

Original article

## Epidemiology of restless legs syndrome as diagnosed in UK primary care

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### Abstract

**Background and purpose:** Restless legs syndrome (RLS) is a sensorimotor disorder with a general-population prevalence of 5–10%. Although, data on the prevalence of clinically diagnosed RLS are limited, and there are none regarding incidence, a shortfall compared with general-population values is likely, as not all patients are driven to consult. There may also be poor awareness of the condition among primary care physicians (PCPs).

**Patients and methods:** The General Practice Research Database was used to gather prevalence and incidence data from UK PCPs and to investigate PCP awareness over the period 1994–1998. A total of 1,561,692 persons were covered by the database on January 1, 1999.

**Results:** A diagnosis of RLS was registered in 3877 patients, giving a prevalence of 0.25%. Incidence values were also low (41.0 per 100,000 person-years), increased with age and were higher in women than in men. Although, at least one RLS diagnosis was made in 94% of medium-to-large practices, sufferers were more likely than age/sex-matched controls to be diagnosed with conditions commonly confused with RLS in 2 years before receiving their RLS diagnosis. Furthermore, at the time of diagnosis, many sufferers were prescribed medications not effective in RLS (principally, oxerutins and quinine).

**Conclusion:** These data are largely consistent with a lack of awareness of RLS among PCPs in the UK in the period studied.  
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**Keywords:** Restless legs syndrome; Prevalence; Incidence; Epidemiology; Primary care; UK

### 1. Introduction

Patients with restless legs syndrome (RLS; also known as Ekbom syndrome) report an irresistible urge to move their legs, and accompanying sensations that they commonly describe as twitching, burning or painful. Symptoms are worse or exclusively present at rest, in the evenings and at night, and are relieved by movement. For some patients, RLS is mild and causes little inconvenience. In others, however, the impact on sleep is considerable, compromising work and social activities [1,2].

A minority of RLS cases is secondary to a pre-existing condition (pregnancy, renal failure and iron-deficiency anemia), and resolve with that underlying condition [1,3–5]. Although, many causes of secondary RLS (such as rheumatoid arthritis and diabetes) have been suggested, supporting data are limited and the treatment of these conditions has not been conclusively shown to alleviate RLS. For most patients, namely those with idiopathic RLS, a number of treatments are used, including benzodiazepines, opiates, antiepileptics and dopaminergic agents. Current opinion suggests that dopaminergic therapies are the most effective treatment [1].

Minimal criteria for the diagnosis of RLS were published by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 [6], and updated in 2003 [7]. The 1995 criteria have been widely adopted in epidemiological

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studies of the disorder in general populations worldwide, commonly yielding prevalence values in the range 5–10% [8,9]. Not all patients with the condition will be driven to consult or require treatment, however, and therefore the prevalence of diagnosed RLS will be lower. Data from a multinational questionnaire-based survey in a primary care setting (the RLS Epidemiology Symptoms and Treatment (REST) study) support these assertions. It estimates prevalence in a general practice population of RLS symptoms with appreciable negative impact on quality of life of about 3.4%, but a population diagnosed prevalence of only 0.3% [10]. Further work is clearly needed to confirm the prevalence of diagnosed RLS, to evaluate, for the first time, the incidence of the disorder and to investigate the awareness of physicians.

As an alternative to the questionnaire-based approach to epidemiological study, we used the General Practice Research Database (GPRD) [11] to gather information relating to RLS in primary care. The GPRD is a collection of chronological medical records, of up to 12 years duration, supplied by primary care physicians (PCPs) in the UK. PCPs can join if their data entry meets certain quality standards. The records detail the symptoms, diagnoses, investigations and referrals of all patients of the participating practices. A total of 1,561,692 persons were covered by the database on January 1, 1999 (2.5% of the UK population). The objectives of the research were to estimate the prevalence and incidence of diagnosed RLS, to investigate physician awareness by examining the proportion of practices diagnosing RLS, and to establish the prevalence of relevant co-morbid conditions. The records were also used to explore associations between RLS and postulated secondary causes and the treatments prescribed following an RLS diagnosis.

## 2. Patients and methods

### 2.1. Prevalence and incidence of diagnosed RLS in UK primary care

GPRD records for patients with a diagnosis of RLS were identified using the Oxford Medical Information System and Read codes specific for RLS (Oxmis 7816LR and Read F13z200). These coding systems are used to standardise entries to the database.

