Movement Disorders
Vol. 25, No. 5, 2010, pp. 534–541

CME

Review

How Common Is the Most Common Adult Movement Disorder? Update on the Worldwide Prevalence of Essential Tremor

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Abstract: Essential tremor (ET) is among the more prevalent neurological disorders, yet prevalence estimates have varied enormously, making it difficult to establish prevalence with precision. We: (1) reviewed the worldwide prevalence of ET in population-based epidemiological studies, (2) derived as precisely as possible an estimate of disease prevalence, and (3) examined trends and important differences across studies. We identified 28 population-based prevalence studies (19 countries). In a meta-analysis, pooled prevalence (all ages) = 0.9%, with statistically significant heterogeneity across studies (I^2 = 99%, $P < 0.001$). In additional descriptive analyses, crude prevalence (all ages) = 0.4%. Prevalence increased markedly with age, and especially with advanced age. In the meta-analysis, prevalence (age ≥ 65 years) = 4.6%, and in additional descriptive analyses, median crude prevalence (age ≥ 60–65) = 6.3%. In one study of those age ≥ 95 years, crude prevalence = 21.7%. Several studies reported ethnic differences in prevalence, although more studies are needed. Greater than one-third of studies show a gender difference, with most demonstrating a higher prevalence among men. This possible gender preference is interesting given clinical, epidemiological, and pathological associations between ET and Parkinson's disease. Precise prevalence estimates such as those we provide are important because they form the numerical basis for planned public health initiatives, provide data on the background occurrence of disease for family studies, and offer clues about the existence of environmental or underlying biological factors of possible mechanistic importance. © 2010 Movement Disorder Society

Key words: essential tremor; epidemiology; prevalence; clinical

Essential tremor (ET) is considered to be among the more prevalent neurological disorders and arguably, aside from restless legs syndrome,[1,2] the most common adult-onset movement disorder.[3] It is seen with great frequency by general physicians, geriatricians, and neurologists.[4] However, prevalence estimates have varied a great deal[3] making it difficult to establish prevalence with precision. Establishing a precise prevalence estimate is important for several reasons. First, a precise prevalence estimate forms the numerical backbone for planned public health initiatives. Second, knowledge of the expected background occurrence of a disease in the population provides important contextual information for the interpretation of phenotypic data in family studies. Third, subgroup differences in prevalence can offer initial clues about the existence of environmental or underlying biological factors that might be of etiological or mechanistic importance. Finally, and perhaps

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Potential conflict of interest: Nothing to report.

Received 10 February 2009; Revised 15 April 2009; Accepted 18 September 2009

Published online 19 February 2010 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22838

TABLE 1. *Crude prevalence of ET in population-based studies*

Author	Year	Country	Prevalence (%)	Ages	Examined all subjects (whom)
Osuntokun[8]	1987	Nigeria	0.01	All	Unclear from study description
Li[9]	1985	China	0.01	All	No
Dotchin[10]	2008	Tanzania	0.04	All	No
Haimanot[11]	1990	Ethiopia	0.04	All	No
Al Rajeh[12]	1993	Saudi Arabia	0.1	All	No
Attia Romdhane[13]	1993	Tunisia	0.2	All	No
Chouza[15]	1994	Uruguay	0.2	All	No
Tan[14]	2005	Singapore	0.3	≥50	No
Hornabrook[16]	**1976**	**New Guinea**	**0.4**	**All**	**Yes (field officer)**
Salemi[17]	**1994**	**Italy**	**0.4**	**All**	**Yes (neurologists)**
Haerer[18]	1982	USA	0.4	≥40	No
Acosta[19]	1989	Spain	0.6	All	Yes (nurses, General practitioners)
Glik[20]	**2008**	**Israel**	**0.8**	**≥65**	**Yes (neurologist)**
Mancini[21]	**2007**	**Italy**	**0.8**	**≥41**	**Yes (General practitioners)**
Das[22]	2008	India	1.4	≥60	No
Larsson[7]	1960	Sweden	1.4	All	No
Bharucha[23]	1988	India	1.6	All	No
Sur[24]	**2008**	**Turkey**	**3.1**	**≥18**	**Yes**
Liu[6]	1997	China	3.2	≥50	Yes (neurologists)
Wenning[32]	2005	Austria	3.4	50–89	Yes (neurologists, geriatricians, other medical specialists)
Louis[25]	**1995**	**USA**	**2.2 [3.9]**	**≥65**	**No but information provided on sensitivity of screening instrument**
Dogu[27]	**2003**	**Turkey**	**4.0**	**≥40**	**Yes (neurologists)**
Louis[29]	**2009**	**USA**	**5.5**	**≥65**	**Yes (handwriting samples reviewed by movement disorder specialist)**
Bergareche[26]	**2001**	**Spain**	**4.8 [6.4]**	**≥65**	**No but information provided on sensitivity of screening instrument**
Benito-Leon[28]	**2003**	**Spain**	**4.8 [7.0]**	**≥65**	**No but information provided on sensitivity of screening instrument**
Rautakorpi[5]	**1982**	**Finland**	**5.6 [9.7]**	**≥40**	**No but information provided on sensitivity of screening instrument**
Moghal[30]	**1994**	**Canada**	**14.3**	**≥65**	**Yes**
Khatter[31]	**1996**	**USA**	**20.5**	**≥65**	**Yes (not specified)**

