



# General health and mortality in Tourette syndrome and chronic tic disorder: A mini-review

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## ABSTRACT

Current knowledge on the general somatic health and causes of death in Tourette syndrome and chronic tic disorder is very limited. Here, we review the available literature on the topic, while highlighting strengths and weaknesses of the studies conducted to date. These previous works have suggested associations between Tourette syndrome and chronic tic disorder and a range of health conditions, including autoimmune disorders, common allergies and respiratory diseases, sleep difficulties, and metabolic and cardiovascular outcomes. Additionally, the risk of mortality in tic disorders might be higher than that of the general population, but specific causes of death have rarely been studied, except for substance use-related deaths and suicide, which are significantly higher in individuals with Tourette syndrome and chronic tic disorder. Many of these emerging findings require replication and extension but, taken together, they suggest that it might be sensible to monitor the general health and suicide risk of individuals with Tourette syndrome or chronic tic disorder across the lifespan. We suggest further avenues for research on this topic.

## 1. Introduction

Tourette syndrome (TS) is a childhood-onset neurodevelopmental disorder characterized by multiple motor and vocal tics present for at least one year. When only motor or vocal tics are present, a diagnosis of persistent (chronic) motor or vocal tic disorder (CTD) is given (American Psychiatric Association, 2013). TS/CTD have a relatively low prevalence (up to 1% of children and adolescents) (Scahill et al., 2014; Scharf et al., 2015), but can be impairing in several domains, such as educational attainment (Pérez-Vigil et al., 2018) and peer relationships (Zinner et al., 2012). In addition, TS/CTD nearly always present with multiple psychiatric comorbidities, which are often more impairing than the tics themselves (Hirschtritt et al., 2015).

The long-term prognosis of TS/CTD is widely thought to be generally positive, with many individuals experiencing an improvement of their tics or their associated impairment as they reach young adulthood (Black et al., 2020; Bloch and Leckman, 2009; Kim et al., 2019). From this, it could be assumed that the long-term health status of most

individuals with TS/CTD might be approximately the same as that of individuals without tic disorders. However, this is not the picture that emerges from the literature on other early-onset neuropsychiatric disorders, such as autism spectrum disorder or attention-deficit/hyperactivity disorder (ADHD), which are known to be prone to develop multiple health complications over time (e.g., Mitchell et al., 2013; Spencer et al., 2014; Vancampfort et al., 2014; Zheng et al., 2017). In turn, these complications are known to increase mortality risks in these individuals (Correll et al., 2017; Li et al., 2016). By contrast, very little is known about the general health of individuals with TS/CTD. Here, we review and summarize the current knowledge regarding the somatic health (i.e., non-psychiatric) and causes of death of individuals with TS/CTD. We highlight the strengths and weaknesses of the research conducted to date and outline suggestions for future research in this neglected area.

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## 2. Autoimmune diseases

Autoimmunity has long been proposed to be potentially important in the etiology of a range of neuropsychiatric disorders, including TS (Hoekstra et al., 2002). A widely discussed model of autoimmunity postulates that obsessive-compulsive disorder (OCD), as well as associated phenotypes like tics, may arise in a similar way to Sydenham's chorea, the neurological manifestation of rheumatic fever (Swedo, 1994; Swedo et al., 1998). According to this still-debated model, obsessive-compulsive symptoms, tics, and other associated psychiatric symptoms may arise as a consequence of an autoimmune reaction to group A beta-hemolytic streptococci (GAS) infections in genetically vulnerable individuals (Swedo, 1994; Swedo et al., 1998). The hypothesized molecular mechanisms, evidence, and controversies surrounding this model are covered comprehensively elsewhere (Cunningham, 2014; Gilbert, 2019). Recent insights from the European Multicentre Tics in Children Studies (EMTICS) – the largest prospective cohort study of the contribution of different genetic and environmental risk factors for tic onset and exacerbation in children and adolescents (EMTICS Collaborative Group, 2018; Schrag et al., 2019) – found no evidence for a role of new GAS infections in relation to exacerbations of tic disorders, and no indication for a temporal association between new GAS exposures and the onset of tics. Thus, it is possible that the co-occurrence of GAS infections and tic exacerbations may be simply due to chance, and that assessing GAS exposure in children with tic disorders may not be clinically meaningful (EMTICS Collaborative Group, 2018).

