University of Hertfordshire UH 25 Research Archive

Citation for published version:

Amanda K. Ludlow, and Samantha L. Rogers, 'Understanding the impact of diet and nutrition on symptoms of Tourette syndrome: A scoping review', *Journal of Child Health Care*, December 2017.

DOI:

https://doi.org/10.1177/1367493517748373

Document Version:

This is the Accepted Manuscript version.
The version in the University of Hertfordshire Research Archive may differ from the final published version.

Copyright and Reuse:

Enquiries

If you believe this document infringes copyright, please contact the Research & Scholarly Communications Team at rsc@herts.ac.uk

Understanding the impact of diet and nutrition on symptoms of Tourette

Syndrome: A Scoping Review

ABSTRACT

Anecdotal reports frequently suggest some dietary involvement in the maintenance of tics in children with Tourette Syndrome (TS). This scoping review aimed to 1) understand the possible influence of diet as a trigger of tics 2) map out the existing studies documenting dietary interventions in children with TS. Current evidence suggests no single diet to benefit individuals with TS. However, reports from parents of children with TS suggest that certain allergens in food may exacerbate tic related symptoms. For example, an increase in tics has been related to the consumption of caffeine and refined sugar. Moreover, oligoantigenic diets and sugar-free diets have been identified as significantly reducing tics. More research is urgently needed to develop more accurate guidance for parents and children with TS, as many have reported using dietary and nutritional supplements, despite the lack of evidence detailing any benefits, side effects and recommended doses.

Key words: Tourette Syndrome, tic, diet, nutrition,

INTRODUCTION

Tourette Syndrome (now known as Tourette Disorder in the Diagnostic Statistical Manual 5; APA, 2013) is a life-long neurodevelopmental disorder, characterized by repeated twitches, movements or sounds, otherwise known as tics. Tics can be sudden, rapid and include both non-rhythmic motor movement *and* vocalisation. While the frequency of tics may differ, typical age of onset is between the ages of 7-12 years, and need to be present for at least a year in order to gain an official diagnosis of Tourette Syndrome (TS). However, when symptoms involve persistent motor or vocal tics, a diagnosis of Persistent (chronic) motor or tic disorder (symptoms more than a year), or a diagnosis of provisional tic disorder (symptoms present for less than a year), is given (APA, 2013). Tic disorders are considered to be more common than TS, and have a prevalence rate of between 1% and 29% (depending on the methods adopted, the diagnostic criteria employed, and whether or not the sample was a non clinical or clinical sample; Robertson, 2008). For example, high prevalence rates are often reported when the inclusion criteria involves children who show intermittent and unpredictable motor or vocal tics, and which appear out of context of normal motor activity (e.g. Lanzi et al., 2004). However, these children may not reach the threshold for a diagnosis of a tic disorder. In contrast, when using community samples of children between the ages of 5 and 18 years, prevalence figures for TS consistently range between 0.4-3.8% (Robertson, Eapen and Cavanna, 2009).

Tics are often classified into simple and complex categories. Simple motor tics can be behaviours such as eye blinks, shrugs and grimaces; more complex tics can include the touching of objects and/or people. Furthermore, simple vocal tics can include coughs and grunts, whereas more complex vocal tics might involve repetition of their own (palilalia), or someone else's (echolalia), speech (Chilvers et al., 2010). In addition to motor and vocal classification of tics, there is some unpredictability surrounding the symptoms. For example, the body parts affected by tics, and the frequency and severity of the tics, can change over time (Singer, 2005).

The severity and frequency of tics has also been shown to be influenced by an assortment of environmental factors, particularly those leading to increased levels of anxiety, stress, excitement and fatigue (e.g. Findley et al., 2003). Importantly, anecdotal reports and some studies seeking to determine the relationship between environmental factors and tic symptomology have hinted at the role diet and nutrition could play in tic related behaviours (Silva, Munoz, Barickman and Friedhoff, 1995). Yet, while dietary and nutritional factors have been found to affect a range of neurological conditions, there appears to be relatively little research addressing diet and nutrition in TS.

