

## Reviews

## Descriptive Epidemiology of Cervical Dystonia

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### Abstract

**Background:** Cervical dystonia (CD), the most common form of adult-onset focal dystonia, has a heterogeneous clinical presentation with variable clinical features, leading to difficulties and delays in diagnosis. Owing to the lack of reviews specifically focusing on the frequency of primary CD in the general population, we performed a systematic literature search to examine its prevalence/incidence and analyze methodological differences among studies.

**Methods:** We performed a systematic literature search to examine the prevalence data of primary focal CD. Sixteen articles met our methodological criteria. Because the reported prevalence estimates were found to vary widely across studies, we analyzed methodological differences and other factors to determine whether true differences exist in prevalence rates among geographic areas (and by gender and age distributions), as well as to facilitate recommendations for future studies.

**Results:** Prevalence estimates ranged from 20–4,100 cases/million. Generally, studies that relied on service-based and record-linkage system data likely underestimated the prevalence of CD, whereas population-based studies suffered from over-ascertainment. The more methodologically robust studies yielded a range of estimates of 28–183 cases/million. Despite the varying prevalence estimates, an approximate 2:1 female:male ratio was consistent among many studies. Three studies estimated incidence, ranging from 8–12 cases/million person-years.

**Discussion:** Although several studies have attempted to estimate the prevalence and incidence of CD, there is a need for additional well-designed epidemiological studies on primary CD that include large populations; use defined CD diagnostic criteria; and stratify for factors such as age, gender, and ethnicity.

**Keywords:** Cervical dystonia, epidemiology, prevalence, incidence

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## Introduction

Cervical dystonia (CD) is a chronic neurologic disorder characterized by involuntary patterned contractions of cervical musculature resulting in abnormal movements or postural changes of the head, neck, and shoulders.<sup>1</sup> Dystonia is variously classified according to whether it is primary (idiopathic) or secondary. Primary CD, the most common form of CD, is thought to be of multifactorial origin, probably resulting from a combination of genetic and environmental factors.<sup>2,3</sup> Less frequently, CD may be secondary to exogenous causes, part of a dystonia-plus syndrome, or associated with hereditary degenerative disorders.<sup>3,4</sup>

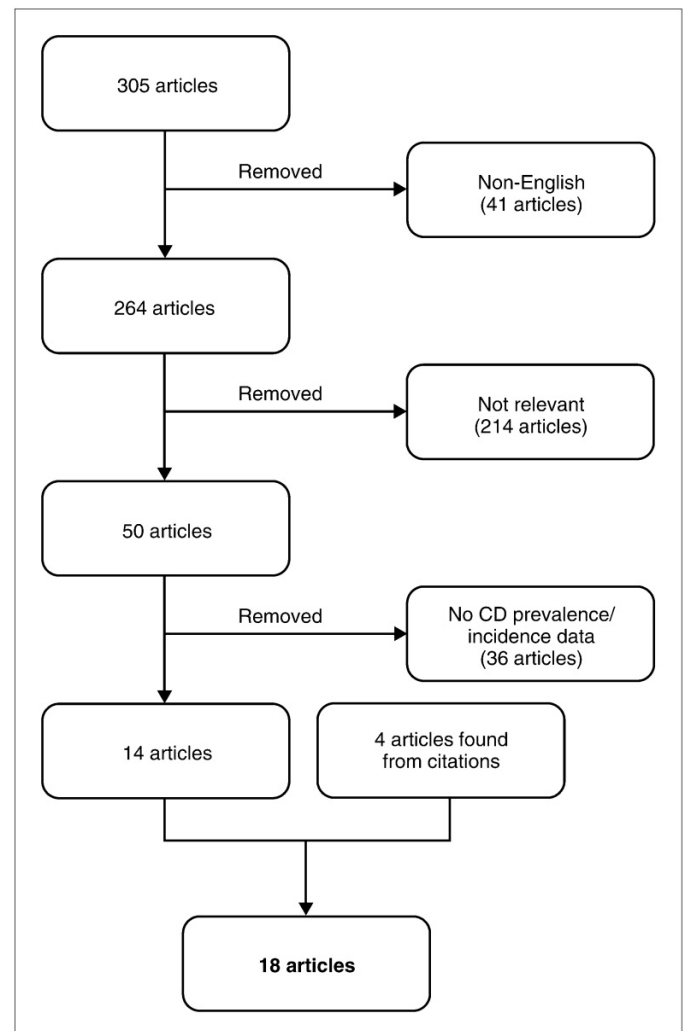
The pattern of neck muscle involvement in patients with CD is variable, leading to clinically heterogeneous directional presentations, such as torticollis, laterocollis, retrocollis, or anterocollis.<sup>5</sup> Individuals may also have additional signs and symptoms, such as shoulder elevation, neck/shoulder pain, head oscillation due to dystonic tremor produced by uneven contractions of the cervical muscles, arm tremor, and use sensory tricks.<sup>3,5-8</sup> At present, there are no validated clinical diagnostic guidelines to allow easy differentiation of CD from other disorders of the neck that may simulate dystonia.<sup>9,10</sup> Because of this, along with the wide variability in CD clinical features among individual patients, the diagnosis of CD is open to misinterpretation and misdiagnosis.<sup>5,11</sup> Overall, family studies indicate that as many as one quarter to half of people with dystonia may be undiagnosed or misdiagnosed.<sup>12-15</sup> Other studies have documented that the diagnosis of CD may be delayed for several years, with many patients visiting numerous physicians in the interim.<sup>16,17</sup> Furthermore, it is common for mild cases of CD to go undiagnosed.<sup>5</sup> Finally, neurologists may have different attitudes on the recognition of dystonia, which is dependent on their experience and the site and severity of dystonia.<sup>18</sup> As such, there is currently a lack of consistent findings regarding the relative frequency of CD.

