Association between migraine and asthma: matched case-control study

Gail Davey, Philip Sedgwick, Will Maier, George Visick, David P Strachan and H Ross Anderson

SUMMARY

Background: *Earlier studies have suggested a link between asthma and severe headache, and also between migraine and wheezing illness. Recent analysis have also shown an increase of asthma among cases with a prior history of migraine but without a history of hay fever, allergic rhinitis or eczema.*

Aim: *To examine whether there is an association between migraine and asthma in the United Kingdom.*

Design of study: *Matched case-control study using the General Practice Research Database (GPRD).*

Setting: *Practices in the United Kingdom providing data on 5 110 619 patients to the GPRD.*

Method: *The subjects were the patients with one or more diagnoses of migraine plus treatment for migraine. Each case was matched by general practice, sex, and age, with one control who had never been given a diagnosis of migraine. Case and control groups were compared for prevalence of asthma, chronic obstructive pulmonary disease, respiratory symptoms treated with inhalers or hay fever. Investigations were carried out to determine whether the association between migraine and asthma was stronger among patients with hay fever or those without hay fever, and whether patients with migraine had an increased prescription of other (non-migraine and non-asthma) medications.*

Results: *Among 64 678 case-control pairs, the relative risk of asthma in patients with migraine was 1.59 (95% CI = 1.54 to 1.65) among definite cases, and 0.75 (95% CI = 0.67 to 0.83) among those whose selection as case included β-blocker prophylaxis. Among definite migraine cases, relative risks of chronic obstructive pulmonary disease, respiratory symptoms, eczema, and hay fever (pollinosis), were all raised (at 1.22, 1.85, 1.55, and 1.67, respectively). The association between migraine and asthma was stronger in patients without a diagnosis of hay fever, than in those with hay fever (relative risk = 1.32 and 1.19, respectively). The relative risk of prescription for a range of non-migraine, non-asthma medications was raised, the exception being anti-diabetic medication.*

Conclusion: *This large case-control study provides evidence for an association between migraine and asthma. Frequent attendance at a general practice surgery may confound this association. However, if the association is real, its elucidation may help the understanding of disease mechanisms shared by migraine and asthma.*

Keywords: *migraine; asthma; association; hay fever.*

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Introduction

MIGRAINE is characterised by severe headache accompanied by autonomic and neurological symptoms.[1] A range of underlying mechanisms for migraine have been postulated, including 'neurogenic inflammation',[2] defects in arachidonic acid[3] or serotonin[4] metabolism, cyclical changes in ovarian steroids concentrations,[5] food allergy,[6] and atopy.[7]

Asthma has been described as 'pulmonary migraine'[8] or 'acephalic migraine'.[9] Case reports and a few population-based studies have reported an association between migraine and asthma.[10,11] Observational evidence of intergenerational association has been found in hospital-based studies. Parental history of migraine was found to be more common among asthmatic children than among age and sex-matched controls in a small hospital-based study in Turkey (odds ratio [OR] = 5.5, 95% confidence interval [CI] = 1.3 to 25.0).[10] The United States Collaborative Perinatal Project found that asthma was more common in children of mothers with migraine than in those whose mothers were migraine-free.[11]

An early population-based cross-sectional study suggested an association between asthma and severe headache in men.[12] An association between migraine and wheezing illness was also found in a cross-sectional study of schoolchildren in the United Kingdom.[13]

More recently, analysis of a 1958 British birth cohort identified an increased incidence of asthma among subjects with a prior history of migraine at one or more follow-ups (at 7, 11, 16, 23 or 33 years).[14] This association was confined to subjects without a history of hay fever, allergic rhinitis or eczema ('non-atopics').

These results suggest a link between migraine (vascular reactivity) and asthma (bronchial reactivity) that is independent of allergic mechanisms. A shared functional abnormality of smooth muscle in blood vessels and airways offers a plausible explanation for this link.

This study sought to confirm an association between migraine and obstructive airways disease, by testing whether patients consulting with migraine had an increased prevalence of asthma, chronic obstructive pulmonary disease (COPD), respiratory symptoms treated with inhalers, or hay fever. Investigations were made to find whether the association between migraine and asthma was stronger among patients without hay fever than among those with hay fever, and whether patients with migraine had increased prescription of other (non-migraine and non-asthma) medications.