Another body of work has focused on the co-occurrence and family history of autoimmune diseases in individuals with TS or CTD. What is the evidence that individuals with TS or CTD have higher than expected rates of rheumatic fever/Sydenham's chorea? And how about other autoimmune diseases that are not currently conceptualized as being related to streptococcal infections?

A systematic literature review (Pérez-Vigil et al., 2016) identified 5 studies reporting on the association between rheumatic fever, with or without Sydenham's chorea, and tic disorders (de Alvarenga et al., 2009; Hounie et al., 2004; Mercadante et al., 2000; Sampaio et al., 2009; Walker et al., 2005), two of which did not include control groups (Sampaio et al., 2009; Walker et al., 2005). Of the studies that included control groups, two (Hounie et al., 2004; Mercadante et al., 2000) found significantly higher rates of tic disorders among pediatric rheumatic fever cases who also had Sydenham's chorea than in their respective controls without autoimmune diseases. Mercadante et al. (2000) also found significantly higher rates of tic disorders in rheumatic fever cases without Sydenham's chorea. The third study (de Alvarenga et al., 2009) found a similar prevalence of tic disorders between psychiatric patients with and without rheumatic fever. Thus, there is some data to support the association between TS/CTD and rheumatic fever, particularly when accompanied by Sydenham's chorea.

Regarding other autoimmune diseases that are not known to be triggered by streptococcal infections, the published literature is extremely scarce and plagued by methodological issues, such as small patient samples, the absence of control groups or the lack of blind assessors (Pérez-Vigil et al., 2016). A recent population-based study from Sweden, including a cohort of 7279 individuals with a diagnosis of TS or CTD, found that individuals with tic disorders were 36 % more likely to have a diagnosis of autoimmune diseases (any diagnosis from a list of 40 different autoimmune diseases), compared to unaffected individuals from the general population (Mataix-Cols et al., 2018). Further analyses also revealed increased odds of most individual autoimmune diseases in patients with TS/CTD, compared to individuals without these disorders. Hashimoto's thyroiditis (106 % increased odds), celiac disease (67 % increased odds), scarlet fever (62 % increased odds), type 1 diabetes mellitus (37 % increased odds), and psoriasis vulgaris (33 % increased odds) emerged as the conditions most strongly associated with TS/CTD. Other autoimmune diseases, such as Crohn's disease or vitiligo, were also associated with TS/CTD, but did not reach statistical significance

because of limited statistical power (Mataix-Cols et al., 2018). Thus, there seems to be a significant association between TS/CTD and autoimmune diseases in general, regardless of whether they are thought to be triggered by streptococci or not.