Assessment of CD epidemiology may help to provide insight into the cause of the disorder and improve medical education, public awareness, and patient health services. Furthermore, it may highlight misconceptions around prevalence and help to define the societal burden of CD. We performed a systematic literature search to examine the prevalence and incidence of primary CD and analyzed methodological differences among studies with three objectives in mind: to search for more precise estimates of the prevalence and incidence of primary CD, to determine whether differences exist in prevalence rates among geographic areas and by gender and age distributions, and to make recommendations for future studies.

## Methods

Relevant articles were identified through searches of MEDLINE (via PubMed) and EMBASE. PubMed search strings involved the following: Medical Subject Heading (MeSH) terms “cervical dystonia,” “wryneck,” “torticollis,” “spasmodic torticollis,” or “intermittent torticollis;” MeSH major topics “epidemiology,” “incidence,” or “prevalence;” MeSH subheading “epidemiology;” or Title/abstract “epidemiology,” “incidence,” “prevalence,” “natural history;”

“disease frequency;” or “surveillance;” or Publication type “Clinical Trial,” “Editorial,” “Letter,” “Addresses,” “Bibliography,” “Biography,” “Clinical Trial, Phase I,” “Clinical Trial, Phase II,” “Clinical Trial, Phase III,” “Clinical Trial, Phase IV,” “Comment,” “Controlled Clinical Trial,” “Dictionary,” “Directory,” “Duplicate Publication,” “Festschrift,” “Interview,” “In Vitro,” “Legal Cases,” “Legislation,” “News,” “Newspaper Article,” “Overall,” “Patient Education Handout,” or “Periodical Index.” EMBASE search strings were as follows: explosion search “cervical dystonia,” “torticollis,” “epidemiological data,” “incidence,” or “prevalence;” Abstract/title “wryneck,” “epidemiology,” “incidence,” “prevalence,” “disease frequency,” “surveillance,” or “natural history;” or Item type “editorial,” “letter,” “note,” “short survey,” or “clinical trial.” PubMed and EMBASE searches were limited to those conducted in humans and published in English between January 1, 1991 and March 1, 2013.



**Figure 1. Diagram of literature sorting to identify articles that fit the search criteria.**

Excluding duplicates, this search strategy yielded 305 citations (Fig. 1). By applying the predefined criteria of an English language-only full-text original article reporting data on primary CD prevalence or incidence, 41 non-English language articles were deleted, as were 214 articles that did not fit the predefined criteria. The full text of the remaining 50 articles was examined in detail to determine whether they met the predefined criteria, and an additional 36 articles that did not contain CD prevalence/incidence data were excluded. The reference lists of the 14 remaining articles were reviewed for any additional articles missed in the literature search, yielding another 4 articles, for a total of 18 studies that met our methodological criteria and provided prevalence and/or incidence data on primary CD.

## Results

### Prevalence studies

The crude prevalence estimates from the 16 studies that provided prevalence data ranged between 20 and 4,100 cases per million (Table 1).<sup>1,19-33</sup> This large variability is associated with differences in study design and study populations.