Method

A matched case-control study was designed using the

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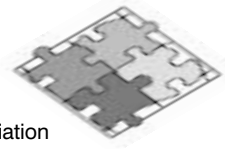

What do we know?

Case reports and a few population-based studies have reported an association between migraine and asthma

What does this paper add?

The association between migraine and asthma was confirmed in a very large case-control study. This association was stronger in patients without a diagnosis of hayfever, consistent with non-atopic mechanisms. However, there were also associations of migraine with other chronic diseases, suggesting that frequent attendance at a GP surgery may increase the probability that migraine is diagnosed.

General Practice Research Database (GPRD). The GPRD is a national database comprising anonymised medical records on about 6% of residents of England and Wales. Demographic, morbidity and prescription data are recorded by general practices and data quality has been established in previous studies.[15,16] Cases were permanently registered patients selected on the basis of migraine diagnosis and treatment at any time during the period of recording. Fourteen Oxford Medical Information System (OXMIS) diagnostic codes and three British National Formulary (BNF) medication codes were used to characterise migraine diagnosis and treatment, respectively (Boxes 1 and 2).

'Possible' migraine cases were those with one or more diagnoses but no prescriptions, or only one prescription, for migraine therapy. These 'possible' cases were excluded from further analysis. 'Definite' migraine cases were ascribed four categories:

OXMIS code	Diagnostic term	Percentage cases
3459M	Epilepsy migraine	0.02
346A	Migraine	91.67
346B	Migraine abdominal	1.16
346C	Migraine headache	3.60
346CL	Migraine classic	0.66
346CO	Migraine common	0.33
346D	Migraine visual disturbance	0.67
346E	Migrainous neuralgia	0.68
346EP	Paroxysmal migrainous neuralgia	0.12
346F	Migraine facial	0.19
346GB	Migraine basilar	0.12
346HT	Histamine headache	0.02
346PH	Ophthalmic migraine	0.15
3460MH	Migraine hemiplegic	0.60

Box 1. OXMIS codes used for assignment of first migraine diagnosis.

Category 1: one or more diagnoses with one or more prescriptions for migraine prophylaxis;
Category 2: one diagnosis with two or more prescriptions for acute migraine attack;
Category 3: two or more diagnoses with two or more prescriptions for acute migraine attack; and,
Category 4: patients prescribed β-blockers as prophylactic treatment because of the possibility that the treatment could induce asthma, or that β-blockers would be contraindicated in patients with a diagnosis of asthma.

The specificity of selection of migraine cases was confirmed by comparison with clinical review of the patient records of 100 randomly selected cases.

For each case, a control who had never had a diagnosis of migraine was matched by general practice, sex, and year of birth. Thirty-two cases could not be matched by exact year of birth and were subsequently matched within a ten-year age band. Asthma, chronic obstructive pulmonary disease, respiratory symptoms, and hay fever were defined according to combinations of OXMIS codes developed and validated earlier.[17] Disease outcome was defined in three ways: diagnosis alone, relevant therapy alone, and diagnosis plus relevant therapy. Statistical Analysis Software was used for data manipulation. For each disease outcome, the relative risk (RR) of migraine if the outcome was present to the risk of migraine if the outcome was absent was calculated as the ratio of discordant pairs (case affected, control unaffected:case unaffected, control affected). A 95% CI was calculated for each relative risk,[18] and differences between discordant pair ratios were tested for significance using 2 x 2 tables and a Yates' corrected χ^2 test.

Results

We identified a total of 64 678 potential cases (48 571 females and 16 107 males; ratio 3.02:1). Migraine diagnosis category is tabulated against year of birth among cases in Table 1.

