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Systematic review

Methods Development

Multiple sclerosis and fracture risk: traditional meta-analysis versus mega-analysis of individual patient data

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Abstract

Introduction

The aim of this systematic review was to evaluate the difference between a traditional meta-analysis and a mega-analysis of individual patient data when combining observational studies.

Materials and methods

We used data from two studies that evaluated the risk of fracture in patients with multiple sclerosis using the British General Practice Research Database and the Danish National Health Registries. The published results were pooled together in an inverse-variance fixed effect meta-analysis. Using patient level data, we made the study populations as comparable as possible regarding the index date, calendar time, selection of incident/prevalent patient and follow-up. The individual patient data of these populations were combined in a mega-analysis. Cox proportional hazards models were used to estimate hazard ratios (HRs) of fracture, adjusted for shared confounders.

Results

A traditional meta-analysis of the original studies resulted in pooled adjusted hazard ratios of 1.13 [95%CI 1.03–1.23] for any fracture, hazard ratio 1.22 [95%CI 1.07–1.41] for osteoporotic fracture, and hazard ratio 2.47 [95%CI 1.72–3.53] for hip fracture. The mega-analysis of individual patient data showed an adjusted hazard ratio of 1.20 [95%CI 1.12–1.28] for any fracture, hazard ratio 1.36 [95%CI 1.24–1.50] for osteoporotic fracture, and hazard ratio 3.27 [95%CI 2.65–4.04] for hip fracture. The traditional meta-analysis of the original studies showed significant heterogeneity, which disappeared in a meta-analysis that pooled the two more comparable studies together. This meta-analysis yielded similar results as the mega-analysis with individual patient data.

Conclusion

A crucial step in performing a multi-country study is to reduce the level of heterogeneity between studies as much as possible before combining the data.

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Introduction

Over the past years, an increasing number of multi-country studies have been performed in Europe. Different methods can be used to combine data from separate registries. The vast majority of published meta-analyses are based on aggregate patient data from completed studies[1]. Therefore, this type of meta-analysis can be done relatively quickly and easily. However, a 'mega-analysis' that combines individual patient data from various data sources has many theoretical advantages compared to a traditional meta-analysis, such as the ability to use common definitions, to explore heterogeneity at a patient level and to perform subgroup analyses of patient level data[1,2]. To date, studies that compare the two methods with actual patient data are scarce.

The objective of the present study was to combine the results of two observational studies in (1) a traditional meta-analysis, by pooling the estimated risks from the published papers together, and (2) a mega-analysis of individual patient data, by using common definitions, selecting study populations with comparable patient characteristics and adjusting for the same set of confounders.

Materials and methods

Data sources

We used data from two published articles that evaluated the risk of fracture in patients with multiple sclerosis (MS) using the British General Practice Research Database (GPRD), currently known as the Clinical Practice Research Datalink, and the Danish National Health Registries[3,4].

The GPRD comprises computerised medical records for over 10 million patients under the care of general practitioners (GPs) in the UK. The data recorded in the GPRD since 1987 include demographic information, prescription details, clinical events, hospital admissions and their major outcomes. A recent review of all validation studies found that medical data in the GPRD were generally

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of high quality[5]. The GPRD comprises a dynamic study population, where both patients and practices can enter and leave the database over calendar time. From the GPRD, we selected all patients with a record of MS between January 1987 and August 2009. GPRD data were linked to the national Hospital Episode Statistics (HES) for approximately 45% of all practices. We had access to HES data between April 1997 and March 2008.