Studies are ordered from lowest to highest prevalence (%).

All values in brackets account for the sensitivity of the initial screening process (i.e., values are higher because they include an estimate of the number of false negatives).

In bold are the studies that: (1) either examined all subjects or provided information on screening questionnaire and (2) provided separate age-stratified estimates of prevalence among elderly aged 60 and older.

most basic, is that investigators need to be able to confidently identify and count cases before they can study them further.

Ten years ago, we reviewed the worldwide prevalence literature on ET; at that time, there were 14 population-based prevalence studies.[3] Since, then the number has increased markedly. Also, a number of the more recent studies have used improved methodologies (e.g., direct examination rather than reliance on a two-phase screening procedure), which makes their review even more timely and important. The purpose of this report was to: (1) review the worldwide prevalence of ET in population-based epidemiological studies, (2) derive as precisely as possible an estimate of prevalence, and (3) examine trends as well as important differences across studies. To address these aims, two methods were used: meta-analysis and a descriptive-analytic approach.

STUDIES

We searched for all population-based studies on the prevalence of ET published as full papers in scientific journals referenced by MEDLINE and EMBASE up to December 2008; in addition, a manual search was conducted using references cited in published original and relevant review articles. As keywords we used "essential tremor" and "prevalence." We included all population-based prevalence studies that provided data on the number of cases and total population size.

We included 28 population-based prevalence studies (Table 1),[5–32] which was a doubling since the previous review 10 years ago.[3] These 28 studies were from 19 countries and 5 continents (Asia = 10, Europe = 8, North America = 5, Africa = 4, and South America = 1). Several countries were represented by more than one study (USA = 4, Spain = 3, China = 2, India = 2, Italy = 2, and Turkey = 2). Crude prevalence estimates had a vast range, from 0.01 to 20.5% (Table 1), which represents a 2,050-fold difference between the highest and lowest estimates.

META-ANALYSIS

We performed a meta-analysis using Comprehensive Meta Analysis software (version 2.2.048, Biostat,

