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Meta-analysis: Adulthood prevalence of Tourette syndrome

Jessica L.S. Levine[a], Natalia Szejko[b,d], Michael H. Bloch[a,c,*]

[a] Yale Child Study Center, Yale University School of Medicine, New Haven, CT, United States of America
[b] Department of Neurology, Medical University of Warsaw, Poland
[c] Yale Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States of America
[d] Department of Bioethics, Medical University of Warsaw, Poland

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ABSTRACT

Background: Tourette syndrome (TS) is estimated to have a prevalence of 0.30–0.77% in school aged children. Longitudinal studies suggest that roughly half-to-two-thirds of children with TS experience a substantial improvement in tic symptoms during adolescence. By contrast, few studies have examined adulthood prevalence of TS. Accurate prevalence estimates across the lifespan are needed to support regulatory and public health decisions.

Methods: We searched PubMED and EMBASE for studies that examined the prevalence of TS in adults. We conducted a random-effects meta-analysis of logit event rates to estimate prevalence of TS across studies. Too few studies are available to conduct moderator analysis or examine publication bias. We also examined the risk ratio of TS prevalence in adults for males compared to females.

Results: Three studies involving 2,356,485 participants were included. There were significant differences in TS adulthood prevalence estimates between studies ranging from 49 to 657 cases of TS per million adults. Overall prevalence of TS in adulthood was estimated to be 118 cases of TS per million adults (95%CI: 19–751 cases per million adults). There was a large amount of heterogeneity between studies (I^2 = 99%) that was likely related to differences in their methods of identification of TS cases. By contrast, the male:female ratio of risk of adulthood TS was similar between studies with a Risk Ratio = 2.33 (95% CI: 1.72–3.16).

Conclusion: Estimates of adulthood prevalence of TS are sparse and likely highly affected by differences in method of case identification. Diagnosis and diagnostic estimates of TS could be aided by including a requirement for impairment as well as potential remission criteria similar to other psychiatric conditions.

1. Introduction

Tourette's Syndrome (TS) is a neuropsychiatric disorder characterized by multiple motor and vocal tics, lasting at least one year in duration with an onset prior to age 18 (American Psychiatric Association, 2013). The typical age of onset of tics is between four and six years old, with the most severe occurring between 10 and 12 years old (Leckman et al., 1998). Longitudinal studies have demonstrated that roughly half to two-thirds of children with TS have significant improvement in tic symptoms by adulthood (Bloch and Leckman, 2009; Leckman et al., 1998). While there is typically a substantial decline in tic symptoms during adolescence, some of the most severe cases occur during adulthood (Cheung et al., 2007). Better understanding the prevalence of TS across the lifespan has important public health and regulatory consequences.

Most of previous systematic reviews on the prevalence of TS has focused specifically on its prevalence in children. A recent systematic review reported prevalence rates of TS in children at 0.77% (95% CI: 0.39–1.51) (Knight et al., 2012). This is comparable with other reported TS prevalence rates of between 0.3% and 0.9% in children (Scharf et al., 2015; Yang et al., 2016b). Tics are more prevalent in boys than girls with prevalence rates of TS estimated to be over 4-fold higher among males in childhood (Knight et al., 2012). However, given that TS is one of the only DSM-5 diagnoses not to require associated distress or impairment, many children with tics do not require treatment (Murphy et al., 2013). Nonetheless, children with tics are at increased risk for several psychiatric comorbidities including obsessive-compulsive disorder, attention-deficit hyperactivity disorder, as well as developmental disorders, learning disabilities and disruptive behaviors (Bloch and Leckman, 2009; Kurlan et al., 1994).

By contrast, there have been very few systematic reviews and meta-analyses that have concentrated on the adulthood prevalence of TS.

* Corresponding author at: Child Study Center, Yale University School of Medicine, 230 S. Frontage Road, New Haven, CT 06520, United States of America.
E-mail address: michael.bloch@yale.edu (M.H. Bloch).