There are several important reasons to address diet and nutrition in TS. Firstly, medication is one of the main forms of treatment, and although it is relatively successful in treating symptoms, it has been associated with a range of adverse effects including sedation, increased levels of depression and anxiety, as well as having a debilitating effect on motor function. First-generation antipsychotics (FGAs), also known as neuroleptics, conventional or typical antipsychotics, have the tendency to

cause movement disorders, extrapyramidal side effects and tardive dyskinesia. While more newly marketed atypical drugs, such as ripseridone, aripiprazole, clozapine are considered to be safer, they are still associated with a range of adverse side effects, including type II diabetes (Scahil et al., 2006). Importantly, weight gain has been associated with all types of antipsychotics, although it has been more frequently linked to the newer atypical drugs, and can lead to additional immediate and long-term health risks including obesity, diabetes mellitus, and hyperlipidemia (Bak et al., 2014).

Degrauw, Li and Gilbert (2009) conducted one of the only studies addressing the affect of medication on both growth and weight in TS. The effects of neuroleptic drugs on body mass index (BMI) were assessed in neuroleptic-treated and non-neuroleptic-treated children and adolescents with TS (groups were matched for age and gender). Results revealed that neuroleptic-treated children gained significantly more weight than untreated controls after 1 year (but not 2 or 3 years). More recently, Pringsheim, Ho, Sarna, Hammer and Pattern (2017) evaluated the risk of adverse effects of antipsychotics (Risperidone, and Aripiprazole) over a mean period of 10 months and 3 days in 57 children with TS. They found a significant increase in both BMI and waist circumference percentiles. While the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guidelines have now been issued to help professionals monitor weight gain and growth, it is unclear which professionals choose to follow these guidelines (Pringsheim et al., 2011). There also exists a clear need for more longitudinal studies, not only addressing fluctuation in weight following administration of medication, but also studies that control for dietary effects in TS.

Secondly, is well known that not only does a child's early eating habits form the basis for their dietary habits as an adult, but can also lead to poor physical and mental health (Wachs, 2009). Importantly, both anecdotal and case reports suggest that many individuals with TS are more likely to consume an unhealthy diet, and show a predisposition to being overweight, compared to those without TS. For example, Liang, Sun, Ma, and Liu (2015) investigated the dietary behaviour, food variety and nutrient intake in 48 adult patients with TS over a 24 hour period. Results revealed over half of those surveyed reported consuming low levels of protein, calcium, zinc, retinal, thiamine, riboflavin and vitamin C. Participants also reported consuming more carbohydrates and fats than may be considered healthy. Therefore, specific nutritional guidelines appear to be needed for individuals with TS to follow.

Finally, more alternative treatments are needed aside from the pharmaceutical and behavioural-based interventions (e.g. habit reversal) that are currently being offered (Himle, Woods, Piacentini and Walkup, 2006). Table 1 illustrates the current treatments that are on offer for TS, and some of the associated difficulties with these treatments. Furthermore, anecdotal reports and TS forums often describe benefits in the reduction of tics after the incorporation of nutritional and dietary changes (Mantel, Meyers, Tran, Rogers and Jacobson, 2004), yet little empirical research has been carried out to support these reports. This is in stark contrast to the vast number of studies addressing nutrition and diet in several disorders comorbid with TS, such as Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD). For example, improvements in behavioural symptoms of ASD have been reported with the use of various supplements, including omega-3 fatty acids

(Amminger, 2007) and vitamin C (Dolske et al., 1993). In children with ADHD, symptoms have been shown to improve with flax oil and Vitamin C supplements (Joshi et al., 2006).

Given the impact of motor and vocal tics on the lives of individuals with TS, the suggestion they are more vulnerable to unhealthy eating habits, and also the multiple adverse effects of the use of pharmaceutical interventions, it is important to increase our understanding of what role, if any, dietary factors and eating behaviours play in the frequency and severity of tics.