In Denmark, separate registries of computerised medical records on all contacts to hospitals and on the use of drugs can be linked for the entire population and patients are followed from birth until death. Information on hospital admissions comes from the National Hospital Discharge Register[6], which covers all inpatient contacts from 1977 onwards and from 1995 also all outpatient visits to hospitals, outpatient clinics, and accident and emergency rooms. In general, the validity of registrations is high[7]. The Danish Medicines Agency keeps a nation-wide register of all prescription drugs sold at pharmacies throughout the country from 1996 onwards[8]. For our data set, the end of data collection for all hospital and pharmacy records was December 2007. These data were linked to the Danish Multiple Sclerosis Registry (DMSR), a nation-wide database covering approximately 90% of all patients with MS, which started operating in 1949[9]. Patients' records are reviewed by a neurologist and classified according to their expertise[10]. The DMSR provided us with data until December 2007.

Study populations

Original studies

The GPRD study included all patients aged 18 years or older with at least one recorded diagnosis of MS during the period of GPRD or HES data collection (1987–2009)[3]. Patients with a history of MS before the start of data collection were excluded. The index date was defined as the date of the first record of MS after starting the valid data collection. Due to the dynamic character of the GPRD, the study population captured a case-mix of incident and prevalent MS patients, reflected in a mean age of 44.9 years at index date[3].

In Denmark, we had information about all patients (aged 18+) with an accepted diagnosis of MS in the DMSR between 1 January 1949 and 31 December 2007. To capture information on both fractures that were treated in an inpatient setting (recorded from 1977) as well as fractures that were treated in an outpatient setting (recorded from 1995), the beginning of the follow-up was from 1 January 1996. In the original study, incident MS patients were studied from the disease onset: the index date was defined as the 31st December of the year of the first symptom of the disease[4].

All MS patients (from the GPRD and the Danish registries) were matched to six control individuals. For the GPRD, patients were matched by year of birth, sex, and practice; in Denmark they were matched by year of birth, sex, and region. In both registries, control persons were assigned the same index date as their matched MS patient. MS patients and controls were followed from their index date to the end of data collection, emigration, the date of transfer of the patient out of the practice area, or the patient's death.

Adjusted study populations

Using the individual patient data, we made the study populations from the GPRD and from Denmark as comparable as possible in terms of patient characteristics and definitions, as follows:

- Index date: instead of following patients in the Danish population from the year of the first symptom of the disease, we now followed patients from the year of diagnosis because the first record of MS in the GPRD was probably closer to the time of diagnosis than to the time of the first symptom. We defined the index date as 31st December of the year of diagnosis in Denmark.
- Calendar time: we defined the start of the follow-up as 1 January 1996 in both the databases. In the GPRD study, this meant restricting the study population to those patients with a first MS record after 1 January 1996. In the Danish study, this meant selecting those patients with an MS diagnosis after 1 January 1996.
- Selection of incident/prevalent MS patients: because the GPRD population captured a case-mix between incident and prevalent patients (reflected in a mean age of 44.9 years at index date), we similarly created a case-mix of incident and prevalent patients in the Danish population. This was done by adding prevalent patients to the study who were diagnosed from 1 January 1972 onwards; all patients were followed from 1 January 1996. The incident and prevalent patients together had a mean age at index date of 44.9 years (the same as in GPRD). The distribution of ages at the index date was also similar between these case-mix populations: the 10th percentiles of ages in GPRD were [18, 28, 33, 37, 40, 44, 47, 51, 56, 62, 95] and in Denmark they were [18, 29, 34, 38, 41, 45, 48, 51, 55, 61, 86].
- Duration of follow-up: because the mean duration of follow-up was longer in the Danish registries than in GPRD, we cut off the follow-up time for patients in Denmark to a maximum time period of 5.7 years. This resulted in a mean duration of follow-up of 4.7 years in both groups of patients.

Outcome

In both the registries, the study outcome was the first fracture after the index date. The types of fracture were classified according to the In-

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ternational Classification of Diseases (ICD-10) categories. For any fracture we included S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, and T12. An osteoporotic fracture was defined as a fracture of the radius/ulna, humerus, rib, femur, hip, pelvis, or vertebrae. In both databases, the total follow-up period was divided into 30-day intervals. The presence of risk factors was assessed by reviewing the computerised medical records for any evidence of risk factors before the start of an interval. Potential confounders have been previously listed[3,4].