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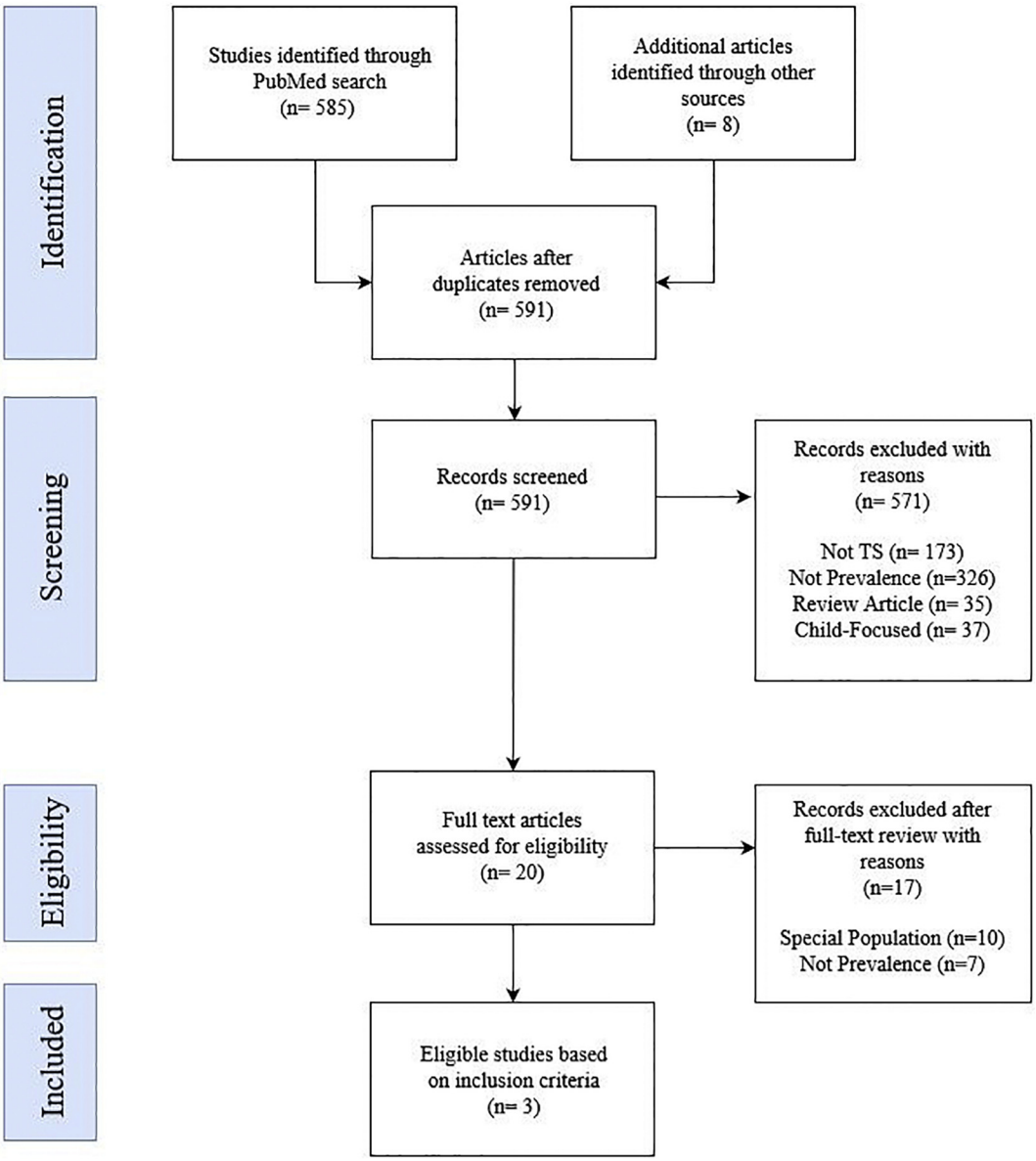

Fig. 1. PRISMA flow chart of articles for selection of studies.