The prevalence of diagnosed RLS was defined as the proportion of patients with records in the GPRD on January 1, 1999, who had been diagnosed with the disorder before that date. The yearly incidence of diagnosed RLS was defined as the number of patients first diagnosed with RLS divided by the total person-years of patients registered. The period covered was January 1, 1994, to December 31, 1998, and only patients whose records had been in the GPRD for at least 2 years before the diagnosis were included.

Study periods up to January 1, 1999, were selected as thereafter practices began to use alternative software to

avoid Year 2000 compliance issues. This resulted in a loss of continuity in patient data.

### 2.2. Awareness of RLS among practices

The awareness of RLS among practices was estimated by counting the number of practices for which there was at least one diagnosis of RLS in the GPRD before January 1, 1999. Only practices with at least 2000 patients were included because smaller practices are likely to be atypical.

### 2.3. RLS misdiagnoses, secondary causes and treatments for RLS

Conditions likely to be misdiagnosed RLS or those known or postulated to cause secondary RLS were identified through a literature search [1,12]. The prevalences of each of the conditions were established for a group of GPRD patients with a diagnosis of RLS (the RLS group). These prevalences were compared with those in a control group also derived from the GPRD.

The RLS group comprised patients diagnosed with RLS between January 1, 1994, and December 31, 1998 (study period) and who could be randomly matched by age, gender and primary care practice to a control patient experiencing at least one medical event (receiving a diagnosis or a prescription, undergoing an investigation or other procedure in primary care or hospital) in the same period. Only RLS and control group patients with records for at least 2 years before the index date were included. All individuals were assigned an index date; this was either the day on which the RLS diagnosis was recorded for the first time (RLS group) or a randomly chosen date in the study period on which control patients had experienced a medical event. Diagnoses assigned to patients in 2 years before the index date were recorded.

The proportions of patients in each group receiving ferrous compounds (to treat iron deficiency) and/or erythropoietin (to treat end-stage renal disease) or receiving antipsychotic drugs or antidopaminergic antiemetics (known to induce or worsen RLS) were established for 2 years before the index date.

The drugs commonly used to treat RLS were identified through a literature search [1,12] and by identifying drugs prescribed on the index date for a random sample of 100 patients from the RLS group. The proportions of the RLS and control groups receiving these treatments on the index date were then recorded.

### 2.4. Statistical analyses

Crosstabs and multivariate conditional logistic regression analysis were used to compare, between RLS and control groups, the presence of conditions that might cause RLS. Other data were analysed using crosstabs

and univariate odds ratios. SAS™ software was used for all analyses.

### 3. Results

#### 3.1. Prevalence and incidence of diagnosed RLS in UK primary care

##### 3.1.1. Prevalence

On January 1, 1999, a total of 3877 out of 1,561,692 patients registered on the database had been diagnosed with RLS, giving a prevalence for diagnosed RLS of 0.25%. The mean age of these patients with RLS was 64.3 years.

Prevalence generally increased with age (Fig. 1). In adults (aged at least 20 years), the prevalence was 0.32%, whereas in persons aged at least 65 years, the prevalence was 0.79%. Overall, the prevalence in women was higher (0.37%) than that in men (0.13%), and was higher than that for men in all age categories (Fig. 1).

##### 3.1.2. Incidence

Between January 1, 1994, and December 31, 1998, 3378 patients were first diagnosed with RLS, giving an overall incidence of 41.0 per 100,000 person-years. Incidence increased with age (Fig. 2). Among adults aged 20 years and older and among those aged at least 65 years, the incidences were 51.0 and 96.5 per 100,000 person-years, respectively. The incidence among men also increased with age, while that among women reached a peak at 60–69 years and declined thereafter (Fig. 2). Overall, the incidence among women (55.4 per 100,000 person-years) was more than twice that among men (24.3 per 100,000 person-years), and was higher than that for men in all age categories.

#### 3.2. Awareness of RLS among practices

On January 1, 1999, 94% (221/236) of practices with over 2000 patients had at least 1 patient with a diagnosis of RLS, with a total of 3848 diagnosed RLS patients in these practices; 6% (15) of practices with over 2000 registered patients had no patient with an RLS diagnosis (small practices were excluded from this analysis).