### Differences in study design

Ten studies<sup>22-27,29-31,33</sup> pooled patients from tertiary and quaternary referral centers for movement disorders, two studies<sup>20,28</sup> used a record-linkage system (i.e., medical records of patients were assessed in a standardized way at clinics and/or hospitals from a given area), and four studies<sup>1,19,21,32</sup> ascertained patients with CD from the general community (door-to-door studies or population-sample studies based on paper or electronic surveys). Regardless of study design, a common major methodological limitation was that no study was based on published, validated criteria for diagnosing CD, as there are none. Because of the lack of uniform criteria, the gap between symptom onset and diagnosis is an issue to consider with descriptive studies.

Service-based studies and record-linkage systems<sup>20,22-31,33</sup> did not take into account subjects who were not seeking medical advice or who were misdiagnosed; therefore, they provided estimates that were mostly in the low end of the range of variability (20 to 183 cases per million) (Table 1).

In contrast, population-based studies<sup>1,19,21,32</sup> provided estimates that were in the middle to the high range of variability (100 to 4,100 cases per million). Among these studies, the door-to-door surveys performed in China and Egypt<sup>19,21</sup> screened for all forms of adult-onset dystonia but only identified individuals with CD, probably owing to the lack of a systematic approach to the diagnosis of dystonia. This may well have affected the resulting prevalence estimates. The Indian survey<sup>32</sup> assessed 52,377 people with a two-step procedure: screening by a questionnaire followed by examination of subjects who screened positive. In this study, limb dystonia was the most common type of primary dystonia (210 per million for writer's cramp and 133.5 per million for writing tremor); it was much more frequent than CD (38.1 per million) and blepharospasm (57.2 per million). Because the screening instrument had specific questions for upper limb movements rather than for neck or eyelid movements, this study was also affected

by an ascertainment bias, meaning that the study likely did not equally identify all existing cases due to the sampling procedure. Finally, the U.S. survey<sup>1</sup> yielded the highest prevalence estimate of CD of 4,100 per million. However, as acknowledged by the authors, this e-mail survey was characterized by several limitations, including a 3% response rate, no physician confirmation of diagnosis, potential overestimation of prevalence due to a higher rate of response from those with CD, underrepresentation of non-Caucasians, and potential underrepresentation of lower-income households (i.e., those without computers). Therefore, the point prevalence rate might have been overestimated in this survey by a combination of a chance-cluster of cases and ascertainment bias.

Other factors in the design of the studies also may have had an effect on prevalence estimates, as suggested by the following observations. Studies considering focal CD alone<sup>20,30,32</sup> tended to obtain lower estimates than studies including both focal and segmental dystonia. Service-based studies recruiting cases from both neurological and non-neurological services<sup>20,26-31,33</sup> tended to provide higher estimates than studies based on neurological services alone.<sup>22-25</sup>

### Differences in study population characteristics

The selected studies differed in size, as well as age and ethnicity of the study populations. The source populations ranged from 42,000 to 5,792,937 individuals (Table 1). In general, the studies based on very large populations suffered most from ascertainment bias because of difficulties in validating the diagnosis by dystonia experts.

Theoretically, differences in the age and gender structure of the study population may affect the comparison of prevalence estimates. In this regard, most studies provided only crude estimates that are difficult to apply to other populations with different demographics. Precisely how these factors affect prevalence estimates is difficult to assess, even taking into account that the studies performed in China, India, and southern Italy standardized their crude rates by age.<sup>19,32,33</sup> Interestingly, the various studies reported similar gender ratios (Table 1), suggesting that the gender structure of the study population is unlikely to have a significant effect on prevalence data comparisons.

Ethnic differences across study populations might also have influenced prevalence estimates, as suggested by the Norwegian study.<sup>27</sup> In this study, the prevalence of late-onset dystonia was considerably higher in people of European descent (283 per million) than among first-generation immigrants of Asian and African descent (34 per million).

### Incidence

Our literature search identified three studies that examined the incidence of primary CD.<sup>17,20,34</sup> In the earliest study based on the Rochester Epidemiology Project, CD occurred in 10.9 per million person-years.<sup>20</sup> This estimate is considered low because case ascertainment was based on a review of medical charts of patients evaluated at the Mayo Clinic between 1950 and 1982 rather than on subject examination. Although the Rochester Epidemiology Project was likely well suited to identify rare diseases, the information on