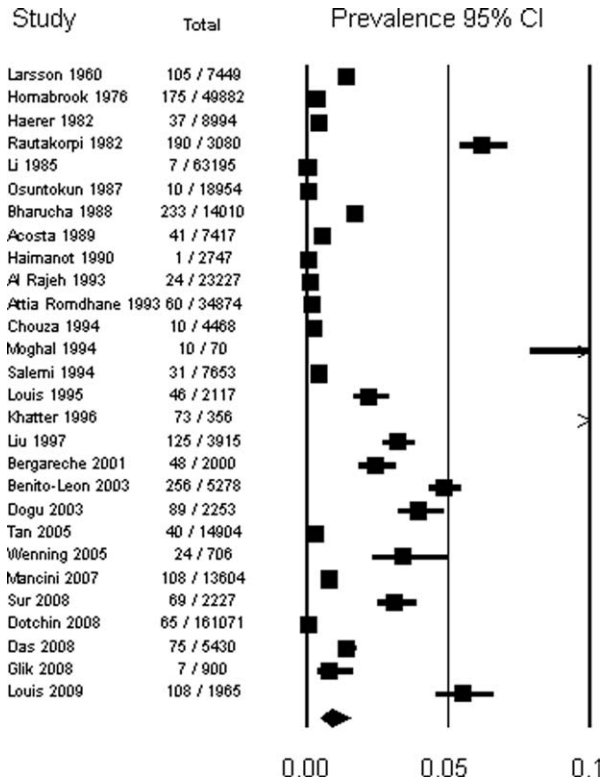

FIG. 1. Forest plot of meta-analysis of the prevalence estimates from all 28 included studies (random-effects model).

Englewood, NJ). Data were pooled according to the number of cases and the total population screened in each study, and event rates and respective 95% confidence intervals (CI) were calculated. Pooled prevalence rates and 95% CIs were calculated using a random effects model. To evaluate whether the results of the studies were homogenous, the Cochran's Q test was used. The quantity I^2, which describes the proportion of variance across studies due to heterogeneity rather than chance, was calculated. We also extracted all available data on the study population, including age structure, recruitment methods, type of screening questionnaire and clinical examination, and definition of ET. Sensitivity analyses were performed based on factors that could influence the study heterogeneity (e.g., definition of ET). Quality of published methodology data and related susceptibility to bias were assessed through a checklist approach for recruitment methods, inclusion criteria, and clinical criteria for ET.

The 28 studies identified 2,067 ET cases from a total of 462,746 participants screened. When pooling all studies, the overall estimated prevalence of ET = 0.9% (95% CI 0.5–1.5%) (Fig. 1), but there was considerable heterogeneity across studies (I^2 = 99%, $P < 0.001$). We performed a number of additional analyses. First, a sensitivity analysis was performed, excluding the two studies with the widest CIs.[30,31] In this analysis, the estimated prevalence = 0.7% (95% CI 0.4–1.2%), with considerable heterogeneity across studies still remaining (I^2 = 99%, $P < 0.001$). Second, after excluding studies without an explicit definition of ET,[8,9,11,13,15,19] the estimated prevalence = 1.5% (95% CI 0.8–2.7%)(I^2 = 99%, $P < 0.001$). Third, in a subgroup analysis excluding studies that did not conduct neurological examinations on all cases,[5,7–15,18,22,23,26,28] the estimated prevalence = 2.2% (95% CI 1.1–4.5%) (I^2 = 99%, $P < 0.001$). Finally, a subgroup analysis restricted to studies that provided data on cases aged ≥65 years [20,25,26,28–31] yielded an estimated prevalence = 4.6% (95% CI 2.5–8.3%) (I^2 = 98%, $P < 0.001$). In each analysis, considerable heterogeneity across studies was found. Hence, the conclusions one may draw from pooling the studies should be regarded cautiously and this justifies the descriptive-analytic approach and narrative review conducted in the remainder of this manuscript.

DESCRIPTIVE-ANALYTIC APPROACH

Pertinent Methodological Issues That Arise When Interpreting Data From Prevalence Studies

A number of factors may account for the large difference in prevalence estimates. Based on data from population-based studies, it is clear that only a small proportion of ET cases seek medical attention for their tremor, with as few as 0.0[10]–0.5%[7] seeking such attention, particularly if cases reside in medically underdeveloped areas.[7,10] Thus, clinic-based studies[33,34] will tend to underestimate disease prevalence, with the above data[7,10] suggesting that estimates based on clinic-derived samples could ascertain fewer than 1% of ET cases in the population. Nevertheless, the 28 studies under consideration are all population-based studies,[5–32] so that this issue should not account for the differences in these particular prevalence estimates.