<div align="center">Table 1 here</div>

<div align="center">**Current review**</div>

In contrast to a literature review, which aims to evaluate the existing literature related to a clearly defined research question (Davis, Drey and Gould, 2009), a scoping review adopts transparent and rigorous methodology to identify gaps in the literature and enhance future research (Arskey and O'Malley, 2005). Therefore, a scoping review can provide a first assessment of a body of emergent research. The purpose of the current scoping review was to a) understand the possible influence of different vitamins and food types on Tics; b) map out the existing studies documenting dietary interventions in individuals with TS. Here the term 'dietary interventions' referred to any alteration or treatment of an individual's diet with a planned goal, and included any supplement, vitamin, food and/or diet.

<div align="center">**METHODS**</div>

The search used the electronic databases of PubMed, Medline, PsychInfo and Web of Science to identify relevant research. Publication year was not restricted. Combinations of the following search terms were used: TS, Tourettes Disorder, Gilles de la Tourette Syndrome, food, diet, nutrient, nutrition, vitamins, fatty acids, magnesium, iron, sugar, amino acids and complementary alternative medicines. To provide the most comprehensive list of the literature, the references lists of papers obtained from the search terms were also manually scanned. This resulted in fifteen articles and one book chapter. Articles were further screened for relevance, and five articles were removed as they only referred briefly to disorders comorbid with ASD, OCD and/or ADHD and were not specific to TS. Therefore, the final selection included nine articles and one book chapter, most of which were based on either clinical observations or self-report surveys. Only two articles involved an empirical investigation of the impact of diet and nutrition in TS, and only four studies reported comorbid symptoms of the children and adults with TS. Furthermore, none of the studies used control groups, which highlights a lack of comparative data on children and adults of a similar age without TS. Therefore, due to the limited studies available, all were included in the review (see Table 2 for a summary of the selected studies).

Table 2 here

RESULTS

1) The influence of specific diets and nutrition on tics

Caffeine

Previous research has shown that CNS stimulants such as methylphenidate or cocaine precipitate or worsen tics (Cardoso and Jankovic, 1993), although more recent research has failed to establish a direct link between the use of psychostimulants and an increase in the causation of tics (Erenberg, 2005). Another CNS stimulant, caffeine, has also been suggested to influence the expression of tics in TS. Caffeine is a competitive antagonist at adenosine receptors, and has been shown to enhance the effects of dopamine agonists. The dopaminergic system may therefore modulate or facilitate the expression of tics, as demonstrated by dopamine mimetic receptor blockers (such as haloperidol), which has been shown to have a suppressant action on tics (Jankovic, 1982). Furthermore, tics may worsen due to the further stimulation of an already overactive dopaminergic system by caffeinated products (Müller-Vahl et al., 2008).

Schaefer, Chow, Louis and Robakis (2017) recently found, when conducting a retrospective chart review of outpatients over age 21, that one third of the patients with TS identified re-emergence of tics following the intake of alcohol and caffeine. The case of two cousins with tic-related symptoms who, over a 3-year period of being observed and having tics recorded, were also reported to display caffeine-precipitated tics (Davis and Osorio, 1998).

Refined sugars

Refined sugar is a processed food and is commonly found as a combination of glucose and fructose, known as sucrose. It is often used by food manufacturers to sweeten food, but has been shown to cause a rapid rise in blood sugar that could increase an individual's risk of mood swings, diabetes, cancer and obesity (Horton

and Yates, 1987). Refined sugar may also exacerbate some psychological disorders. For example, refined sugar has been found to cause more behavioural problems in ADHD (Bateman et al., 2004), and TS respondents have reported a worsening of their tics after the consumption of refined white sugar (Müller-Vahl et al., 2008).

Johnson et al., (2011) proposed that, in the case of individuals with ADHD, the increase of dopamine (caused by sugar intake) might lead to a reduction in the number of D2 receptors and/or a decrease in extracellular dopamine itself. This could potentially lead to desensitization of the dopamine-signalling axis, meaning it is possible that children with ADHD may then ingest more sugar in an effort to correct the dopamine-deficient state. Therefore, children with TS, a population also identified as having dysfunction of the dopamine system, may also show a tendency to consume high sugar foods, which may in turn exacerbate tics.