Table 1. Prevalence Studies on Primary Adult-onset CD

First Author, Year	Study Design	Source of Cases	Type of Dystonia Included	Geographic Region	Population Size	Age of Study Population	Prevalence per 1,000,000	F:M ratio	Age of onset (mean $\pm$ SD, years)
Li 1985 <sup>19</sup>	Door-to-door survey	General population	Focal/segmental dystonia	China	63,195	All ages	30, age-adjusted to the 1960 U.S. population: 30	NR	NR
Nutt 1988 <sup>20</sup>	Record-linkage system	Neurological and non-neurological services	Focal/segmental dystonia	U.S.	56,433	All ages	89	4.5:1	45
Kandil 1994 <sup>21</sup>	Door-to-door survey	General population	Focal/segmental dystonia	Egypt	42,000	All ages	100	0.3:1	34.6 $\pm$ 4.9
Nakashima 1995 <sup>22</sup>	Service-based	Neurological services	Focal dystonia	Japan	244,935	All ages	28.5	1.3:1	NR
ESDE 2000 <sup>23</sup>	Service-based	Neurological services	Focal/segmental dystonia	8 European countries	5,792,937	>20 years	57	1.3:1	NR
Castelon Konkiewitz 2002 <sup>24</sup>	Service-based	Neurological services	Focal/segmental dystonia	Germany	1,322,883	All ages	54	1.3:1	41.6 $\pm$ 14.1
Matsumoto 2003 <sup>25</sup>	Service-based	Neurological services	Focal/segmental dystonia	Japan	1,459,130	All ages	23	0.5:1	42.7 $\pm$ 16.7 F: 47.0 $\pm$ 18.7 M: 40.3 $\pm$ 15.3
Pekmezovic 2003 <sup>26</sup>	Service-based	Neurological and non-neurological services	Focal/segmental dystonia	Yugoslavia	1,602,226	$\geq$ 20 years	59	1.7:1	43.3 $\pm$ 12.1 F: 46.4 $\pm$ 10.4 M: 37.4 $\pm$ 13.0
Le 2003 <sup>27</sup>	Service-based	Neurological and non-neurological services	Focal/segmental dystonia	Norway	508,726	All ages	130	1.9:1	41.2

**Table 1.** Continued

First Author, Year	Study Design	Source of Cases	Type of Dystonia Included	Geographic Region	Population Size	Age of Study Population	Prevalence per 1,000,000	F:M ratio	Age of onset (mean $\pm$ SD, years)
Butler 2004 <sup>28</sup>	Record-linkage system	Neurological and non-neurological services	Focal/segmental dystonia	England	2,605,100	All ages	183.1	2.1:1	42.1
Asgeirsson 2006 <sup>29</sup>	Service-based	Neurological and non-neurological services	Focal/segmental dystonia	Iceland	288,201	All ages	115	2.3:1	41.7 $\pm$ 14.4
Fukuda 2006 <sup>30</sup>	Service-based	Neurological and non-neurological services	Focal dystonia	Japan	247,973	All ages	20	0.7:1	36.6 $\pm$ 8.2 F: 36.0 $\pm$ 15.6 M: 36.0 $\pm$ 3.6
Sugawara 2006 <sup>31</sup>	Service-based	Neurological and non-neurological services	Focal/segmental dystonia	Japan	1,166,967	All ages	28	NR	NR
Jankovic 2007 <sup>1</sup>	Online questionnaire	General population	Focal/segmental dystonia	U.S.	60,062	>18 years	4,100 Census weighted: 3,900	NR	NR
Das 2007 <sup>32</sup>	Door-to-door survey	General population	Focal dystonia	India	52,377	All ages	38.1, age-standardized to the world population: 39.6	1:1	49
Papantonio 2009 <sup>33</sup>	Service-based	Neurological and non-neurological services	Focal/segmental dystonia	Italy	541,653	>17 years	44.3, age- and sex-adjusted to the 2001 Italian population: 44.8	1.4:1	NR

Abbreviations: CD, cervical dystonia; ESDE, Epidemiological Study of Dystonia in Europe; F, female; M, male; NR, not reported; SD, standard deviation.

dystonia incidence was further limited because late-onset focal dystonia was not widely recognized by primary care physicians or even by general neurologists as a neurological disease during most of the study period.<sup>35</sup>

The second study also investigated CD incidence within the Rochester registry, but from 1960–1979.<sup>34</sup> Eleven new cases were identified, yielding an overall incidence rate of 12 per million person-years after age- and sex-adjustment to the U.S. Caucasian population in 1970. However, injury preceded onset in 4 of the 11 patients, suggesting that some patients had secondary rather than primary CD.

A more recent study reviewed the medical records of the multi-ethnic population of a northern California health maintenance organization to identify CD cases diagnosed from 1997–1999 and yielded an incidence estimate of 8 per million person-years for CD.<sup>17</sup> Incidence was significantly higher in the Caucasian population than for persons from other races (12.3 vs. 1.5 per million person-years). Even though this study focused on diagnosed dystonia and its incidences should be considered minimum estimates, they were probably more accurate than the estimates provided by the Rochester registry due to the consistency in coding and the recognition of focal dystonia as a neurological disease.