Arguably, the strongest evidence of the association between TS/CTD and autoimmune diseases originates from a handful of family studies suggesting that the first-degree relatives of individuals with TS or CTD have elevated rates of autoimmune diseases. A Brazilian family study (Hounie et al., 2007; Seixas et al., 2008) found that the rate of OCD and related conditions, including tic disorders, was significantly higher among first-degree relatives of individuals with rheumatic fever than among first-degree relatives of controls (14.7 % vs. 7.3 %) (Hounie et al., 2007), and the risk of OCD and related disorders was increased by the presence of either rheumatic fever or Sydenham's chorea in another family member (Seixas et al., 2008). In another clinic-based study (Murphy et al., 2010), the mothers of 107 children and adolescents with OCD and/or tics were interviewed regarding their history of autoimmune diseases. Nearly 18 % of the mothers reported at least one autoimmune disease; this figure was higher for the mothers of children fulfilling likely criteria for PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection) ( $n = 40$ ; 25 %), compared to the mothers of children with unlikely PANDAS ( $n = 67$ ; 13.4 %). A longitudinal population-based study from Denmark examined the risk of TS ( $n = 2442$ ) in the offspring of mothers with 31 different autoimmune disorders (Dalsgaard et al., 2015). A maternal history of autoimmune diseases was found in 110 cases, corresponding to an increased risk of TS of approximately 22 %. The most common maternal autoimmune disorders were ulcerative colitis, rheumatoid arthritis, thyrotoxicosis, and multiple sclerosis. Finally, the above-mentioned population-based study from Sweden (Mataix-Cols et al., 2018) examined the odds of autoimmune disorders in first, second, and third degree relatives of individuals with TS/CTD ( $n = 7279$ ). Individuals with TS/CTD were significantly more likely to have first-degree relatives, but not second or third degree relatives, with autoimmune disorders. The results were similar after the exclusion of TS/CTD probands with diagnosed autoimmune disorders, as well as relatives with TS/CTD. Taken together, the results of these family studies suggest that there may be shared familial risk factors, genetic and/or environmental, between TS/CTD and autoimmune disorders. In support of the possibility of shared genetic risks, a recent analysis of publicly available genome-wide association study data (Tylee et al., 2018) explored the genetic correlations between a range of psychiatric disorders and immunological and/or inflammatory disorders and revealed significant positive genetic correlations between TS/CTD and both psoriasis ( $rg = 0.25 \pm 0.09$ ) and allergy ( $rg = 0.24 \pm 0.05$ ).

One interesting finding from the Mataix-Cols et al. (2018) family study was that mothers of individuals diagnosed with TS/CTD were more likely (albeit non-significantly) to have a diagnosis of autoimmune diseases (40 % increased odds), than fathers (31 %) and siblings (17 %). These results may suggest that, in addition to shared genetic factors, maternal-specific factors, such as the placental transmission of antibodies to the offspring, which may in turn activate the immune system in the child and alter normal brain development, cannot be ruled out (Dalsgaard et al., 2015). Given the increased attention to maternal immune activation in neuropsychiatric disorders (Estes and McAllister, 2016; Knuesel et al., 2014), future studies could examine whether maternal infection and active autoimmune diseases during pregnancy are associated with an increased risk of TS in their offspring and how this risk varies as a function of interaction with genetic and other environmental risk factors (Mataix-Cols et al., 2018). Another possible, not incompatible, contributor to the association between TS and autoimmune diseases may be chronic stress, which is known to be strongly associated with autoimmune diseases (Song et al., 2018). In this light, autoimmune diseases may not only be etiologically important in TS but chronic stress associated with TS may also potentially increase the subsequent risk of autoimmune diseases. Future studies are needed to

explore this possibility.

In sum, the literature suggests a familial, potentially genetic, link between TS and a broad range of autoimmune disorders, which is not limited to streptococcus-related conditions. At present, we cannot fully rule out shared environmental effects or additional mother-specific factors, such as the placental transmission of antibodies to their offspring. The role of chronic stress in TS as potential risk factor for the subsequent development of autoimmune diseases is also a possibility that remains unexplored. Clinically, it would be sensible to broadly screen for autoimmune diseases in patients with TS, particularly in those with a documented or suspected family history of autoimmune diseases.