Magnesium deficiency

Magnesium is a mineral that has a crucial role in how the body regulates and functions, and it is also essential to the biochemical systems that contribute to the body's health maintenance. The classic symptoms of mineral deficiency can often be linked to their physiological role of controlling healthy levels of calcium and potassium in the body (Laires, Monteiro and Bicho, 2004). A deficit in Magnesium can result in seizures, anxiety, muscle spasms and tics, migraine headaches, depression and chronic fatigue (Galland, 1993). All of these symptoms are frequently observed in a range of neuropsychiatric conditions (such as TS). However, the potential contribution of magnesium deficiency is currently unclear.

Grimaldi (2002) reported that children with TS have a magnesium deficiency, which has been attributed to neuromuscular hyperexcitability, as well as a rise in convulsions, chorea and athetoid movements. A magnesium deficiency has also been suggested as the precipitating event for biochemical effects on substance P, kynurenine, NMDA receptors and vitamin B6, which may provoke the symptoms evidenced by children with TS, such as facial muscles ending in tongue protrusions. Furthermore, a magnesium deficiency has been related to an increased release of dopamine, more defensive behaviour and greater modulation of serotonin receptors. It can also lead to other symptoms, including migraine, which is found to be more frequent among patients with TS (Planells, Lerma, Sanchez-Morito, Aranda and Llopis, 1997).

In other psychological disorders (such as ASD), oral supplementation of magnesium and vitamin B have been shown to significantly improve the ability to interact in social situations, and to increase communication and intellectual abilities (Mousain-Bosc et al., 2006). Research is needed to investigate the potential of using magnesium and vitamin B6 as a method of treatment in TS, for the reduction of symptoms. If successful, this could help reduce tics and the need for pharmacological interventions (including neuroleptic drugs). Importantly, magnesium and B6 can both be administered via food intake and are associated with few side effects (Garcia-Lopez, et al., 2009).

Iron deficiency

Iron is critical for producing haemoglobin, a protein that helps red blood cells deliver oxygen throughout the body. An iron deficiency is one of the most commonly

reported nutritional deficiencies found in the general public; it results in a lack of oxygen getting to tissues and organs, which can lead to anaemia. Iron deficiency, with or without anaemia, can also impair emotions and cognition, and in other psychological disorders, has been associated with developmental delay in infants, mood changes and lack of concentration in children (Latif, Heinz and Cook, 2002).

Low ferritin and serum iron levels have frequently been found in both children and adults with TS. Whilst, in the brain, small caudate nucleus and putamen (forming the dorsal striatum) are considered part of the pathophysiology of TS, further examination within this group found this to be particularly the case for those with lower ferritin iron levels (Gorman et al., 2006). It has been suggested that low levels of iron may contribute to hypoplasia of the caudate putamen, increasing the risk for both development and severity of tics. In addition, the inability to control tics may be a result of smaller cortical volumes, also linked to low levels of iron (Gorman et al., 2006). Iron metabolism has also been implicated in the pathophysiology of TS, through its impact on the metabolism of dopamine and, possibly, other neurotransmitters (Cortese et al., 2008).   Therefore, given the biological links showing low levels of iron may be symptomatic of children with TS, the relationship between iron supplements and symptoms of TS may be warranted.

Gluten intolerance

Anecdotal reports have suggested that children with TS have abnormal reactions to gluten, and the chemical manipulation of this protein has been suggested to result in a substance that exacerbates tics. It can also contribute to difficulties in the breakdown

of a protein found in dairy products, called casein (Millward, Ferriter, Calver and Connell-Jones, 2008).