There is one previous meta-analysis that gives an estimate of the prevalence of TS in adults. Knight et al. (2012) suggest that the prevalence of TS is 0.05% in the adult population (Knight et al., 2012). However, there is significant heterogeneity in the studies reviewed. Roughly half of the articles included were studies that actually examined prevalence rates of TS in adolescents (16–17 years old) not adults. Given what we know about the clinical course of TS, we expect the prevalence rates of TS to vary substantially around this age as symptoms improve. Additionally, studies examining TS in high-risk populations (e.g. psychiatric inpatients) were included in the meta-analysis (Knight et al., 2012). Given what we know about the high comorbidity of TS with other psychiatric disorders, we would expect the prevalence of TS to be overestimated in this population.

The goal of the current meta-analysis is to appraise and meta-analyze the previous studies examining prevalence of TS in adults (older than age 18 years). We also plan to examine male: female ratio of TS in adulthood studies. Understanding the male: female prevalence rate in adulthood and comparing it to childhood is important because it may give us clues to whether there are gender specific differences in long-term outcome. Previous longitudinal studies have not been sufficiently powered to detect even fairly substantial gender differences in outcome. Understanding the overall prevalence rate of TS across the lifespan including adulthood is important for making public health decisions and also regulatory issues such as TS orphan disease status with the US Food and Drug Administration.

2. Methods

Two reviewers (JL, NS) searched the electronic database of PubMed on January 10th, 2019 for relevant studies using the search: (tourette syndrome[MeSH Terms] OR tic disorders[MeSH Terms] OR tics[MeSH Terms] OR “tic disorders”[Title/Abstract]) AND (population[Title/Abstract] OR prevalence[Title/Abstract] OR epidemiology[Title/Abstract] OR epidemiological[Title/Abstract]OR incidence[Title/Abstract] OR epidemiologic[Title/Abstract]) Limit: Humans. These studies were further reviewed for additional relevant citations.

The titles and abstracts of the studies obtained through the search were examined by two reviewers (JL, NS) in order to determine article inclusion. Discrepancies were addressed by the reviewers through discussion and eventually conversation with the senior reviewer (MHB).

Eligibility for the meta-analysis was based on the following criteria: (1) examining TS and (2) examining prevalence. Articles were excluded based on the following criteria (1) meta-analyses or review papers and (2) study focused exclusively on children (0–18 years old) or (3) examining TS prevalence rates in special populations (e.g. twin studies, Developmental or intellectual disabilities, psychiatric inpatients, etc.). Data collected on each article included year, country, age range, date of sampling, diagnostic criteria, identification method, sample size, TS cases, prevalence (per million), and male:female ratios.

All statistical analyses were completed in Comprehensive Meta-Analysis Version 3.0 (Biostat, 2016). Our primary outcome of interest was prevalence of TS. A random effects model was used as the primary method for meta-analysis. We also utilized a logit transformation of prevalence (event rate) given the low rate of TS observed in the population. Because of the small numbers of studies completed in the area we were unable to examine publication bias or moderators associated with measured prevalence. Moderators of potential interest that we were unable to examine included location of studies, mean age, study quality, diagnostic criteria of TS utilized, method of TS assessment, requirement of current tics or distress/impairment for case identification of TS. We also utilized risk ratio to examine the prevalence rate of TS in males compared to females in previous studies. A random-effects model was also utilized for this analysis.

3. Results

3.1. Selection of studies

Fig. 1 is a PRISMA diagram that depicts our procedure for selection of studies. Our search yielded 591 potential citations that were possibly eligible for inclusion. Further examination of the full-texts of these papers identified only 3 studies involving 2,356,485 participants that were eligible for inclusion in our meta-analysis (Burd et al., 1986; Schlander et al., 2011; Yang et al., 2016a). Most studies examining prevalence estimates of TS did not include data for adult populations. Table 1 depicts the characteristics of included studies that are described in greater detail.

3.2. Prevalence of TS in adulthood

Fig. 2 depicts of forest plot describing the overall prevalence of TS reported in adults in individual studies. The methodology and results of individual studies examining TS prevalence are discussed in detail in following sections. There were significant differences in TS adulthood prevalence estimates between studies ranging from 49 to 657 cases of TS per million adults. Overall prevalence of TS in adulthood was estimated to be 118 cases of TS per million adults (95%CI: 19–751 cases per million adults). There was significant heterogeneity in estimates of prevalence between studies (Q-value = 295, df = 2, $p < .001$, $I^2 = 99\%$). We were unable to examine possible publication bias in the literature because of the small number of included studies.