### 3. Common allergies and asthma

Preliminary evidence suggests that tic disorders are associated with a number of allergies and respiratory diseases, including asthma. The first reports on the association between tics and allergies date from the 1980's. Finegold (1985) reported on a series of four individuals in an allergist's office (three with TS and one with highly suspected TS), all with high immunoglobulin E (IgE) serum levels and positive skin tests, which presented with comorbid allergies. Mandell (1986) described a sample of 26 children and young adults with TS, 80 % of which also presented with allergies. Comings and Comings (1987) conducted a clinical survey among patients with TS, divided in three grades of severity. The survey included one question about the frequency of allergies, including asthma, hay fever, allergic rhinitis, skin allergies (eczema and others), and allergies to pets, drugs (penicillin and others), foods (milk and others), and others. The sample included 247 consecutive patients with TS and 47 random controls. No significant differences between cases and controls were found in the frequency of allergies, except for skin allergies, where patients with TS, specifically those that were more severe, had a significantly higher frequency. Kim et al. (1997) reported on four children (ages 7–11) referred to an allergy clinic to rule out atopy. Of the four patients, two were confirmed to be atopic. Ho et al. (1999) assessed 72 consecutive young patients with TS and compared them with general population data from the International Study of Asthma and Allergy in Childhood Taiwan Group on the Multiple Allergens Simultaneous Tests (MAST). A total of 45 children, out of the initial sample of 72, had positive results in the MAST, of whom 41 (56.9 %) had clinical evidence of allergy, including rhinitis, asthma, and atopic dermatitis or urticaria. This percentage was higher than that observed in the general population (44.3 %;  $p < 0.05$ ). More recently, Yuce et al. (2014) also reported on the association between TS ( $n = 19$ ) and allergic diseases, assessed using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. The study population also included cases of OCD ( $n = 13$ ), cases with both TS and OCD ( $n = 13$ ), and control subjects from the pediatric outpatient clinic at the same hospital ( $n = 35$ ). The group with TS only did not differ from the controls in any of the assessed variables, but both the OCD and the TS plus OCD groups had a significantly higher number of allergic diseases. The comorbid group also had a higher proportion of individuals with positive skin prick test and eczema, compared to controls. This may indicate an additive effect of the joint exposure to both TS and OCD, which will need to be confirmed in much larger samples.

The results from these specialist clinic-based studies have been confirmed by a handful of more recent population-based epidemiological studies. Yang et al. (2017) used data from the Canadian Community Health Survey, which included 122 participants with TS (the diagnosis was self-reported, based on the question 'do you have Tourette syndrome?'). After controlling for age and sex, the participants with TS, compared to 122,762 participants without the disorder, reported significantly higher rates of asthma (20.05 % vs 8.54 %, respectively; odds ratio = 2.61). These self-reported results are in line with the results of a Taiwanese register-based study including 845 young cases of TS (up to age 18), compared to matched controls (Chang et al., 2011). Chang and collaborators described that individuals with asthma had an 82 %

increased risk of TS (Chang et al., 2011). Other allergic diseases were also significantly associated with a diagnosis of TS, including allergic rhinitis (odds ratio [OR] = 2.18), dermatitis (OR = 1.61), and allergic conjunctivitis (OR = 1.33) (Chang et al., 2011). Moreover, the authors reported that the risk for TS increased with the number of allergies and with age. In another register-based study from Taiwan (Chen et al., 2013), 1816 cases of tic disorders only, 5811 cases of ADHD only, 349 cases with comorbid tics and ADHD, and 31,904 controls were compared on the diagnoses of allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis. The OR for any allergic diseases in the cases with tic disorders only, compared to controls, was 2.88, which was significantly higher than the odds for allergic diseases in the ADHD only (OR = 1.64). Interestingly, the risk for those with both tics and hyperactivity was even higher (OR = 3.73). Additionally, patients with ADHD and allergic diseases, compared to those with ADHD but without allergic diseases, had an increased risk of tic disorders, and this risk seemed to be dose-dependent (OR for tic disorders in hyperactivity cases with  $\geq 3$  allergic diseases = 3.72; with 2 allergic diseases = 2.52; with 1 allergic disease = 1.87). The mechanisms that underlie the associations between tic disorders and ADHD, and allergic diseases – and whether these share etiological factors or their co-occurrence is the result of causal effects – deserves further examination.

In summary, there seems to be an association between TS and a number of common allergies and respiratory diseases. Future studies will need to replicate and determine the strength of these associations. The mechanisms behind these associations remain to be elucidated, but the involvement of immunological factors seems plausible (Martino et al., 2015). Moreover, the study of this association deserves one further consideration. Tics may include respiratory movements and sounds such as coughing, throat clearing or sniffing. These symptoms have the potential to be misdiagnosed as upper and lower respiratory system infections, such as asthma, rhinitis or other forms of allergy. Similarly, eye blinking could potentially be confounded for allergic conjunctivitis by the non-trained eye (Kim et al., 1997; Tan et al., 2004). Hence, assessment of respiratory disorders and allergies in the population of individuals with tics should be performed cautiously in order to avoid potential misclassifications, and tic disorders should be included in the differential diagnosis of allergies and respiratory diseases, particularly at young ages (Tan et al., 2004).