Celiac disease, a common digestive condition caused by an abnormal immune reaction to gluten, is more likely to occur in association with other psychological disorders such as ADHD, Autism, Learning and tic disorders (Pynnönen et al., 2005). A recent case reported in the literature involved a 13-year-old female with a 10-year history of tics and Obsessive-Compulsive Disorder. Despite a family history for celiac disease, she failed to show symptoms of the disease herself, but instead met the criteria for Non-Celiac Gluten Sensitivity. After 1-week of being placed on a gluten-free diet (GFD) her tics were reported to diminish, and within a few months the tics appeared to completely disappear (Rodrigo, Huerta and Salas-Puig, 2015). However, to date, no empirical studies have directly addressed the use of a gluten diet in individuals with TS.

Low levels of Amino acids

Protein in food is broken down into Amino acids, which are essential acids for every aspect of the body. Amino acids give cells their structure, are essential for repairing tissue, have an important role in the transport and storage of nutrients, and are important for every metabolic process. There is some evidence to suggest that children with TS suffer from low levels of amino acids, such as 5-hydroxtryptophan (5HTP), which could be alleviated through a healthy diet and/or dietary supplements.

N-acetylcysteine (NAC) is commonly found in food and is an antioxidant derived from amino acid, L'cysteine synthesized by the body. In addition to showing few side

effects, NAC has been found to be effective in the treatment of a range of clinical disorders including OCD, and adult trichotillomania (Grant et al., 2009). More recently N-acetylcysteine, has been addressed as a possible treatment in TS, targeting repetitive behaviours by reducing frequency and intensity of premonitory urges via the modulation of glutamate (Bloch et al., 2016).

2) Dietary interventions in children with TS

Despite the suggestion that certain allergens in food might exacerbate tic-related symptoms in children with TS (Brunn, 1984), there is very little research addressing nutritional factors (such as food additives, allergies and diets) on tics and other symptoms of TS. Furthermore, the limited research available has produced contradictory findings with some results identifying no effect of food intake and/or special diet on symptom fluctuation (Silva et al., 1995), and other findings showing specific foods increase symptoms in as many as 40% of children with TS (Bornstein, Stefl and Hammond, 1990). In the case of Silva et al., (1995), the survey used a small sample (*N=14*), did not include a comparison group, and only addressed vitamin and mineral supplements. The combination of these factors therefore hinders the interpretation of these findings. In comparison, Bornstein et al., (1990) included a wider sample of individuals with TS (*N=763*) ranging in age from 4- to 76-years (mean 18.6), but failed to report the use of any medication.

Mantel et al., (2004) directly addressed the use of nutritional supplements in TS by administering a survey of Complimentary Alternative Medication (CAM) use to 500 people on the mailing list of the New York Chapter of the Tourette Syndrome

Association, and the subscription list of *Latitudes* (a newsletter addressing CAM use for neurological conditions). The study surveyed 115 individuals with TS and found a staggering 101 respondents (87.7%) used supplements to control tics. Amongst the most commonly used supplements, were vitamin B (60-70 respondents), followed by vitamin C/E, calcium and magnesium (55 respondents). Furthermore, younger participants were more likely to report a reduction in motor and vocal tics with the use of supplements than older participants. For example, 70% of 11- to 18-year-olds reported a reduction in motor tics, and 55% in vocal tics, with the use of supplements, whereas only 50% of respondents over 18-years-old felt they had seen a reduction in motor tics, and 40% in vocal tics. While no incentives were offered for taking part in the study, respondents were recruited from a publication whose readership was aimed at CAM treatments for neurological conditions. Therefore, it is important to highlight that respondents may have been more likely than other individuals with TS to already use a CAM, and consequently be more complimentary about its effects.

Kompoliti, Fan and Leurgans (2009) further investigated the use of CAM, and surveyed 100 adult patients and parents/caregivers of children with TS. CAM treatments related to nutrition assessed the use of dietary supplements, vitamins, and diet alterations. The findings revealed that 64% of the sample had used at least one CAM; 21 used vitamin supplements; 15 used dietary supplements; and 9 used diet alterations. Dietary supplements used included flaxseed oil (9%) and fish oil (14%). However, no details were provided regarding the specific vitamins used, or how regularly they were taken. There was also no measure given, which assessed changes in tics with the use of dietary supplements. The data gained from the study demonstrated many of the respondents were using CAM in addition to their current

medication (60%), making the reported benefits of CAM difficult to determine. Importantly, the motivations for using CAM were not related to dissatisfaction with current and/or conventional treatments, tic severity or side effects of medication