Fig. 3 is a forest plot examining the risk ratio of the prevalence in TS in males compared to females among adults with TS. The male:female ratio of risk of adulthood TS was similar between studies with a Risk Ratio = 2.33 (95% CI: 1.72–3.16, z = 5.43, p < .001). There was no significant heterogeneity between studies (Q-value = 3.6, df = 2, $p = .51$, $I^2 = 0\%$). We were unable to examine possible publication bias in the literature because of the small number of included studies.

3.3. Individual studies of adulthood prevalence of TS

3.3.1. Burd et al. 1986

Burd et al., 1986 investigated TS prevalence among adults in North Dakota (Burd et al., 1986). North Dakota maintained a registry of all patients diagnosed with TS at the time. The prevailing DSM-III criteria for TS were utilized at the time for the diagnosis of TS which included

Table 1
Studies examining prevalence of Tourette syndrome in adults.

	Country	Age range	Date of sampling	Diagnostic Criteria	Identification method	Sample size	TS cases	Prevalence (per million)				Male: female Ratio	
								Adults	Male adults	Female adults	Children	Adults	Children
Yang et al., 2016b	Canada	18+	2010, 2011	DSM-IV-TR	CCHS 2010 and 2011 Population Survey	112,513	74	660	898	465	3300	1.9 (1.2–3.1)	5.3
Schlander et al., 2011	Germany	18+	2003	ICD-10	Physician Diagnostic Coding Data from Nordbaden database (outpatient database)	1,795,416	91	51	76	22	280	2.6 (1.7–4.0)	3.0
Burd et al., 1986	North Dakota, USA	19+	¯1985	DSM-III	Identification of Cases Through Mail and Telephone Survey of Physicians	448,536	22	49	76	30	520	3.4 (1.3–9.3)	9.3

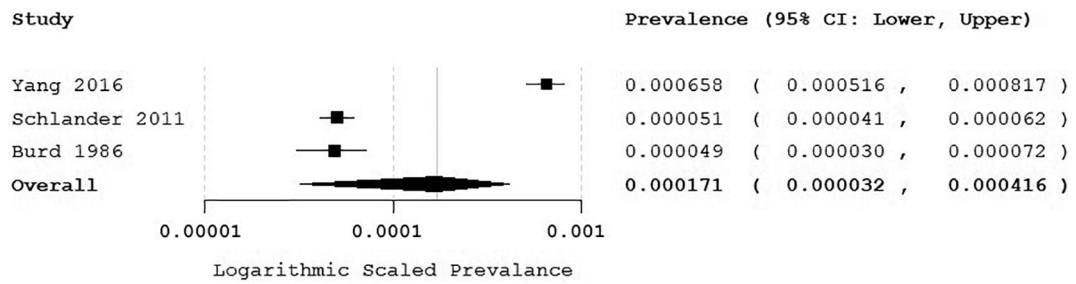

Fig. 2. Prevalence of Tourette syndrome in adults.

an impairment criterion that tics cause "marked distress or significant impairment in social, occupational, or other important areas of functioning." Individuals with TS were identified through survey of all psychiatrists, neurologists and pediatricians who practiced in the state. Physicians were initially asked to participate via mail survey and then through telephone call if they did not respond. Only 2 out of 411 physicians refused participation. All participants in the local North Dakota Support group for TS were identified through these methods. Burd et al. identified 22 TS cases among 448,556 adults in North Dakota with an estimated TS prevalence of 49 per million adults. The adult prevalence in male adults was 3.4-fold greater (95%CI: 1.26–9.28) than females. In comparison, the prevalence of TS in North Dakota school-aged children was of 520 per million with male to female ratio of 9.3:1 (Burd et al., 1986).