### 4. Sleep disorders

Sleep difficulties in TS were first mentioned in the seminal paper by Gilles de la Tourette, 1885, where he described that two out of his nine patients with tics had sleep disorders. Since then, the body of literature on tic disorders has continued to support the notion that sleep difficulties are relatively common in this group of patients, as summarized in two recent systematic reviews (Hibberd et al., 2020; Jiménez-Jiménez et al., 2020), the first of which specifically focusing on children and adolescents with TS. Both reviews reported a broad spectrum of sleep problems in individuals with tic disorders, with an extremely wide prevalence range (from 7 to 80 %) (Hibberd et al., 2020; Jiménez-Jiménez et al., 2020). The most common sleep difficulties reported in this population are insomnia, excessive daytime sleepiness, disorders of arousal (including sleep walking, sleep talking, sleep terrors, and enuresis), persistence of tics during sleep, and presence of periodic limb movements during sleep (Jiménez-Jiménez et al., 2020). A minority of studies have focused on objective sleep assessments using polysomnographic measures, reporting decreased sleep efficiency, decreased percentage of delta sleep, increased nocturnal awakenings, and increased periodic limb movements during sleep (Jiménez-Jiménez et al., 2020). Overall, sleep problems seem to appear more often in individuals with TS and comorbid ADHD, compared to those without comorbid ADHD, and in children than in adults with TS, although the adult literature is very limited (Hibberd et al., 2020; Jiménez-Jiménez et al.,

2020).

A series of studies have specifically focused on sleep-related breathing disorders. Glaze et al. (1983) described apneic episodes in eight out of 12 children and young adults with TS. In another early study of 112 consecutive children and adults with TS seen at a neurology department (Jankovic and Rohaidy, 1987), 34 underwent a polysomnographic study; of these, eight (23.53 %) were diagnosed with obstructive sleep apnea. Sverd and Montero (1993) recruited TS probands and their full and half-siblings (64 families, total  $n = 178$ ) to study sudden infant death syndrome and other infant apneas. Results showed that 15 of the 64 families under study (23.44 %) had history of sudden infant death syndrome and/or life threatening apneic events, with a prevalence of 6.6 % cases of these conditions in the probands with TS or their full and half-siblings. This translated into a 2- to 5-fold increased risk of apnea in infancy and subsequent sudden infant death syndrome in TS cases and their siblings, compared to the general population (Mehanna and Jankovic, 2010; Sverd and Montero, 1993). Comings and Comings (Comings and Comings, 1993) reported on a series of seven families (109 individuals) with at least one member with TS in which several members ( $n = 14$ ) either had died of sudden infant death syndrome, had near miss sudden infant death syndrome or had documented cyanotic episodes of sleep apnea. The authors hypothesized that familial/genetic vulnerability for TS may be a contributing factor to an increased risk of sudden infant death syndrome. Ghosh et al. (2014) reported central apnea in two and obstructive sleep apnea in another two of 31 children with TS only (13 % in total). No cases of apnea were reported in the group of 48 patients with TS and ADHD. Similarly, Modafferi et al. (2016) did not find any cases of sleep apnea in a sample of 36 children with TS or CTD from a pediatric clinic, although they did present with other sleep difficulties (including snoring), which were more common than in the controls. Lee et al. (2017) did not find differences in the prevalence rate of sleep apnea in children with ( $n = 1124$ ) and without ( $n = 3372$ ) TS in a Taiwanese population cohort, which was very low in both groups (0.2 % vs. 0.4 %, respectively). These mixed findings suggest that more research is needed to confirm the association between tic disorders and a range of respiratory problems, as well as their potential association with fatal outcomes.