However, the age structure of the population is important; this is because the prevalence of ET is a function of age.[5,14,16–18,21–23,25–29,32] Nonindustrialized countries and those with higher birth rates will have a young age structure.[8,10–13,15,16] For example, in the study in Saudia Arabia,[12] 90.5% of enrollees were ≤40 years of age (vs. 1.5% over age 60) and, in New Guinea,[16] 66.9% were under age 30 (vs. 3.9% age ≥60). Similarly, in Nigeria,[8] 71.5% were ≤30, whereas only 6.0% were age ≥60. The crude prevalence (all ages) in these countries was low, ranging from 0.01 to

TABLE 2. *Crude prevalence of ET (older age categories) in population-based prevalence studies*

Author	Year	Country	Prevalence ≥60 years* (%)	Prevalence in oldest age group (%)
Glik[20]	2008	Israel	0.8 (≥65 years)	1.5 (≥80 years)
Mancini[21]	2007	Italy	2.1 (≥61 years)	3.3 (81–90 years) and 3.6 (≥90 years)
Salemi[17]	1994	Italy	2.3 (≥60 years)	5.4 (≥80 years)
Louis[25]	1995	USA	2.2 [3.9] (≥65 years)	4.6 [8.4] (≥85 years)
Hornabrook[16]	1976	New Guinea	4.1 (≥60 years)	No data
Louis[29]	2009	USA	5.5 (≥65 years)	9.9 (85–94 years) and 21.7 (≥95)
Dogu[27]	2003	Turkey	6.3 (≥60 years)	8.7 (≥80 years)
Bergareche[26]	2001	Spain	4.8 [6.4] (≥65 years)	9.7 [12.9] (≥85 years)
Sur[24]	2008	Turkey	6.5 (≥61 years)	9.3 (≥71 years)
Benito-Leon[28]	2003	Spain	4.8 [7.0] (≥65 years)	7.3 [10.6] (≥85 years)
Moghal[30]	1994	Canada	14.3 (≥65 years	No data
Rautakorpi[5]	1982	Finland	9.0 [15.6] (≥60 years)	11.8 [20.7] (≥80 years)
Khatter[31]	1996	USA	20.5 (≥65 years)	No data

Table includes studies that: (1) either examined all subjects or provided information on screening questionnaire and (2) provided separate age-stratified estimates of prevalence among elderly aged 60 and older.

Studies are ordered from lowest to highest prevalence (%) in the ≥60 year age stratum.

All values in brackets account for the sensitivity of the initial screening process (i.e., values are higher because they include an estimate of the number of false negatives).

*In some studies, age stratum was ≥60 while in others (as indicated), it was ≥61 or ≥65.

0.4% (median = 0.07%).[8,10–13,15,16] By contrast, the study in Italy[17] had an older age structure (15.1% age ≥60) as did that among the Parsi community of India (44% age ≥50),[23] yielding crude prevalence estimates (all ages) of 0.4[17] and 1.6% (median = 1.0%).[23]

A third issue is whether each study subject was examined (and by whom) or whether they were screened first and then examined based on a positive response to a screening questionnaire. Screening questionnaires for ET generally have only modest sensitivity (generally in the 60–70% range),[35,36] particularly for mild, previously-undiagnosed population-dwelling ET cases. Some studies screened their subjects, but also provided data on the sensitivity of their screening questionnaire,[5,25,26,28] thereby allowing one to calculate an estimated prevalence that approximated a situation in which all subjects had been examined (Table 1). Of the studies that did this or that examined each subject (see bolded studies in Table 1), the large majority provide higher estimates of prevalence.[5,16,25–31] A related issue is that neurologists (and furthermore, movement disorder specialists) are more likely to provide accurate estimates of the prevalence of ET than general practitioners or nonphysicians. Indeed, the motor manifestations of ET are relatively restricted, and the main clinical manifestation (kinetic tremor) may be a feature of diverse disorders of the central and peripheral nervous systems.[37,38] Furthermore, kinetic tremor of the arms may be found to some extent as a normal finding in the ageing population.[39] It is, therefore, not surprising that studies have shown that 30–50% of "ET" cases do not have ET, but rather, have other diagnoses.[40,41]

Finally, the definition of ET is critical. While most prevalence studies defined ET, six did not.[8,9,11,13,15,19] With few exceptions,[20,24,26–29] the large majority of studies used definitions that either did not specify the examination that was performed on participants or the minimal severity of tremor that was required to qualify for a diagnosis.