Statistical analysis

We provided baseline characteristics of MS patients from the original study populations. In the original studies, Cox proportional hazards models had been used to provide an estimate of the relative risk (hazard ratio [HR]) of fracture among MS patients, adjusted for any potential confounders that changed the HR > 1% in an age-/sex-adjusted analysis. We conducted an inverse-variance fixed effect meta-analysis of these two original studies. In this analysis, the overall log HR is simply a weighted average of the individual log HRs, with the weights inversely proportional to the variance of the log HR of each study[11]. The crude and adjusted HRs were pooled for any, osteoporotic and hip fracture.

We then provided baseline characteristics of MS patients and controls from the more comparable study populations. Cox proportional hazards models were used to estimate HRs of fracture among these groups of patients (first, separately for GPRD and Denmark). A minimal confounder set was used for every fracture type, including risk factors that were present both in the GPRD as well as in the Danish registries. We combined the individual patient data of these more comparable populations in a mega-analysis. Fracture risks were estimated using Cox models. We adjusted the HRs for confounders that were present in both registries, and for a binary variable indicating the data source (i.e. GPRD or the Danish registries). In addition, we conducted an inverse-variance fixed effect meta-analysis of the two more comparable populations. All statistical analyses were conducted using SAS ® 9.1/9.2 and Review Manager ® 5.1 software.

Results

Baseline characteristics of the original study populations from the GPRD and the Danish registries are presented in Table 1. The study population from the GPRD consisted of 5565 MS patients and 33,360 population-based controls. For these patients, the mean age at index date was 44.8 years and the mean duration of follow-up was 5.7 years. In Denmark, there were 2963 MS patients and 15,436 controls. Their mean age at index date was 36.9 years, and patients were on average followed longer than in GPRD with a mean duration of 7.2 years.

In the original GPRD study, there was a 1.2-fold increased risk of any fracture (adj. HR 1.23 [95%CI 1.09–1.38]) and an almost 3-fold increased risk of hip fracture (adj. HR 2.79 [1.83–4.26]) (Table 2). In the Danish study, there was no overall increased fracture risk (adj. HR 1.01 [0.89–1.15]) and the risk of hip fracture was not statistically significantly increased (adj. HR 1.81 [0.93–3.54]).

A traditional meta-analysis of the two original studies showed significant heterogeneity for any and osteoporotic fracture (Table 3). The pooled adjusted HRs were 1.13 [1.03–1.23] for any fracture, HR 1.22 [1.07–1.41] for osteoporotic fracture, and HR 2.47 [1.72–3.53] for hip fracture.

Table 1 Baseline characteristics of MS patients and controls from the original studies

	GPRD		Denmark	
	MS patients	Controls	MS patients	Controls
Characteristic	*n* = 5565	*n* = 33,360	*n* = 2963	*n* = 15,436
Mean duration of follow-up after index date, yrs	5.7	6.0	7.2	7.2
Sex female	70.0%	70.0%	66.5%	65.8%
Mean age at index date	44.8	44.7	36.9	37.1
Body mass index				
<20	8.0%	5.9%	–	–
20–25	34.6%	34.1%	–	–
25–30	23.7%	26.4%	–	–
>30	16.0%	16.4%	–	–
Unknown	17.8%	17.2%	–	–
Smoking				
Never	38.4%	45.5%	–	–
Current	27.7%	21.5%	–	–
Ex	14.6%	12.9%	–	–
Unknown	19.3%	20.2%	–	–