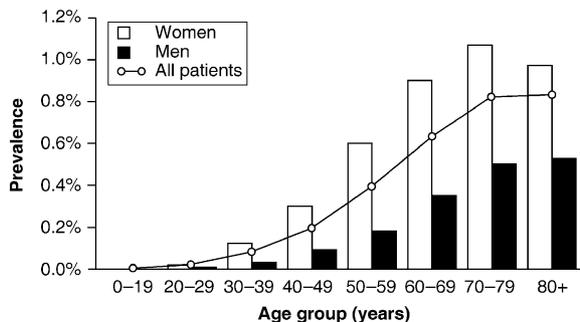


Fig. 1. Prevalence of diagnosed restless legs syndrome.

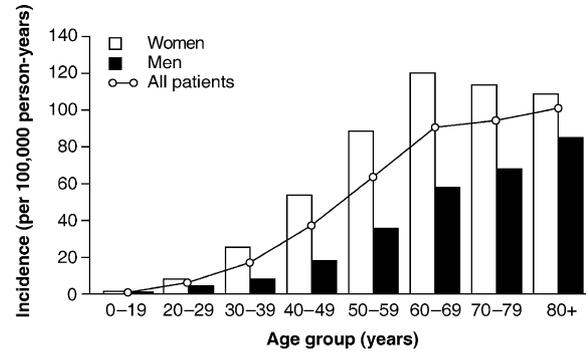


Fig. 2. Incidence of diagnosed restless legs syndrome.

#### 3.3. Co-morbidities

A total of 3319 of the 3378 patients diagnosed with RLS during 1994–1998 could be matched with a control patient. Each group had a mean age of 61.8 years and 72.1% were female.

Table 1 shows the conditions that may have been misdiagnosed RLS. In 2 years before the index date, sleeping problems, cramps, and ‘leg problems other than RLS’ were significantly more common in the RLS group compared with the control group ( $P < 0.05$ ).

Table 2 lists the conditions that have been shown or postulated to be causes of secondary RLS and for which a diagnosis was made in 2 years before the index date. Compared with controls, patients with RLS were significantly more likely to have a history of end-stage renal disease or depression ( $P < 0.05$ ), but significantly less likely to have diabetes or iron-deficiency anemia ( $P < 0.05$ ). In the RLS group, the most common co-morbidities were depression (15.4%), anxiety (8.3%) and diabetes mellitus (4.2%).

The group with newly diagnosed RLS was significantly more likely to have previously received erythropoietin than the control group (10 patients versus 1 patient, respectively; odds ratio, 10.03; 95% CI, 1.28–78.4), but similar proportions of each group had previously received ferrous compounds (RLS group, 230 patients; control group, 210 patients; odds ratio, 1.10; 95% CI, 0.91–1.34). Significantly more patients in the RLS group had received a prescription

Table 1  
Diagnoses assigned to patients in 2 years before the index date (the date of the restless legs syndrome (RLS) diagnosis in the RLS group)

	Number (%) of patients		Univariate odds ratio (95% CI)
	RLS group (N=3319)	Control group (N=3319)	
Sleeping problems	449 (13.5)	254 (7.7)	1.89 (1.61–2.22) <sup>a</sup>
Leg problems other than RLS	435 (13.1)	193 (5.8)	2.44 (2.05–2.92) <sup>a</sup>
Cramps	128 (3.9)	50 (1.5)	2.62 (1.88–3.65) <sup>a</sup>
Polyneuropathy	25 (0.8)	18 (0.5)	1.39 (0.76–2.56)

<sup>a</sup> Significant ( $P < 0.05$ ) difference between groups.