3.3.2. Schandler et. al 2011

Schlander et al. reported TS prevalence in Nordbaden, a region in Southwest Germany (Schlander et al., 2011). The authors analyzed healthcare claims data from Statutory Health Insurance, which included the complete outpatient claims data of 2.238 million patients, representing 82% of the regional population in 2003. The Statutory Health Insurance claims data is used for reimbursement purposes from physicians so underreporting of claims visits is unlikely. The investigators identified both all persons with a reported diagnosis of a tic disorder (any ICD-10 code of the F95) and patients with combined chronic vocal and multiple motor tic disorder (Tourette syndrome, F95.2). In the original manuscript prevalence estimates were divided into six different age groups (0–6, 7–12, 13–18, 19–29, 29–49 and > 50) and both prevalence of TS and tic disorders were estimated (Schlander et al., 2011). In adults, the estimated prevalence of TS was 51 per million adults with a 2.6-fold greater risk in male adults compared to female adults (95% CI: 1.65–3.97). The estimated prevalence of TS in pediatric populations was 280 per million children with a male:female risk ratio of 2.97 (95% CI: 1.97–4.47). Although no impairment criterion is included in ICD-10 diagnosis of TS, individuals identified using this methodology would still need to visit for TS symptoms or be identified by their treating doctor as having TS, which typically would involve identifying some level of impairment or distress associated with TS in the identified proband.

3.3.3. Yang et al 2016

Yang et al.2016 examined the national prevalence of TS based on the Canadian Community Health Survey of 2010 and 2011 (Yang et al., 2016a). The Canadian Community Health Survey examines physical and mental health characteristics (among other things) across 97% of the Canadian population over 12 years of age. Excluded from CCHS are full-time members of the armed services, institutionalized populations, persons living on Aboriginal settlements and a few additional remote populations. The prevalence of TS was established through questions asked as part of the common content of the survey which was ascertained from all respondents. The CCHS uses multistage random cluster design to interview eligible participants by telephone or in person. Canada-level response rate for the CCHS in 2010 was 71.5% and for 2011 was 69.8%. The diagnosis of TS was established through the following script, "Now I'd like to ask about neurological conditions, which are conditions that affect the brain, spinal cord, nerves or muscles" and "We are interested in conditions which are expected to last or have already lasted 6 months or more and have been diagnosed by a doctor or other health professionals." Participants were then asked, "Do you have Tourette's syndrome?" Respondents who responded "yes" were categorized as the TS population whereas those who responded "no" were categorized as the non-TS/general population (Yang et al., 2016a). Neither current or recent tics nor significant distress/impairment were required for a diagnosis of TS.

Yang et al. 2016 identified 74 cases of TS among 112,513 Canadian adults for an overall estimated prevalence of 660 cases per million adults (95% CI: 420–900 per million adults). Male adults had a 1.93-fold (95% confidence interval: 1.21–3.08) risk of being diagnosed with TS compared to female adults. By contrast, Yang et al. 2016 estimated the prevalence of TS in adolescence (12–17 years) being 3330 cases per 100,000 adolescents (95% CI: 1910–4770 per 100,000 adolescents) and a male:female prevalence risk ratio among adolescents was 5.31 (95% confidence interval: 2.38–11.81) (Yang et al., 2016a).

4. Discussion

This meta-analysis and systematic review sought to estimate the prevalence of TS in adult populations. The current data are sparse but meta-analysis of the available literature suggested that the prevalence is around 118 cases of TS per million adults (95%CI: 19–751 cases per

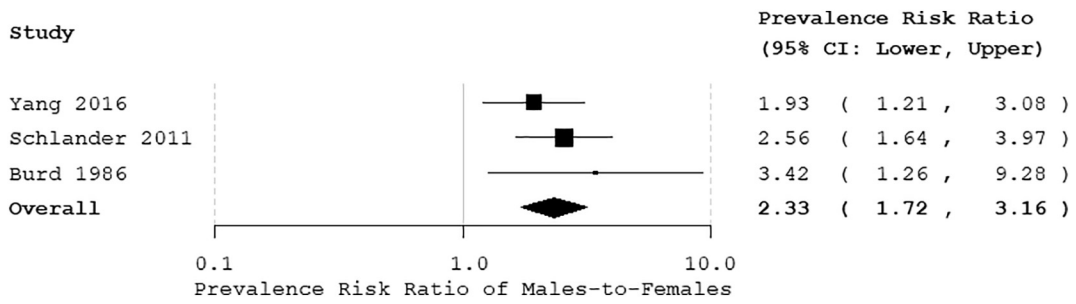

Fig. 3. Male: female risk ratio of Tourette syndrome in adults.