As highlighted by Hibberd et al. (2020), the methodological quality of many studies on this topic has been moderate and there is substantial room for improvement. For example, the vast majority of studies reporting on subjective symptoms (e.g., not using objective polysomnographic measures) were based on self-reported (or parent-reported) questionnaires rather than using clinician-reported diagnoses. Further, many of these questionnaires lumped together a wide range of sleep problems, including insomnia, hypersomnia, and different parasomnias (e.g., sleep walking, night terrors, enuresis, bruxism, nightmares). Each of these sleep difficulties may call for different interventions and, therefore, it would be helpful from the clinical point of view to study them separately. As suggested by Jiménez-Jiménez et al. (2020), future research should focus on prospective studies with long-term follow-ups, include control groups, unmedicated TS individuals, and employ multi-modal assessments (specific subjective and objective measures) of sleep-related disorders.

## 5. Metabolic and cardiovascular diseases

The presence of metabolic syndrome and cardiovascular diseases has been the focus of attention in a number of psychiatric conditions such as schizophrenia, bipolar disorder, depression, stress-related disorders, anxiety disorders, and OCD (Albert et al., 2013; Butnorienė et al., 2015; Henderson et al., 2015; Isomura et al., 2018; Moreira et al., 2019; Song et al., 2019; Vancampfort et al., 2015). However, the cardiometabolic profile of patients with tic disorders has seldom been studied in its own right, but rather as a side effect of the psychotropic treatment prescribed for the tics, particularly antipsychotics (Gulisano et al., 2011; Pringsheim et al., 2017; Pringsheim and Pearce, 2010; Rizzo et al., 2012). For

example, Pringsheim and Pearce (2010) followed 73 children with TS for a mean of 3.3 years and concluded that metabolic complications of antipsychotic therapy were extremely common in this group, with 62 % of the children developing abnormal lipid levels, abnormal body mass index values or both abnormalities over the course of their screening examinations while being treated with antipsychotics. In a further prospective, longitudinal study (Pringsheim et al., 2017), 57 children who had started risperidone or aripiprazole were monitored for a mean of 10 months. By the end of the follow-up, 26 % of the sample had had a significant weight increase and 19 % had discontinued the medication because of metabolic effects. In another study (Rizzo et al., 2012), children with TS in treatment with pimozide ( $n = 25$ ) had significantly higher levels of glycemia, while patients on treatment with aripiprazole ( $n = 25$ ) presented with higher levels of cholesterolemia after 24 months, compared to unmedicated children with TS ( $n = 25$ ). These studies, although valuable, are small, have short follow-up times, and lack a control group not exposed to the tic disorders, which limits the generalizability of the results. A larger study that did include controls is the previously mentioned Canadian population-based survey by Yang et al. (2017). Among a number of chronic health conditions, participants self-reported on whether they were normoweight (body mass index lower than 25) and whether they had high blood pressure. The survey did not find significant differences in these two variables between cases and controls. However, it is important to highlight that the outcomes were self-reported (as was the exposure) and that participants in this survey, particularly those with TS, were relatively young (mean age for the cases with TS was 28, while the mean age for the non-TS was 44, although risks were adjusted by age).

A recent Swedish population-based study compared 7804 individuals diagnosed with TS or CTD with more than 14 million individuals without the disorder on a range of metabolic and cardiovascular disorders (Brander et al., 2019). Over the 40-year follow-up period, tic disorder cases showed an increased risk of cardiometabolic disorders, compared to the general population (adjusted hazard ratio [aHR] = 1.99). Specifically, individuals with TS or CTD had higher risks of obesity (aHR = 2.76), type 2 diabetes mellitus (aHR = 1.67), and circulatory system diseases (aHR = 1.76), which included, among others, ischemic heart diseases, arrhythmia, and cerebrovascular diseases. The risks were already evident from childhood (the between-group difference was significantly different from age 8). Risks were significantly reduced with the exclusion of individuals with comorbid ADHD, while excluding other comorbidities did not significantly affect the results. Nonetheless, those with TS without comorbid ADHD still had a 52 % increased risk of developing cardiometabolic disorders. A major strength of this study was the inclusion of a sibling comparison. The risk of metabolic and cardiovascular disorders was substantially reduced (aHR = 1.37) when individuals with tic disorders were compared to their full siblings (i.e., those sharing the same mother and father and, therefore, about 50 per cent of their genes and a number of shared environmental factors, such as parental socioeconomic status and parental psychopathology). This may indicate that there are genetic and/or environmental risk factors that may partially influence both the disorder and the cardiovascular outcomes (e.g., pleiotropic genetic effects). Kuhn et al. (2019) suggested that the increased metabolic risk profile found in tic disorders could reflect a potential alteration of the reward and/or learning circuitries involving the dopaminergic system. TS has been related to increased tonic and phasic dopamine transmission (Maia and Conceição, 2017) which, in turn, it is closely linked to the functioning of the human reward system, including food intake and, consequently, homeostatic processes and metabolism. However, the risk remained significant in the sibling comparison, suggesting that at least part of the observed health complications might be attributable to unhealthy lifestyle factors such as lack of physical activity and poor diet.