Arriving at a More Refined Estimate of Prevalence

The issues outlined earlier may be used to derive a more refined estimate of disease prevalence. First, population-based studies provide the most valid estimates. Second, it would be useful to derive at least two separate summary estimates, one based on data from all ages and a second based on older ages (e.g., age ≥65). Third, given the tendency for two-phase studies (screening questionnaire followed by physical examination) to under-ascertain ET cases, it is preferable to use those studies that either examined each subject or provided data on the sensitivity of their screening questionnaire so that adjustments could be made for false negatives.

Using this strategy, the calculated prevalence of ET (all ages) = 0.4%; this is based on two studies[16,17] (Table 1). Furthermore, the crude prevalence in older age groups (age 60–65 and older) ranges from 0.8 to 20.5% (see unbracketed values as well as bracketed values [values that account for the sensitivity of the

TABLE 3. *Crude prevalence (%) of ET across age strata in different studies*

	0-9 Yrs	10-19 Yrs	20-29 Yrs	30-39 Yrs	40-49 Yrs	50-59 Yrs	60-69 Yrs	70-79 Yrs	80-89 Yrs	≥90 Yrs
Hornabrook[16]	0.0			0.07	0.6	1.7	4.1			
Salemi[17]	0.0		0.05		0.2		1.1	2.9	5.4	
Glik[20]							0.6	0.7	1.5	
Mancini[21]							1.0	2.7	3.3	3.6
Sur[24]			0.8	0.8	1.6	2.9	3.9	9.3		
[a]Bergareche[26]							0.5	8.2	12.9	
[a]Louis[25]							2.8	4.3	8.4	
Dogu[27]					2.8	3.5	5.9	6.5	8.7	
[a]Benito-Leon[28]							5.4	6.7	7.4	8.3	10.6
Louis[29]							2.5	6.8	9.9	21.7
[a]Rautakorpi[5]					3.9	8.9	12.0	22.1	20.7	

In some instances, values for age category X to Y are placed in category X-1 to Y-1 (e.g., values for age category 61 to 70 are placed in category 60 to 69).

[a]Values account for the sensitivity of the initial screening process (i.e., values include an estimate of the number of false negatives).

initial screening process] in Table 2).[5,16,17,20,21,24–31] If one removes potential outliers (e.g., the two studies with the lowest[20,21] and the two with the highest prevalence estimates[5,31]), the crude prevalence range (age 60–65 and older) = 2.3–14.3% (median = 6.3%) (see bracketed and unbracketed values in Table 2).[16,17,25–30] Furthermore, the prevalence continues to rise with age, with crude prevalence estimates in the oldest age groups (80s, 90s and older) ranging from 1.5 to 21.7% (median = 9.0%) (see bracketed and unbracketed values in Tables 2 and 3).[5,17,20,21,25–29]

Additional Patterns in Prevalence

Age

As shown in the 15 adequately powered studies that provided age-stratified data,[5,14,16–18,21–29,32] the prevalence of ET increases markedly with age, and especially with advanced age (Table 3), thereby indicating that aging is a risk factor for ET. The same relationship with age is true of a variety of neurodegenerative diseases including Alzheimer's disease and Parkinson's disease.[42,43] There are limited data on the prevalence of ET among oldest old; in one study,[29] the crude prevalence was reported to be 21.7% among those age ≥ 95 (Table 3).

ET is not a disease exclusively of adults. Children with ET may come to medical attention,[44] and most of these young-onset cases are familial.[45] Although there are few data, the two population-based prevalence studies that provided data, reported crude prevalence in children (age ≤18) = 0.0%,[16,17] suggesting that while children with ET are seen in clinical settings, on a population-level, ET occurs rarely in children.