Table 2

Causes and reported determinants of restless legs syndrome (RLS): occurrence in 2 years before the index date (the date of the RLS diagnosis in the RLS group)

	Number (%) of patients		Odds ratio (95% CI) <sup>a</sup>
	RLS group (N=3319)	Control group (N=3319)	
Depression	512 (15.4)	420 (12.7)	1.24 (1.07–1.44) <sup>b</sup>
Anxiety	275 (8.3)	241 (7.3)	1.09 (0.91–1.32)
Diabetes mellitus	140 (4.2)	206 (6.2)	0.66 (0.52–0.82) <sup>b</sup>
Iron-deficiency anemia	127 (3.8)	159 (4.8)	0.77 (0.60–0.98) <sup>b</sup>
Hypothyroidism	55 (1.7)	59 (1.8)	0.91 (0.63–1.32)
Pregnancy <sup>c</sup>	42 (1.8)	51 (2.1)	0.84 (0.53–1.31)
Parkinsonism	32 (1.0)	21 (0.6)	1.49 (0.85–2.61)
Rheumatoid arthritis	27 (0.8)	30 (0.9)	0.95 (0.56–1.60)
End-stage renal disease (including dialysis)	17 (0.5)	4 (0.1)	4.76 (1.59–14.3) <sup>b</sup>
Fibromyalgia	10 (0.3)	8 (0.2)	1.26 (0.47–3.40)
Vitamin B12 deficiency	0 (0.0)	2 (0.1)	N/A <sup>d</sup>
Attention deficit-hyperactivity disorder	0 (0.0)	0 (0.0)	N/A <sup>d</sup>
Sjögren's syndrome	0 (0.0)	0 (0.0)	N/A <sup>d</sup>
Tourette's syndrome	0 (0.0)	0 (0.0)	N/A <sup>d</sup>

<sup>a</sup> Calculated by multivariate stepwise conditional logistic regression analysis (for the diagnoses assigned to at least 5 patients in either group).

<sup>b</sup> Significant ( $P < 0.05$ ) difference between groups.

<sup>c</sup> Percentage refers to women.

<sup>d</sup> N/A, not applicable.

for antipsychotics and/or neuroleptic antiemetics compared with the control group (560 patients versus 454 patients, respectively; odds ratio, 1.28; 95% CI, 1.12–1.47).

### 3.4. Treatments for RLS

Drugs prescribed on the index date are listed in Table 3. Benzodiazepines, oxerutins and quinine were more likely to be prescribed to patients with RLS than to patients in the control group. Dopaminergic agents (L-dopa and dopamine agonists) were rarely prescribed in either group.

## 4. Discussion

This is the first study to estimate the incidence of diagnosed RLS in a primary care population. Based on the GPRD (a UK primary care database), the incidence was found to be 41.0 per 100,000 person-years. The incidence was greater in women compared with men and increased with age. Very similar patterns were apparent for the prevalence of diagnosed RLS: the overall rate was low at 0.25%, was higher in women than in men and increased with age. Diagnoses were as recorded in primary care, which means the group of patients studied is a subgroup of the wider population with RLS symptoms and that criteria used for diagnosis are uncertain and likely to vary.

The prevalence figure of 0.32% in people aged at least 20 years is consistent with the results of the primary care survey of the REST programme, in which a low overall prevalence of diagnosed RLS (0.3%) was estimated [10],

and with various reports indicating a higher prevalence of RLS among women compared with men [9,13]. The results of the present study also indicate this is not just a disease of the elderly, which is consistent with numerous reports of symptoms starting early in life for many sufferers [14,15]. The low prevalence of diagnosed RLS compared with general-population values of 5–10% [8,9], however, is at least partly due to the fact that sufferers in the latter case are identified using the IRLSSG or similar criteria; these criteria do not assess symptom severity or frequency, and so such studies include patients whose symptoms are mild and/or infrequent and are thus not driven to consult a physician. Another factor, however, is likely to be the lack of awareness of RLS or its diagnostic criteria among

Table 3

Drugs prescribed on the index date (the date of the restless legs syndrome (RLS) diagnosis in the RLS group)

Drug class	Number (%) of patients	
	RLS group (N=3319)	Control group (N=3319)
Benzodiazepines	649 (19.6)	110 (3.3) <sup>a</sup>
Oxerutins (rutosides)	497 (15.0)	3 (0.1) <sup>a</sup>
Quinine	375 (11.3)	7 (0.2) <sup>a</sup>
Opiates	250 (7.5)	172 (5.2) <sup>a</sup>
Iron-modification therapy	57 (1.7)	14 (0.4) <sup>a</sup>
Baclofen	18 (0.5)	4 (0.1) <sup>a</sup>
L-dopa	17 (0.5)	3 (0.1) <sup>a</sup>
Clonidine	16 (0.5)	4 (0.1) <sup>a</sup>
Antiepileptics	6 (0.2)	2 (0.1)
Dopamine agonists	3 (0.1)	0 (0.0)
Any of the above	1707 (51.4)	287 (8.6) <sup>a</sup>

<sup>a</sup> Significant ( $P < 0.05$ ) difference between groups.

physicians, such that misdiagnoses are common. In the REST data, the primary care prevalence rates of RLS symptoms are higher than those of the population-based studies [10]. This is not unexpected as the primary population is a selection of the general population.