Relative risks of a range of disease outcomes were calculated by category of migraine diagnosis. When calculating relative risk of asthma, *category 4* (β-blocker prophylaxis) was considered separately for the reasons given under the Method. Relative risk of asthma in those with a diagnosis of migraine was raised in categories *1, 2* and *3*, but not in *category 4*. The effect of restricting the analysis to case-control pairs followed up for a minimum of three years was checked to explore for possible diagnostic bias, but this had no material effect on the relative risk (Table 2). There was no significant variation in relative risk of asthma by age of the case-control pair for pairs born from 1941 onwards, but lower relative risks occurred in older age groups.

BNF code	Description	Therapy included (generic or proprietary name)
4.7.4.1	Treatment of acute migraine attack	Migraleve, Migravess, Paramax, Domperamol, dihydroergotamine mesylate, ergotamine tartrate, isometheprine mucate, naratriptan, rizatriptan, sumatriptan, zolmitriptan, tolfenamic acid
4.7.4.2	Prophylaxis of migraine	Pizotifen, clonidine hydrochloride, methysergide
2.4 (named in 4.7.4.2)	β-blockers for prophylaxis of migraine	Propranolol, metoprolol, nadolol, timolol

Box 2. British National Formulary codes used for assignment of migraine therapy.

Table 1. Frequencies of migraine diagnosis by category and year of birth.

Year of birth	Migraine diagnosis			
	Category 1 ≥1 diagnosis, ≥1 prophylaxis	Category 2 1 diagnosis, ≥2 therapies	Category 3 ≥ 2 diagnoses, ≥2 therapies	Category 4 ≥1 diagnosis, β-blocker
1891–1900	0	2	1	1
1901–1910	59	43	46	40
1911–1920	421	288	409	265
1921–1930	1079	736	1260	627
1931–1940	2173	1142	2615	1180
1941–1950	3687	1695	5710	2175
1951–1960	3292	1733	5515	2310
1961–1970	3444	1578	4844	2228
1971–1980	3730	1291	3401	1196
1981–1990	3012	310	885	208
1991–2000	44	0	1	2
Total (%)	20 941 (32.4)	8818 (13.6)	24 687 (38.2)	10 232 (15.8)

Table 2(a). Relative risk of asthma by migraine diagnosis category.

Migraine diagnosis category[a]	Asthma diagnosis by pair		Relative risk	95% CI
	Case — yes Control — no	Case — no Control — yes		
1 to 3	7300	4584	1.59	1.54 to 1.65
4	664	890	0.75	0.67 to 0.83

[a]See Table 1.

Table 2(b). Relative risk of asthma by migraine diagnosis category: restricted to pairs with three or more years of follow-up for both cases and controls.

Migraine diagnosis category[a]	Asthma diagnosis by pair		Relative risk	95% CI
	Case — yes Control — no	Case — no Control — yes		
1 to 3	5023	3263	1.54	1.47 to 1.61
4	452	574	0.79	0.70 to 0.89

[a]See Table 1.

For other conditions, migraine diagnosis categories 1 to 4 were combined. Relative risks of COPD, 'respiratory symptoms', eczema, and hay fever were raised significantly in all categories (Table 3).

In those who did not have a diagnosis of hay fever, the association between asthma and migraine was stronger (RR = 1.32, 95% CI = 1.28 to 1.37) than among those in the smaller group with a diagnosis of hay fever (RR = 1.19, 95% CI = 1.05 to 1.36), though this difference was not significant (χ^2 = 2.2, P = 0.14). These risks were not materially changed if diagnosis and relevant therapy were used as the outcome measure. The rates of prescription of several categories of non-migraine, non-asthma medication were compared between definite migraine cases and controls, to investigate the specificity of the relationship with asthma and the potential for diagnostic bias. The relative risk was raised for most medications except for anti-diabetic medication (Table 4).

Discussion

This large case-control study provides evidence for an association between migraine and asthma. A number of factors indicate that the raised relative risk of 1.59 represents a real association, but others suggest caution in attributing it to a causal relationship.