Ethnicity

Ethnic differences, if present, might reflect differences in the prevalence of susceptibility genotypes but they could also reflect differences in exposure to environmental factors that have been associated with ET.[46] Although there may be ethnic differences in the prevalence of ET, there is a need for more data. Several studies have made direct comparisons between racial/ethnic groups. An early population-based study in New Guinea reported differences in the prevalence of ET among populations defined by different languages (e.g., high prevalence in villagers living in the Bena Bena and Kamano populations vs. no cases among the Gimi or Yagaria).[16] Tan et al.[14] studied the prevalence of ET in a community-based study in Singapore, comparing Singaporean Chinese, Malays, and Indians. The prevalence of ET was marginally higher in Indians

than Chinese ($P = 0.08$) and no Malays with ET were identified. A study in Copiah county, Mississippi, reported a nonsignificant trend for ET to be higher among whites than African–Americans, although the study relied on an initial screening questionnaire, which could have biased results toward lower prevalence among less educated participants.[18] Similarly, an initial study in northern Manhattan reported a nonsignificant trend toward higher prevalence in whites than African–Americans; however, that study also relied on an initial screening questionnaire.[25] By contrast, a later study of a different sample of the same population, which did not rely on a screening questionnaire, reported a significant ethnic difference in the prevalence of ET, with the prevalence among whites being the lowest.[29] More data are clearly needed.

One may also compare studies of ET that sampled different ethnic groups in the same country. For example, a study in the Basque region of Spain[26] reported a prevalence estimate that was similar to that in Madrid.[28] By contrast, a study of the Parsi community in Bombay, India[23] reported a higher prevalence than a study largely of Hindus in West Bengal.[22] The problem, however, with these types of cross-study comparisons is that differences in study design (screening tools, definition of ET) easily could account for differences.

One may also compare studies of ET that sampled different populations and ethnic groups and used similar or identical study protocols. For example, population-based studies in Turkey, Arabs in Israel, and Basques in Spain did not rely on screening questionnaires and all used the same examination and a similar definition of ET. The crude prevalence of ET was 0.8% (age ≥65 in Arabs in Israel),[20] 6.3% (age ≥60 years in Turkey),[27] 6.5% (age ≥61 years in Turkey),[24] and 6.4% (age ≥65 Basques in Spain),[26] suggesting that there may be regional and possibly ethnic differences in the prevalence of ET.

Gender

Overall, the median value for the ratio of crude male prevalence: crude female prevalence = 1.08:1. Nine studies do not provide data[6–9,12,13,15,19,30] and one study had only one ET case.[11] Of the 18 remaining studies, 11 (61.1%) found no gender difference (male: female ratio ranging from 1.19:1 to 0.78:1; median = 0.95:1),[17,18,20,22–24,26–29,32] six (35.3%) found a statistically higher prevalence among men (male: female ratios = 1.43, 1.50, 1.64, 1.65, 1.90, and 2.26:1),[5,10,14,21,25,31] and one (5.9%) showed a statistically higher prevalence among women (male: female ratio = 0.39:1).[16] Hence, while the majority of studies do not show a gender difference, a sizable minority (more than one-third) show a statistically significant gender difference, with nearly all of those showing a higher prevalence among men than women. In those that showed a higher prevalence among men, the median male: female ratio was 1.65:1.[5,10,14,21,25,31] This possible male predominance in ET is interesting given the clinical,[47–49] epidemiological,[50,51] and possible pathological associations between ET and Parkinson's disease,[52] a disease in which the prevalence in men is higher than that of women.