To summarize, the current literature, although scarce and in need of replication, suggests that an association exists between TS/CTD and adverse metabolic and cardiovascular outcomes. Therefore, clinicians



should do their best to carefully monitor cardiometabolic health in patients with tic disorders of all ages, particularly those with comorbid ADHD and those with known risk factors and/or using antipsychotic medication. Whether lifestyle modification programs are indicated and feasible in individuals with tic disorders is an important question for future research.

## 6. Premature mortality, substance use-related deaths, suicidality, and accidents

The expected consequence of all the above-described health-related problems is perhaps a potential increased risk of mortality and premature death in individuals with tic disorders. However, very few studies so far have focused on studying life expectancy and mortality in this patient group. In the largest study to date, Meier and collaborators conducted a prospective cohort study using the Danish national registers (Meier et al., 2017). The cohort of more than 3 million individuals included 6781 with tic disorders, of whom 4831 were diagnosed with TS. The risk of premature death was about 100 % higher among those with tic disorders (mortality rate ratio = 2.02), and 63 % higher in those with TS (mortality rate ratio = 1.63). These risks remained similar after excluding individuals with comorbid ADHD, OCD, and substance abuse (mortality risk ratios = 2.30 and 1.81 for the broader group of tic disorders and for the group with TS only, respectively), indicating that the observed increased risk of mortality was not dependent on the psychiatric comorbidities under examination. However, the study did not control for other relevant confounders, such as familial factors, and the conclusions were based on a relatively small sample of individuals with tic disorders and an even smaller number of deceased cases ( $n = 46$ ), which made it difficult to study specific causes of death in this group.

In another population-based cohort study, Virtanen et al. (2020) prospectively followed a cohort of more than 14 million individuals in Sweden, 7832 of whom had a registered TS or CTD diagnosis. Compared to the general population, individuals with TS/CTD were at increased risk of subsequent alcohol-related disorders, drug-related disorders, and substance-related criminal convictions, even after controlling for unmeasured familial confounders and accounting for psychiatric comorbidities. Individuals with TS/CTD also had a 2.54 times higher risk of substance-related death, including causes of death due to alcohol or other psychoactive drugs, alcohol- or drug-related somatic conditions or poisonings by alcohol or drugs. However, death was a rare outcome in this study and some analyses, such as sibling comparisons, could not be conducted due to limited statistical power.

Only a handful of studies have previously reported on deaths by suicide in tic disorders. Robertson et al. (1995) presented two cases of TS who completed suicide. Both patients presented with “multiple stresses,” including social stigma, restrictions on autonomy, illness or treatment disrupted normal functioning, limited opportunities for social activities, and burdened families. Margolese et al. (2002) conducted a retrospective study in 58 adolescent and adult patients with TS who received risperidone. During the study period, one patient died by suicide while taking the drug. Walby et al. (2006) investigated the impact of a number of psychiatric disorders on completed suicide. Among the cases under study, one case of suicide had a previous diagnosis of TS. Davila et al. (2010) reported on a retrospective case series of 10 patients with TS attending a specialist clinic at a university hospital. Of these, three died by suicide and seven had attempted suicide. The authors reported that all patients had at least three comorbid psychiatric diagnoses. In the largest study to date, 7736 Swedish individuals with a diagnosis of TS or CTD were matched to 10 population controls on sex, birth year, and county (Fernández de la Cruz et al., 2017). A total of 32 cases and 74 controls died by suicide during the study period. Cases were more than 4 times more likely to die by suicide ( $OR = 4.39$ ) and nearly 4 times more likely to attempt suicide ( $OR = 3.86$ ) than controls. Importantly, after adjusting for psychiatric comorbidities, these risks were slightly reduced but remained substantial, indicating that, although comorbidities can