million adults) but that there is a lot of heterogeneity between studies such that prevalence estimates of TS vary > 10-fold between studies. This variance in prevalence estimates is most likely related to methods of case identification (whether a recent diagnosis by an MD was required or subjects were asked regarding whether they had previous tic symptoms) and the changes in diagnostic criteria for TS (if impairment or distress was required for diagnosis or not). The heterogeneity in ascertainment and assessment methods between studies as well as the changing diagnostic criteria for TS remains a major limitation to accurately determining the prevalence of TS (Robertson, 2008).

Although overall conclusions are severely limited by the small number of studies examining the prevalence of TS, a couple important leads from available data that deserve further investigation, research and debate are (1) The prevalence of TS in adults is much smaller than that in children and (2) there is some evidence that the male:female ratio in the prevalence of TS may decrease during adolescents into adulthood.

Our current estimate of TS in adulthood of 118 cases of TS per million adults (95%CI: 19–751 cases per million adults) is roughly one-tenth the prevalence of previous meta-analyses that have examined the prevalence of TS in pediatric populations. Pediatric meta-analyses have estimated the childhood prevalence of TS at around 7700 cases of TS per million children with point estimates ranging from 3000 to 9000 per million. Longitudinal studies of clinical populations suggest that roughly half to two-thirds of children have been estimated to see significant improvements in their tic symptoms (Bloch and Leckman, 2009; Leckman et al., 1998). The changing prevalence estimates of TS between pediatric and adult populations is consistent with clinical observations (Coffey et al., 2000).

Current meta-analyses examining the prevalence ratio of TS in males:females suggests risk ratios around 4:1 in children (Yang et al., 2016b). By contrast, our meta-analysis suggested a much smaller male:female risk ratio in adults – Risk Ratio = 2.33 (95% CI: 1.72–3.16, $z = 5.43$, $p < .001$). Additionally, all three studies reported in this meta-analysis reported a higher male:female risk ratio in pediatric compared to adult populations of TS. This result suggests that girls with TS may be more likely to have persistent symptoms than boys with TS. This preliminary finding deserves further evaluation in larger population datasets. Previous longitudinal studies of adulthood outcome in children with TS have not demonstrated a difference in persistence of symptoms between males and females but have been underpowered to examine this comparison because of the small sample sizes in these studies and the relatively small proportion of girls with TS contained in these samples (Lichter and Finnegan, 2015). Such information is important regarding prognosis of children with TS and may identify an important developmental time-point and interaction to study the biology of TS as hormonal influences (particularly androgens) have been hypothesized to be important in the pathogenesis of TS (Peterson et al., 1992).

Estimates regarding the prevalence of TS are extremely important in determining public health impact of TS and potential FDA drug approval pathways for novel TS medications. For instance, for prospective medications to be approved for an orphan disease indication, “The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States.”(Food and Drug Adminstration, 2018). Prior to recent changes in FDA policy, medications for TS received Orphan Drug status by seeking approval solely in pediatric populations. The Orphan Drug Act originally passed by congress would grant Orphan Drug Approval for an indication in pediatric patients, “If a disease is common (i.e., the prevalence of the disease is 200,000 or greater), a drug may be eligible for orphan designation for a valid orphan subset of the disease.” For example, if the prevalence of the pediatric population affected by the disease is < 200,000 and if it would not be appropriate to use the drug in the adult population of the disease, the drug may be eligible for orphan designation for the pediatric population as an orphan subset.” Medications currently approved for TS in children including aripiprazole and risperidone were approved through this pathway. Qualifying for Orphan Drug Approval significantly reduces the financial barriers to industry of getting FDA approval for candidate medications. The pediatric subpopulation designation was eliminated with clarifications to industry guidance in July 2018 (Food and Drug Adminstration, 2018).