Isolated Head Tremor

Several studies reported data on the proportion of ET cases with isolated head tremor.[10,16,17,25,28] These data indicate that isolated head tremor was generally uncommon (0.0%, 1.6%, 3.2%, 9.1%, 20.0%)[10,16,17,25,28] One problem with these data, in general, is that there is no information on whether tremor in other body regions (esp. the hands) was completely absent or just milder than generally seen in ET, so that the designation "isolated head tremor" is not clear. Furthermore, those studies with higher proportions (9.1 and 20.0%)[10,16] used field officers and research doctors rather than neurologists or movement disorder neurologists to assign diagnoses so that misclassification (e.g., assigning diagnoses of ET to individuals with cervical dystonia) is a real possibility.[40,41]

Previously Undiagnosed ET

Patients living the community who have mild tremor might not seek medical attention for their tremor and the tremor may be mild enough so that their treating physicians do not make the diagnosis when they present for other complaints. Several studies provided data on the proportion of ET cases who were undiagnosed prior to the prevalence survey. These included 100% (Tanzania),[10] 97.1% (Finland),[5] 92.8% (Turkey),[24] 91.0% (Turkey),[27] 90.0% (Singapore),[14] and 79.7% (Spain).[28] These countries, which represent a broad socioeconomic range, indicate that the large bulk of community-dwelling ET cases are previously undiagnosed and that the ET patients who are seeking medical attention for their tremor represent a small proportion of all ET cases.

SYNTHESIS

The nearly thirty population-based studies of the prevalence of ET come from a broad collection of countries on five continents. Although limited in its

external validity by the significant heterogeneity across studies, a pooled estimate yielded an overall prevalence (all ages) = 0.9% (95% CI 0.5–1.5%). In an additional descriptive review, we found among studies that either directly examined each subject or provided data on the sensitivity of their screens, prevalence (all ages) = 0.4%. Prevalence increased markedly with age. In the meta-analysis, prevalence (age ≥ 65 years) = 4.6%, and in descriptive analyses, median crude prevalence (age ≥ 60–65) = 6.3%.

The prevalence estimates we have reported for ET confirm the view of this disorder as very common; in fact, ET is often viewed as the most prevalent movement disorder among adults.[3] One population-based study in Austria among persons aged 50–89 years,[32] directly compared the prevalence of ET (3.1%) with other movement disorders, noting that it was indeed higher (e.g., the prevalence of primary dystonia = 0.8%, secondary dystonia = 1.1%, tics = 0.4%, and chorea < 0.2%). One exception in that study[32] was restless legs syndrome, whose prevalence (10.8%) was greater than that of ET (3.1%).However, in other studies, the prevalence of restless legs syndrome in adults (mean age 52.9 years) has been significantly lower (1.8%),[2] suggesting that the prevalence of ET may indeed be higher than that of restless legs syndrome. In most studies, the prevalence of ET is markedly higher than that of Parkinson's disease.[6,12,13,19,22,29–31] ET is also more prevalent than many common neurological diseases aside from movement disorders (epilepsy, stroke, and multiple sclerosis).[53]

Age is clearly a risk factor for ET, as most studies indicate a marked age-associated rise in prevalence. By the seventh decade, most studies estimate a prevalence of 2.3–14.3% (median = 6.3%) and the prevalence continues to rise with age so that it may be higher than 20% in the oldest old. Several studies suggest the presence of ethnic differences but more data are needed. With a critical mass of studies accumulating over the past decade, a picture of a slight male predominance may be emerging, which is interesting given clinical,[47–49] epidemiological,[50,51] and possible pathological associations between ET and Parkinson's disease,[52] a disease in which there is a well-established pattern of higher prevalence among men.

Data on overall disease prevalence and prevalence among patient subgroups is important. These data not only form the numerical basis for planned public health initiatives but they provide initial clues about the existence of underlying biological factors of mechanistic importance. The latter is particularly important in the setting of a disease about which so little is known of the underlying mechanisms.

Author Roles: Elan D. Louis—Research project conception, organization and execution; manuscript writing (writing the first draft and making subsequent revisions). Joaquim J. Ferreira—Research project organization and execution; manuscript writing (making subsequent revisions).

Financial Disclosures: Dr. Louis receives research support from the NIH [NINDS #R01 NS42859 (principal investigator), NINDS #R01 NS39422 (principal investigator), NINDS #R56 NS042859 (principal investigator), NINDS #T32 NS07153-24 (principal investigator), NIA #2P01 AG0027232-16 (principal investigator), and NINDS #R01 NS36630 (co-Investigator)] and the Parkinson's Disease Foundation (principal investigator).

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