The sample in the Kompoliti et al. study was also problematic as a large proportion were well educated and of a high socioeconomic status, with 47% of the sample reported financing CAM themselves. The reported benefits of CAM in lower socioeconomic status groups are therefore less well understood. Interestingly, 80% of those who had reported using a CAM had initiated its use without informing their doctor. This may reflect the little support amongst professionals for the idea of a relationship between diet and tic related symptoms in TS (Kompoliti et al., 2009). In support of this, a survey investigating knowledge of symptoms and treatment, administered to 67 physicians and psychologists, found that amongst those who had treated at least one person with TS, only 13% believed special diets to affect tics (Marcks, Woods, Teng and Twohig, 2004).

In a further survey, carried out by Müller-Vahl, Buddensiek, Geomelas and Emrich (2008), only 34% of 224 respondents with TS (from a pool of 887 people from German Tourette syndrome self-aid group), had ever adopted the use of a special diet to improve symptoms. While the demographics measured included age and gender, no information on comorbid disorders was sought. Sixty per cent of responses were from people with TS, and the remaining 40% were from carers/parents (96% of respondents confirmed the diagnosis was provided by a medical professional). Respondents were asked to rate the influence of 32 different foods and drink items on their tics using a six-point scale (0= no influence, 1= mild improvement, 2= marked

improvement, 3= mild deterioration, 4= marked deterioration 5= I do not eat). Examples of the different food types specified include: meat (pork, beef and poultry), dairy products, yeast, wheat, fruits, preserving agents, refined white sugar, coffee, coke and alcoholic drinks. Respondents were also requested to state the use of previous special diets (such as sugar and gluten free), and to rate whether they believed the diet had had an influence on the presentation of tics, using the aforementioned scale. Müller-Vahl et al.,'s (2008) findings highlighted the influence of some special diets on tics. For example, oligoantigenic (elimination diet that seeks to resolve inflammation in the gut) and sugar-free diets were reported to significantly reduce tics. Moreover, a significant increase in tics was related to the consumption of: coke, black tea, coffee, persevering agents, refined sugar and sweeteners. In fact, 34% of respondents reported tics to worsen with the consumption of coffee, and 47% with the consumption of coke. Following from these results, experimental studies are now needed to address changes in the fluctuation of tics following the intake of some of these identified food types. By closely monitoring any improvements and/or deterioration would enable a clearer understanding of their effects on tics, both short and long term.

There appears to have been only two experimental placebo controlled trials addressing nutrition in TS. In the first of these, Gabbay et al., (2012) investigated the effects of Omega-3 fatty acids (O3FA) on the symptoms of children and adolescents with TS. Essential fatty acids and phospholipids are both required for normal neuronal structure and function and must be supplied through the diet. Gabbay et al., (2012) used a randomised, double blind, placebo-controlled trial of 33 children and adolescents (aged 6- to 18-years) with TS. Children were randomly assigned to O3FA

or placebo (olive oil) for 20 weeks, from a pharmacist. While O3FA were not found to significantly reduce tic scores, and showed little effect on obsessive-compulsive, anxiety and depressive symptoms, they were suggested as being beneficial to some tic-related symptoms. For example, children receiving O3FA reported significantly lower scores on the Yale Global Tic Severity scale than those receiving olive oil. The findings suggest that a diet with high levels of O3FA may help alleviate some tic-related symptoms. The authors noted that the detection of more subtle treatment effects might have been enhanced by a larger sample, and with use of an alternative placebo (olive oil might have had a therapeutic effect due to its antioxidative properties). Further experimental research addressing the effects of 03FA in TS, could also inform the recommended doses required to establish improvements in any symptoms.