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Table 1 (Continued)				
Comorbidity ever before				
Fracture	14.9%	13.5%	14.5%	14.8%
Congestive heart failure	0.6%	0.5%	0.1%	0.1%
Rheumatoid arthritis	0.6%	0.7%	0.3%	0.3%
Renal disease	0.1%	0.2%	0.0%	0.1%
Cerebrovascular disease	2.8%	1.2%	2.6%	0.8%
Inflammatory bowel disease	0.8%	0.6%	1.1%	1.0%
Epilepsy	2.4%	1.3%	1.8%	1.4%
Falling	6.5%	3.0%	–	–
Fatigue	7.9%	5.3%	–	–
Spasticity	1.9%	0.5%	–	–
Disability	15.4%	9.6%	–	–
Drug use 6 months before				
Statins	4.3%	3.3%	0.9%	0.7%
Antiarrythmics	0.3%	0.2%	0.1%	0.0%
Antidiabetics	2.1%	1.9%	1.4%	1.0%
Antidepressants	18.0%	8.4%	7.0%	3.8%
Antipsychotics	1.4%	0.9%	2.1%	1.3%
Anxiolytics/hypnotics	8.5%	4.1%	9.5%	5.2%
Anticonvulsants	6.9%	1.3%	3.1%	1.1%
Opioids	3.0%	1.0%	5.5%	2.6%
Oral/iv glucocorticoids	5.9%	1.6%	3.6%	1.4%
Bisphosphonates	0.8%	0.5%	0.1%	0.1%
HRT	2.6%	2.8%	1.5%	1.6%
Calcium	0.2%	0.2%	0.1%	0.1%
Vitamin D	0.9%	0.6%	0.0%	0.0%

Table 4 shows the baseline characteristics of the adjusted study populations. In both the GPRD and the Danish population, MS patients were on average 44.9 years old at the index date and they had a mean duration of follow-up of 4.7 years. Patient characteristics were comparable between the original and the adjusted GPRD population. In the adjusted Danish population, MS patients were on average older than in the original study (44.9 years *vs* 36.9 years), and they had used more antidepressants, hypnotics/anxiolytics and anticonvulsants at baseline (12.2%, 21.9% and 7.5% *vs* 7.0%, 9.5% and 3.1%, respectively).

The changes that were made to make the two populations more comparable resulted in comparable fracture risks for the GPRD study and in greater fracture risks for the Danish study (Table 5). For GPRD, the fully adjusted HR for hip fracture changed from 2.79 [1.83–4.26] to 2.70 [1.60–4.56]. In the original Danish study, the risks of any, osteoporotic and hip fracture were not significantly increased, while for the adjusted population they were. We found an adjusted HR of 1.19 [1.11–1.28] for any fracture, an adjusted HR of 1.34 [1.20–1.49] for osteoporotic fracture, and an adjusted HR of 3.44 [2.73–4.34] for hip fracture. Table 5 further shows that fracture risks were comparable between the adjusted study populations. For both cohorts, there was a 1.2-fold increased risk of any fracture, a 1.3- to 1.5-fold increased risk of osteoporotic fracture and an approximately tripled risk of hip fracture.

Table 6 shows that the difference in estimates between a traditional meta-analysis and an individual patient data mega-analysis varied between 6% (any fracture) and 32% (hip fracture). The mega-analysis showed an adjusted HR of 1.20 [1.12–1.28] for any fracture, HR 1.36 [1.24–1.50] for osteoporotic fracture, and HR 3.27 [2.65–4.04] for hip fracture. A meta-analysis that pooled the two more comparable studies together yielded similar results as a mega-analysis with individual patient data. When the fully adjusted HRs from Table 5 were pooled in a meta-analysis, the HRs were 1.20 [1.12–1.28] for any fracture, 1.36 [1.24–1.50] for osteoporotic fracture, and 3.31 [2.67–4.09] for hip fracture. In this meta-analysis, there was no significant heterogeneity between the results for any of the fracture types.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave

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Table 2 Risk of fracture in MS patients versus controls: original studies