Therefore, understanding the true population of US citizens effected by TS is critical for determining whether TS still qualifies as an Orphan Drug Indication. The minimal research in adult prevalence of TS hampers our ability to provide an accurate estimate of TS prevalence across the lifespan. With this meta-analysis we attempted to clarify the current estimate of TS prevalence in adults at a point estimate of 118 cases of TS per million adults (95%CI: 19–751 cases per million adults). Given this estimated prevalence rate, the total number of adults in the United States with TS would be estimated at 29,620. But depending on how TS is defined, as adults with tics requiring treatment (current tics associated with clinically significant impairment) vs. ever meeting DSM-5 criteria (regardless of presence of impairment or current tics), the total adult prevalence in the US might vary from around 12,000–13,000 (Burd et al., 1986; Schlander et al., 2011) to around 165,000(Yang et al., 2016a) or even 2 million (if one is to strictly assume children cannot ever lose the diagnosis)(Scharf et al., 2015).

Prevalence estimates of TS in adults (as well as children) will vary greatly based on two factors: whether individuals are required to (1) have any current or recent tic symptoms and (2) distress or impairment associated with tics. Strong evidence exists that many (probably most) children with TS experience a significant reduction in tic symptoms in adolescence and into early adulthood (Bloch and Leckman, 2009). As current DSM-5 criteria does not contain any discussion of remission (unlike Major Depression, for instance), it is unclear when (or if ever) a child with TS would cease to qualify for a diagnosis of TS even after they have potentially grown out of their tic symptoms. Furthermore, the elimination of the distress/impairment criteria for a diagnosis of tic disorders with DSM-III-TR (unlike most other recognized psychiatric conditions) has led to the diagnosis of TS in many adults and children who experience no adverse effects from their tics. As DSM-5 criteria are currently constituted, a 40 year-old who had both motor and vocal tics as a younger child (that may or may not have caused any impairment at their worst) and has had no noticeable tic symptoms for decades would still technically qualify for a TS diagnosis. The peculiarity in TS diagnostic criteria specifically regarding the combination of an absence of a remission status for tic disorders along with the absence of an impairment/distress criteria, has many individuals qualify for the diagnosis of TS who have no current or recent tics and/or have mild tics that do not and have not caused any distress or impairment. Current treatment guidelines, do not recommend any treatment for individuals with TS if current tics do not result in significant impairment or distress. Thus many individuals who technically receive a diagnosis of TS across the lifespan should not receive treatment.

Given the current state of diagnostic criteria and changes in FDA regulatory guidance we would recommend that researchers clearly distinguish between the prevalence of tics, tic disorders and Tourette syndrome. Furthermore, that the prevalence of these conditions be estimated not only according to current DSM-5 criteria or ICD-10 criteria but also be estimated in the context of requiring recent tics with distress and/or impairment, as only the later subset of the TS population would be potentially recommended treatment for the condition. Additionally, when considering the public health impact of TS and FDA regulatory decisions, we would recommend that only the prevalence of individuals with current tics and those experiencing at least some degree of functional impairment and distress be considered as these are the only individuals who would benefit from potential treatments. By contrast, we would recommend the overall diagnostic criteria remain unchanged as there is a strong argument that tics (even in the absence of impairment) are important moderators of treatment effects in other comorbid conditions (e.g. SSRIs response in OCD and possibly pharmacotherapy in

ADHD) (Bloch et al., 2006; Bloch et al., 2009; Cohen et al., 2015; Geller et al., 2003; March et al., 2007). However, specifiers should be added clarifying remission status and degree of current impairment associated with tics. This would allow Tourette syndrome and tic disorders to remain as diagnoses in the medical record that could help guide treatment in comorbid conditions but also not necessarily represent a lifelong diagnosis regardless of the presence of symptoms.

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