The second study addressed the use of amino acids in TS. Bloch et al., (2016) assessed the efficacy of the amino acid *N*-acetylcysteine (NAC) in paediatric TS using a double-blind, placebo-controlled, add-on study. Thirty-one children and adolescents aged 8- to 17-years-old were randomly assigned to either the NAS condition (*N=17*) or the placebo condition (*N*=14). Participants in the placebo trial were offered NAC treatment after completion of the study. Over a 12-week period, the trial failed to demonstrate a benefit of NAC on the severity of tics, as measured by the Yale Global Tic-Scale. The lack of effectiveness of NAC found in TS compared to studies addressing OCD may be due to differences in the clinical presentations of the two disorders (e.g. gender, pathology) and/or the fact that when effectiveness has been reported, this has involved the use of older populations with OCD. The aftermentioned study benefits from not only the adoption of a randomised placebo

design, but also considers secondary symptoms of the disorders including OCD, depression, anxiety and ADHD. However, the authors note important baseline differences between the placebo and NAC groups, such that they differed significantly in the severity of these comorbid symptoms, and use of antipsychotic medication. Both of which could have influenced the effectiveness of NAC.

DISCUSSION

This scoping review aimed to summarise the research that has investigated the effects of certain types of foods on tics, and to map out the existing studies that have explored potential dietary interventions for the alleviation of tics. From the very limited literature available, no one diet has been shown to benefit individuals with TS, although certain diets (such as oligoantigenic and sugar-free diets) were reported to alleviate tics (Müller-Vahl et al., 2008). In addition, children with TS may be more prone to unbalanced, and often energy dense diets, which can predispose children to weight gain and its associated health complications. Therefore more studies addressing dietary habits in this group of children are clearly warranted (Liang et al., 2015).

The literature discussed in this review has highlighted the shortcomings of the few studies that have begun to address this topic. Common limitations include small samples, the use of case studies, no measure for changes in tic frequency, failure to include appropriate comparison groups and, in some cases no consideration of any comorbid disorders (e.g. Davis, 1998). The different methodologies incorporated by

the studies, such as the fact that some report the use of diagnostic criteria, and others simply specify that participants had some sort of tic disorder, further hampers the ability to draw comparisons across studies. Furthermore, many of the studies are based purely on observations or self-report surveys completed by the individual with TS or a parent/caregiver (Mantel et al., 2005).

The importance of more experimental studies, with the inclusion of placebo conditions, is needed to address the influence of diet and nutrition on tics. However, only by research first establishing a clearer relationship between diet and the symptoms of TS, using larger samples of children, may randomised clinical trials be warranted. Further findings would help inform better healthcare guidelines, and could also offer an alternative intervention to pharmaceutical treatments in the management of tics.

The current review outlines the clear need to understand dietary behaviours in TS further. Anecdotal evidence has shown that individuals with TS, and parents and caregivers of children with TS, are investing in the use of dietary and nutritional supplements, despite the lack of evidence detailing any benefits, side effects and recommended doses. Despite the lack of a clear evidence base to support the idea that changes in diet could alleviate some of the symptoms of TS, the manipulation of diet for future studies to further our understanding of this relationship appears to come as little cost, compared to some of the adverse side effects of other treatments currently being offered to TS. Understanding dietary and nutritional factors in TS may be useful in informing our understanding of some of the associated causes of tic

behaviour, and may even provide alternative interventions for improving the quality

of life in these families.

REFERENCES

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (DSM-5®). American Psychiatric Pub.

Amminger GP, Berger G E, Schäfer MR, Klier C, Friedrich MH and Feucht M (2007) Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. *Biological psychiatry* 61(4): 551-553. DOI:10.1016/j.biopsych.2006.05.007

Arksey H, and O'Malley L (2005) Scoping studies: towards a methodological framework. *International journal of social research methodology,* 8(1): 19-32. DOI:10.1080/1364557032000119616

Bak M, Fransen A, Janssen J, van Os J and Drukker M (2014) Almost all antipsychotics result in weight gain: a meta-analysis. *PloS one*, 9(4), e94112.

