information on NSAIDs in this study, as these are over-the-counter medications, which are not registered in DNPR.

Strengths and limitations

The use of national registers to investigate the association of migraine based on both diagnoses and medication with dementia risk is novel. We increased validity of our exposure measures by using register data on migraine diagnoses, including redeemed medication from 1995. Dementia data consisted of valid, clinical diagnoses from hospitals, or dementia prescriptions. The risk of loss to follow-up was low because individuals were followed in national registers. Furthermore, the large study population enabled a 1:5 exposure-matching procedure and, thereby, reasonable statistical power. We ensured that information on covariates, including comorbidities, was obtained before migraine registration for them to be considered as confounders. In our register data, we did not, however, have access to information on health behaviour (e.g., smoking, physical activity, dietary habits), which could therefore not be controlled for. Migraine severity was explored by using number of prescriptions, which has not been investigated before. To reduce reverse causation risk, we only included migraine cases below age 59 years and dementia cases above age 60 years. Thus, we strictly separated the timing of a migraine diagnosis/prescription from the timing of a dementia diagnosis/prescription, and we also included longer time intervals between migraine and dementia in sensitivity analyses.

Current evidence gives no clear indications of treating mild cognitive impairment (MCI) with antidepressant medications as this treatment is possibly ineffective in reducing progression to dementia. However, as treatment choice is up to the individual physician, we cannot rule out that some patients treated with antidepressant medication had MCI rather than dementia, although we expect that this number is limited.

Expert recommendations state that general practitioners or neurologists in primary care should treat individuals with uncomplicated migraine and specialized neurologists in hospital-based centres should treat complicated migraine. This highlights the suggested differences between migraine cases who are in contact with primary health care, while cases diagnosed at hospitals apparently belong to a more severely affected patient group. Even though migraine medication can be prescribed by both general practitioners and at hospitals, we observed that 80% of the migraine cases were identified only via redeemed migraine medication. Thus, most migraine cases were not in contact with hospitals due to migraine, but were managed in primary healthcare. In this study, 48 individuals were simultaneously diagnosed with MO and MA showing that individuals may have mixed symptom emphasizing the complexity in diagnosing migraine. We included migraine patients based on the first registered migraine diagnosis. Yet, this only reflects the time of seeking hospital care.
contact. Consequently, age at migraine diagnosis may not reflect the actual age of migraine onset, but solely when the patient sought treatment, or when a specialist set the migraine diagnosis. In our study, 17% of the study population were registered with migraine. On a global level, the migraine prevalence has been estimated to 14%. Thus, our data corresponds to data from other studies, although migraine in general seems to be underdiagnosed. As regards to the outcome of this study, there are about 60% undiagnosed dementia cases in Denmark, thus, register data also underestimate the actual dementia incidence. The dementia incidence peaks at age 80–90 years, yet, in our study, the oldest individuals were followed up until age 74 years, and we cannot conclude on dementia risk beyond this age. In addition, being in frequent hospital contact due to migraine or other morbidities may increase the likelihood of being diagnosed with dementia as well and may have yielded an overestimation of the association between migraine diagnoses and dementia.

Conclusion

In conclusion, findings of our study support the notion that individuals with a migraine diagnosis are at higher risk of dementia than individuals without a migraine diagnosis. Furthermore, the findings reassure that most migraine cases, who are represented by individuals using migraine medication, but who do not have a hospital-based diagnosis, are not at higher risk of dementia than individuals without migraine. Further studies are needed to understand if the higher dementia risk in patients seeking hospital treatment can be prevented by improved migraine treatment, regular follow-ups, and management of migraine attacks to prevent or delay dementia onset. In addition, the mechanisms between MA, migraine medication and dementia need to be investigated further to elucidate the underlying pathology with the purpose of preventing dementia among individuals with severe migraine.

Author statements

Ethical approval

None needed.

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Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.09.018.

References