GPRD			
	n = 5,565	Mean follow-up (yrs) = 5.7	Mean age at index date = 44.8
	Fracture, *n*=	Age-sex adj HR	Fully adj HR
No MS	1,742	1	1
MS			
Any fracture	394	1.52 (1.36–1.69)	1.23 (1.09–1.38)[a]
Osteoporotic fracture	173	1.73 (1.46–2.04)	1.35 (1.13–1.62)[b]
Hip fracture	37	3.83 (2.58–5.67)	2.79 (1.83–4.26)[c]
Denmark			
	n = 2,963	Mean follow-up (yrs) = 7.2	Mean age at index date = 36.9
	Fracture, *n*=	Age-sex adj HR	Fully adj HR
No MS	1,397	1	1
MS			
Any fracture	308	1.17 (1.03–1.32)	1.01 (0.89–1.15)[d]
Osteoporotic fracture	103	1.24 (1.00–1.54)	1.05 (0.84–1.31)[e]
Hip fracture	16	2.91 (1.59–5.32)	1.81 (0.93–3.54)[f]

[a]Adjusted for age, sex, the use of oral/iv glucocorticoids, antidepressants, hypnotics/anxiolytics, anticonvulsants, opioids in the previous six months, history of falling at index date, history of fracture at index date, history of cerebrovascular disease, epilepsy and history of smoking.
[b]Adjusted for age, sex, the use of oral/iv glucocorticoids, antidepressants, hypnotics/anxiolytics, anticonvulsants, opioids in the previous six months, history of falling at index date, history of fracture at index date, history of cerebrovascular disease, epilepsy, history of smoking and body mass index.
[c]Adjusted for age, sex, the use of oral/ iv glucocorticoids, antidepressants, hypnotics/anxiolytics, anticonvulsants, opioids in the previous six months, history of falling at index date, history of fracture at index date, history of fatigue in the previous six months, history of smoking and body mass index.
[d]Adjusted for age, sex, the use of oral/ iv glucocorticoids, antidepressants, hypnotics/anxiolytics, anticonvulsants, opioids in the previous six months, history of cerebrovascular disease and epilepsy.
[e]Adjusted for age, sex, the use of antidepressants, antipsychotics, hypnotics/anxiolytics, anticonvulsants, opioids in the previous six months, history of cerebrovascular disease and epilepsy.
[f]Adjusted for age, sex, the use of antidepressants, anticonvulsants in the previous six months and history of fracture at index date.

Table 3 Risk of fracture in MS patients versus controls: traditional meta-analysis of the original studies

Meta-analysis			
	n = 8,528		
	Fracture, *n* =	Age–sex adj HR	Fully adj HR
No MS	3139	1	1
MS			
Any fracture	702	1.35 (1.24–1.47)[a]	1.13 (1.03–1.23)[a]
Osteoporotic fracture	276	1.53 (1.34–1.74)[a]	1.22 (1.07–1.41)
Hip fracture	53	3.53 (2.54–4.90)	2.47 (1.72–3.53)

[a]Significant heterogeneity between the two studies ($p < 0.05$).

informed consent to participate in these studies.

The difference in estimates between a traditional meta-analysis of the original studies and an individual patient data mega-analysis, in which the differences between the study characteristics were reduced as much as possible, was 32% for hip fracture. A traditional meta-analysis of the original studies showed significant heterogeneity, which disappeared in a meta-analysis that pooled the two more comparable studies together.

The selection of a different patient group, including not only incident but also prevalent patients, changed the findings in the Danish study. This may be explained by increasing fracture risks with increasing age and worsening of the disease. In a previous study, we found that the risk of osteoporotic fracture increased with age and was most elevated for patients aged 50–59[12]. In another study, we found that the risk of osteoporotic fracture increased with increasing disability[4].