One major strength of the GPRD is its size, comprising data on over five million patients. This, together with the relatively high prevalence of migraine (such that we based the analysis on 64 678 case-control pairs), gave the study huge statistical power. Thus, the relative risk for the association between asthma and migraine could be calculated with precision. An important limitation, however, is the lack of information on potential confounding variables, such as socioeconomic status. Although some information on smoking habits is recorded by GPRD practices, this is known to be incomplete and was not available for our analysis. However, in the British birth cohort study, asthma and migraine were associated even after adjustment for a range of confounding variables, including social class and smoking habit.[14]

The female:male ratio (3:1) among migraine cases is consistent with those calculated in other studies and reviews.[1,19] Similarly, peak age prevalence between 30 and 50 years is

Table 3. Relative risk for COPD, respiratory symptoms and hay fever in patients with migraine compared with controls.

Condition	Diagnosis by pair		Relative risk	95% CI
	Case — yes Control — no	Case — no Control — yes		
COPD	1034	846	1.22	1.12 – 1.34
Respiratory symptoms	17 522	9481	1.85	1.80 – 1.89
Eczema	1024	661	1.55	1.41 – 1.71
Hay fever	8846	5285	1.67	1.62 – 1.73

Table 4. Relative risk for a range of prior prescriptions among migraine patients compared with controls.

Class of medication prescribed	Prescription by pair		Relative risk	95% CI
	Case — yes Control — no	Case — no Control — yes		
Anti-spasmodic	12 094	5095	2.37	2.30 – 2.45
Ulcer healing	11 988	5266	2.28	2.21 – 2.35
Diuretic	8023	4532	1.77	1.71 – 1.84
Antidepressant	18 226	6279	2.90	2.82 – 2.98
Antiepileptic	3012	1253	2.40	2.26 – 2.56
Antibacterial	13 435	4208	3.19	3.09 – 3.30
Antifungal	6580	3806	1.73	1.66 – 1.80
Antiviral	1476	921	1.60	1.48 – 1.74
Antidiabetic	1284	1370	0.94	0.87 – 1.01
Eczema	4167	2478	1.68	1.60 – 1.77
Acne/rosacea	4591	2739	1.68	1.60 – 1.76

consistent with that reported in other sources.[1,19] Both these observations indicate that the case definition used in this study has external validity. Finding a significantly reduced relative risk of asthma among migraine cases that were prescribed β-blocker prophylaxis, provides evidence for internal validity.

Certain findings shed doubt onto the specificity of the association between migraine and asthma. Relative risks of COPD, respiratory symptoms, hay fever and eczema were all raised among patients with migraine compared with those without. In a similar way, relative risks of prescription of a range of non-migraine, non-asthma medications were raised in patients with migraine compared with those without. These findings may be explained by postulating that patients with migraine attend their general practitioners more frequently than those without, making them more likely to be diagnosed with a range of conditions and more likely to be prescribed a range of medications. Frequent attendance would therefore act as a confounder in the migraine–asthma association.

We included two chronic conditions — epilepsy and diabetes — where patients might be expected to attend their doctor regularly regardless of personal and cultural determinants of consulting behaviour. Interestingly, no association with migraine was observed for diabetes, but there was an excess of antiepileptic medication prescribed to patients with migraine (Table 4). Prescriptions for carbamazepine are included in the latter group, and some of these may have been for trigeminal neuralgia, a condition which may sometimes be confused with migraine, and where the threshold of awareness and non-medical factors may influence the patient's consulting behaviour.

Differential attendance could explain the finding that the association between migraine and asthma was stronger in those without hay fever than those with hay fever. Patients with hay fever would be expected to be more frequent attenders than those without, thus the effect of migraine in increasing attendance (and hence likelihood of diagnosis with asthma) would be diminished in comparison with those without hay fever. On the other hand, the relative risk of migraine is lower among patients prescribed anti-diabetic medication (another group who would be expected to attend frequently), so frequent attendance may not entirely explain the association of migraine with other diseases and therapies. Furthermore, the finding is consistent with that in a British birth cohort,[14] where migraine, asthma and atopic diseases were ascertained by questionnaire, independent of consultation with a doctor.

An alternative explanation would be that migraine is more strongly associated with non-atopic asthma, which might also account for the raised risk of COPD in migraine patients. More detailed clinical and epidemiological studies of the association between migraine and asthma may aid the identification of shared disease mechanisms.

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