In the present study, members of the RLS group were more likely to have been previously diagnosed with conditions commonly confused with RLS than were those in the control group, suggesting patients receive an RLS diagnosis only after several consultations. Encouragingly, the data from this study also suggest, however, that practice-wide difficulties in recognising the condition are unlikely as almost all of the larger practices had registered at least one diagnosis in the study period. Unfortunately, it is not possible to explore the awareness of individual physicians within practices using the GPRD.

In theory, our estimate of the prevalence of diagnosed RLS might be slightly elevated because the methodology adopted here assumes that once patients are diagnosed with RLS they continue to suffer from the disorder for the remainder of the study period. Secondary forms of the disorder are likely to violate this assumption, as symptoms resolve with the underlying condition. However, as it is generally believed that most cases of RLS are idiopathic [16], the effect on our prevalence estimate is likely to be small. Of the known secondary causes of RLS, pregnancy was not significantly associated with RLS in the present study; iron-deficiency anemia was less common, and end-stage renal disease more common in the RLS group than in the control group. The negative association between an RLS diagnosis and a history of iron-deficiency anemia may result from the treatment of anemia reducing the risk of RLS development. This would have depressed the overall prevalence of RLS reported in our study. The positive association between an RLS diagnosis and end-stage renal disease was strong, but the condition was uncommon (accounting for only 0.5% of RLS cases).

Of the conditions that have been suggested as causes of secondary RLS, only histories of depression or diabetes had significant associations with an RLS diagnosis. It is possible that symptoms of depression bring the RLS sufferer into contact with a physician and thus increase the likelihood that RLS symptoms will be presented and diagnosed. Although a diagnosis of depression predated that for RLS, it is still possible that depression is a consequence of RLS if physicians recognise depression more easily than they recognise RLS. The negative association between RLS and diabetes may reflect a tendency to ascribe RLS symptoms to neuropathy in patients with diabetes. Modest positive associations between a diagnosis of RLS and prior use of antipsychotics and/or neuroleptic antiemetics are consistent with evidence indicating that these agents induce or worsen RLS symptoms [17,18], but it is unclear from the present study if the drugs were used for more than a short time.

The data gathered on treatments suggest a mixed understanding of the possible aetiologies of RLS.

A surprisingly large number of physicians prescribed oxerutins (e.g. Paroven™) or quinine, which did not fit with prevailing theories on aetiology or the treatment of RLS. In fact, quinine was (and is) recommended by the British National Formulary [19] for nocturnal night cramps, which are often misdiagnosed in place of RLS, and oxerutins/rutosides were licensed in the UK until 1991 for “the long-term relief of symptoms of capillary impairment associated with venous insufficiency, especially...restless legs...” [20]—clearly the legacy of this had yet to resolve. The most common prescriptions were for benzodiazepines, presumably as these agents alleviate the secondary sleep-related symptoms common among RLS sufferers. That very few physicians were prescribing dopamine agonists and L-dopa is perhaps not surprising as the study period predates the publication of many clinical trials demonstrating the efficacy of these drugs [21–24].

Overall, this study indicates that in the period 1994–1998, the incidence and prevalence of diagnosed RLS were low, lending support to the view that RLS was poorly recognised among PCPs in the UK and, therefore, its management was sub-optimal. The lack of awareness may have been exacerbated by the absence of an approved treatment in the UK. REST data suggest awareness of RLS may still be limited, although there has been a steady rise in interest in the condition among the scientific community, and a corresponding increase in the body of published data. Further characterisation of patients presenting with RLS and of physician awareness within practices may help determine strategies for physician education. The simplicity of the diagnostic criteria [16], however, should help to improve diagnosis and management.

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