There have been other examples where different study designs have led to different results, even with the same database. When two case–control studies, both performed in the GPRD, found different risks of fracture for patients using statins, a third study examined this discrepancy in results[13]. It was found that the age-band for matching cases and controls, the selection of potential confounders, the exclusion of high-risk patients, and different definitions for exposure time-windows explained different results in the two studies. Two studies on the use of oral bisphosphonates and risk of oesophageal cancer, both using data from the GPRD, also reached different conclusions[14,15]. They could, however, be explained by a difference in follow-up time and thus the potential to include people with longer durations of bisphosphonate use[14]. Other examples include the risk of venous thromboembolism with third generation

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Table 4 Baseline characteristics of MS patients and controls from the adjusted populations

	GPRD		Denmark	
	MS patients	Controls	MS patients	Controls
Characteristic	*n* = 4607	*n* = 27,621	*n* = 9664	*n* = 50,013
Mean duration of follow-up after index date, yrs	4.7	4.9	4.7	4.9
Sex female	70.0%	70.0%	65.3%	65.6%
Mean age at index date	44.9	44.9	44.9	44.8
Body mass index				
<20	7.7%	5.9%	–	–
20–25	33.8%	33.9%	–	–
25–30	24.9%	26.6%	–	–
>30	17.2%	17.4%	–	–
Unknown	16.4%	16.2%	–	–
Smoking				
Never	40.0%	48.1%	–	–
Current	29.3%	22.7%	–	–
Ex	16.6%	14.6%	–	–
Unknown	14.1%	14.6%	–	–
Comorbidity ever before				
Fracture	16.0%	14.6%	13.9%	11.4%
Congestive heart failure	0.6%	0.4%	0.2%	0.2%
Rheumatoid arthritis	0.7%	0.7%	0.4%	0.5%
Renal disease	0.1%	0.2%	0.0%	0.1%
Cerebrovascular disease	2.9%	1.2%	4.6%	1.2%
Inflammatory bowel disease	0.8%	0.6%	1.1%	0.9%
Epilepsy	2.6%	1.4%	2.6%	1.2%
Falling	7.3%	3.4%	–	–
Fatigue	9.4%	6.3%	–	–
Spasticity	2.1%	0.6%	–	–
Disability	18.1%	11.2%	–	–
Drug use 6 months before				
Statins	5.1%	3.9%	1.1%	1.0%
Antiarrythmics	0.3%	0.3%	0.1%	0.1%
Antidiabetics	2.3%	2.1%	1.4%	1.5%
Antidepressants	19.9%	9.3%	12.2%	4.1%
Antipsychotics	1.6%	0.9%	2.8%	2.0%
Anxiolytics/hypnotics	8.8%	4.1%	21.9%	9.2%
Anticonvulsants	7.7%	1.4%	7.5%	1.2%

contraceptives[16], and the association between the use of proton pump inhibitors and fracture[17].

There is a strong need for comparison between methods to conduct multi-country studies with electronic healthcare databases. The vast majority of published meta-analyses are based on aggregate patient data from completed studies[1]. A meta-analysis that uses individual patient data instead of aggregate patient data has many theoretical advantages[1,2,18,19], such as the ability to use common definitions, to adjust for the same variables across studies, to explore heterogeneity at a patient level and to perform subgroup analyses of patient level data. In the analysis of clinical trial data, there have been a few examples where an aggregate meta-analysis failed to detect a result that was found with individual patient data[20]. To our knowledge, in observational electronic healthcare database research, peer-reviewed comparisons between the two methods are lacking. Our study is the first one to compare a traditional meta-analysis with an individual patient data mega-analysis of observational studies, using real life patient data.

Different patient characteristics between the GPRD and the Danish study caused significant heterogeneity in a meta-analysis that simply pooled the estimates from the original studies together. The most important difference between the studies was the start of follow-up: the Danish study followed incident MS patients from the first symptom of the disease, while the GPRD study comprised a case-mix of incident and prevalent MS patients. Heterogeneity disappeared in a meta-analysis that pooled results from more comparable patient groups together and this method showed similar results as an individual patient data mega-analysis. Because the case-mix between incident and prevalent patients elevated fracture risks compared to the incident Danish MS population, the