play a role in the risk of suicide, tic disorders are likely to increase the risk of suicidal behavior in their own right. A predictors analysis showed that persistence of tics beyond young adulthood and, in line with the suicide literature (Runeson et al., 2010), a previous suicide attempt were the strongest predictors of death by suicide in individuals with TS or CTD (Fernández de la Cruz et al., 2017). Tic severity and presence of comorbidities, particularly OCD, ADHD, and mood disorders, have been associated with a poorer health-related quality of life in individuals with tic disorders (Cavanna et al., 2013; Eapen et al., 2016; Robertson, 2006), which may further contribute to an increased risk of suicide in this patient group (Robertson, 2006).

Another area that has received little attention is the potential risk of accidents in TS/CTD. The previously mentioned Canadian survey (Yang et al., 2017) reported a higher prevalence of injuries in the past 12 months in the TS group ( $n = 122$ ; 27.81 %), compared to the general population controls ( $n = 122,884$ ; 15.09 %). However, this difference was not statistically significant ( $OR = 1.49$  [95 % CI, 0.62–3.60]). In a much larger Swedish cohort study, Mataix-Cols et al. (2020) examined the risk of injury or death due to serious transport accidents and motor vehicle accidents in individuals with TS/CTD ( $n = 3449$ ), compared with unexposed members of the general population ( $n = 6,127,290$ ). Individuals with TS/CTD had an increased risk of transport-related injuries or death (adjusted hazard ratio [aHR] = 1.50 [95 % CI = 1.33–1.69]) and of motor vehicle accident injuries or deaths (aHR = 1.58 [95 % CI = 1.37–1.82]). These risks were independent of familial confounders shared by siblings. Nonetheless, the risks were no longer significant after the exclusion of individuals with comorbid ADHD. Thus, the marginally increased risk of transport and motor vehicle accidents in TS/CTD appears to be primarily explained by comorbid ADHD, which is in line with the known association between ADHD and transport accidents (Barkley and Cox, 2007; Chang et al., 2014).

Taken together, the available data indicate that the risk of premature mortality due to both natural and external causes in individuals with TS/CTD might be significantly higher than that of the general population, but replication studies taking into account relevant confounders are needed, as well as studies focusing on specific causes of death in this population. Screening for drug and alcohol use should become part of the standard clinical routines, particularly in patients with comorbid ADHD. Similarly, long-term monitoring of suicidal ideation and risk, particularly in individuals with severe, persistent tics, psychiatric comorbidities, and previous suicide attempts, is warranted.

## 7. Conclusions

The general health and long-term health outcomes of patients with TS and CTD have received relatively little empirical attention. One contributing factor is that several health outcomes occur later in life and researchers seldom have the resources to follow-up large cohorts of individuals for several decades. Data primarily originating from the vast Scandinavian and Taiwanese nationwide registers, which contain administrative records from entire populations and a wealth of high-quality healthcare data prospectively-collected over several decades, have allowed researchers to have a first approximation to the long-term health consequences of tic disorders. These studies have begun to uncover risks that were previously unappreciated, including increased risks of autoimmune diseases, cardiometabolic disorders, and premature deaths from both natural and unnatural causes. Much work remains to be done, both replicating these studies and extending the evidence base. Collectively, however, the emerging literature suggests that it might be sensible to screen for the relevant conditions and monitor the health status of individuals with TS and CTD across the lifespan, particularly in individuals who already present with known risk factors (e.g., family history of autoimmune diseases, substance use, unhealthy lifestyle, previous suicide attempts).

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## Declaration of Competing Interest

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