### Age and gender distribution

According to prevalence/incidence studies, the peak age at CD onset reported by the various studies is in the fourth to fifth decade, with a mean age of 42 years (Table 1). This is consistent with findings from several large clinical series.<sup>36</sup> A few studies<sup>23,27,33</sup> also provided age-adjusted prevalence estimates by which the rate of CD increased with age but decreased after age 70 in all but one study.<sup>26</sup> This could be due to a referral bias or increased mortality in this age cohort. Although mortality studies have not been performed in primary late-onset dystonia, there is no evidence suggesting increased mortality in patients with CD. However, controlled studies documented an increased risk of psychopathology in patients with CD, especially for symptoms of depression.<sup>37,38</sup> Other associated disorders reported in patients with CD include idiopathic scoliosis<sup>39</sup> and degenerative spine changes,<sup>40</sup> but no positive association was observed between primary adult-onset focal dystonias and age-related medical conditions typically associated with increased mortality, such as arterial hypertension.<sup>41</sup>

Despite methodological differences and variable prevalence estimates, comparable gender ratios were reported in the various studies, with an overall mean female:male ratio of 1.7:1 across studies (Table 1). Several large clinical series have confirmed a female preponderance in CD.<sup>41–43</sup> For example, in the Northern California study, the incidence was 2.5 times higher in females than in males (11.4 per million vs. 4.5 per million person-years)<sup>17</sup> and the female:male age-adjusted incidence rate in the Rochester study was 3.6:1.<sup>34</sup> A comprehensive review of epidemiology of primary dystonia also identified a higher prevalence of CD in females versus males,<sup>44</sup> but its meta-analysis was based on a smaller number of original articles than identified here.

Despite the greater prevalence in females, several studies have reported that CD developed at an earlier age in males than in females.<sup>17,25,26,45</sup> The gender difference in age of CD onset may reflect differences in genetic factors, different exposure to environmental etiologic factors,<sup>45</sup> or gender differences in education and perhaps income level, which may affect whether individuals seek medical care.<sup>46</sup>

Several studies ascertaining family history of adult-onset dystonia by proband interview, a method that yields low diagnostic sensitivity and specificity in detecting affected relatives,<sup>14</sup> suggested a lower age at dystonia onset in familial than in sporadic patients.<sup>47–49</sup> In support of this observation are findings from a recent study of 308 Caucasians, some of who harbored potentially pathogenic sequence variants in *CI21*.<sup>50</sup> The mean age at onset was 41.1 years in those with familial CD versus 47.6 in those with sporadic disease. This study also found a difference in gender distribution between patients with familial and sporadic CD; female:male ratios were 2.7:1 and 3.5:1 in familial and sporadic CD patients, respectively. In contrast, another recent family study ascertaining family history by a highly sensitive and specific procedure failed to find any phenotypic differences in age at onset, gender distribution, or the rate of spread between familial and sporadic patients with extracranial dystonia, including CD.<sup>51</sup>

### Discussion

Despite some valiant attempts to examine CD epidemiology, the studies that have been performed to date all had limitations to varying degrees; therefore, the prevalence and incidence of CD are difficult to determine accurately. If examination of service-based and record-linkage studies is limited to those that recruited subjects who were directly examined by a neurologist or a physician knowledgeable about dystonia diagnosis and included both focal and segmental cases from neurological and non-neurological services, the crude prevalence of CD among individuals seeking medical attention ranged from 28–183 cases per million.<sup>26–29,31</sup> A recently published meta-analysis of primary dystonia suggested an overall CD prevalence of about 50 per million.<sup>44</sup> Despite methodological differences, the estimates of CD incidence are probably consistent across the available studies and suggest a minimum incidence estimate of 8–12 cases per million person-years.<sup>17</sup>

Although some progress has been made in estimating the prevalence and incidence of CD, further research is warranted. Considerations for future studies include more specific guidelines for the diagnosis of CD to recruit sufficiently large populations, stratification for ethnicity, and adjustment of estimates toward a common standard. Because clinical examination of a relatively large population may be challenging to fund and difficult to perform, a two-step procedure, in which subjects are first screened by a questionnaire followed by clinical examination of those who meet examination criteria, may be more feasible, even taking into account the recent attempts on the development of validated screening tools for CD.<sup>52–54</sup> Improved epidemiological assessments of CD may aid in increased awareness, help define societal burden, and result in earlier treatment of patients with this condition.

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