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Table 4 (Continued)				
Opioids	3.4%	1.2%	7.6%	3.2%
Oral/iv glucocorticoids	6.4%	1.6%	4.7%	1.9%
Bisphosphonates	1.0%	0.6%	0.2%	0.1%
HRT	2.7%	2.8%	3.1%	3.2%
Calcium	0.2%	0.2%	0.6%	0.2%
Vitamin D	1.1%	0.7%	0.0%	0.0%

Table 5 Risk of fracture in MS patients vs controls: adjusted populations

GPRD			
	n = 4,607	Mean follow-up (yrs) = 4.7	Mean age at index date = 44.9
	Fracture, *n* =	Age–sex adj HR	Fully adj HR
No MS	1,171	1	1
MS			
Any fracture	267	1.50 (1.31–1.71)	1.23 (1.07–1.42)[a]
Osteoporotic fracture	118	1.83 (1.50–2.25)	1.47 (1.18–1.83)[a]
Hip fracture	22	3.15 (1.92–5.17)	2.70 (1.60–4.56)[b]
Denmark			
	n = 9,664	Mean follow-up (yrs) = 4.7	Mean age at index date = 44.9
	Fracture, *n* =	Age–sex adj HR	Fully adj HR
No MS	3,766	1	1
MS			
Any fracture	989	1.43 (1.33–1.54)	1.19 (1.11–1.28)[a]
Osteoporotic fracture	464	1.66 (1.50–1.84)	1.34 (1.20–1.49)[a]
Hip fracture	147	4.71 (3.78–5.87)	3.44 (2.73–4.34)[b]

[a]Adjusted for age, sex, the use of oral/iv glucocorticoids, antidepressants, hypnotics/anxiolytics, anticonvulsants, opioids in the previous six months, history of fracture at index date, history of cerebrovascular disease and epilepsy.
[b]Adjusted for age, sex, the use of oral/iv glucocorticoids, antidepressants, hypnotics/anxiolytics, anticonvulsants, opioids in the previous six months and history of fracture at index date.

combined analysis of the GPRD and the Danish study obtained higher fracture risks than the combination of the original studies. Other differences that we synchronised between the two studies were calendar time, duration of follow-up and the selection of confounders.

A certain level of heterogeneity will always persist between studies that use different healthcare registries, even after making the best effort in reducing the differences. For example, patients with MS from the UK may be genetically different than MS patients from Denmark; guidelines for treatment of patients may slightly differ between countries, environmental factors may differently alter risks of fracture for MS patients, and residual confounding may alter estimated risks. In a traditional meta-analysis, a small degree of heterogeneity may be accounted for using a random-effect meta-analysis, but this reduces the precision of the estimate and more importantly, cannot explore heterogeneity at a patient level.

Conclusion

A crucial step in performing a multi-country study is to reduce the level of heterogeneity between studies in terms of their design as much as possible, so that only a small amount of unexplained heterogeneity remains, before combining the data. Individual patient data are therefore a major advantage for a multi-country study.

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Conflict of interests

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Table 6 Risk of fracture in MS patients versus controls: mega-analysis of individual patient data of the adjusted populations

Mega-analysis			
	n = 14,271		
	Fracture, *n* =	Age–sex adj HR	Fully adj HR
No MS	4937	1	1
MS			
Any fracture	1256	1.45 (1.36–1.54)	1.20 (1.12–1.28)[a]
Osteoporotic fracture	582	1.70 (1.55–1.86)	1.36 (1.24–1.50)[a]
Hip fracture	169	4.35 (3.56–5.31)	3.27 (2.65–4.04)[b]

[a]Adjusted for age, sex, the use of oral/iv glucocorticoids, antidepressants, hypnotics/anxiolytics, anticonvulsants, opioids in the previous six months, history of fracture at index date, history of cerebrovascular disease and epilepsy.
[b]Adjusted for age, sex, the use of oral/iv glucocorticoids, antidepressants, hypnotics/anxiolytics, anticonvulsants, opioids in the previous six months and history of fracture at index date.

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