Bateman B, Warner JO, Hutchinson E, Dean T, Rowlandson P, Gant C, Grundy J, Fitzgerald C and Stevenson J (2004) The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. *Archives of Disease in Childhood*, 89(6): 506-511. DOI:10.1136/adc.2003.031435

Bloch MH, Panza KE, Yaffa A, Alvarenga PG, Jakubovski E, Mulqueen JM, Landeros-Weisenberger, A and Leckman, J.F (2016) N-Acetylcysteine in the

Treatment of Pediatric Tourette Syndrome: Randomized, Double-Blind, Placebo-Controlled Add-On Trial. *Journal of child and adolescent psychopharmacology*, 26(4): 327-334.

Bornstein RA, Stefl ME and Hammond L (1990) A survey of Tourette syndrome patients and their families: The 1987 Ohio Tourette survey. *The Journal of neuropsychiatry and clinical neurosciences* 2(3): 275-81. DOI: 10.1176/jnp.2.3.275

Brunn RD (1984) An overview of clinical experience. *Journal of the American Academy of Child Psychiatry* 23(2): 126-133. DOI: 10.1097/00004583-198403000-00002

Cardoso FE and Jankovic J (1993) Cocaine- related movement disorders. *Movement disorders* 8(2): 175-178. DOI: 10.1002/mds.870080210

Chilvers R, Stein S and Chowdhury U (2010) Tourette's: 20 CAMHS cases. *Community Practitioner* 83(8): 38-9.

Cortese S, Lecendreux M, Dalla Bernardina B, Mouren MC, Sbarbati A and Konofal E (2008) Attention-deficit/hyperactivity disorder, Tourette's syndrome, and restless legs syndrome: the iron hypothesis. *Medical Hypotheses* 70(6): 1128-1132. DOI: 10.1016/j.mehy.2007.10.013.

Davis K, Drey N and Gould D (2009) What are scoping studies? A review of the nursing literature. *International journal of nursing studies* 46(10): 1386-1400. DOI: 10.1016/j.ijnurstu.2009.02.010

Davis RE and Osorio I (1998) Childhood caffeine tic syndrome. *Pediatrics* 101(6), e4-e4.

Degrauw RS, Li JZ and Gilbert DL (2009) Body mass index changes and chronic neuroleptic drug treatment for Tourette syndrome. *Pediatric neurology,* 41(3): 183-186. DOI; 10.1016/j.pediatrneurol.2009.04.002

Dolske MC, Spollen J, McKay S, Lancashire E and Tolbert L (1993) A preliminary trial of ascorbic acid as supplemental therapy for autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 17(5): 765-774. DOI: 10.1016/0278-5846(93)90058-Z

Erenberg, G (2005) The relationship between Tourette syndrome, attention deficit hyperactivity disorder, and stimulant medication: a critical review. In Seminars in pediatric neurology (Vol. 12, No. 4, pp. 217-221). WB Saunders.

Findley DB, Leckman JF, Katsovich L, Lin H, Zhang H, Grantz H, ... and King RA (2003) Development of the Yale Children's Global Stress Index (YCGSI) and its application in children and adolescents with Tourette's syndrome and obsessive-compulsive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 42(4): 450-457. DOI: 10.1097/01.CHI.0000046816.95464.EF

Gabbay V, Babb JS, Klein RG, Panzer AM, Katz Y, Alonso CM, Petkova E, Wang J and Coffey BJ (2012) A double-blind, placebo-controlled trial of omega-3 fatty acids in Tourette's disorder. *Pediatrics* 129(6): e1493-e1500. DOI: 10.1542/peds.2011-3384

Galland L (1993) Magnesium, stress and neuropsychiatric disorders. *Magnesium and trace elements* 10: 287-287.

Garcia-Lopez R, Perea-Milla E, Garcia CR, Rivas-Ruiz F, Romero-Gonzalez J, Moreno JL, Faus V, Aguas Gdel, C and Diaz, JCR (2009) New therapeutic approach to Tourette Syndrome in children based on a randomized placebo-controlled double-blind phase IV study of the effectiveness and safety of magnesium and vitamin B6. *Trials* 10(1): 16. DOI: 10.1186/1745-6215-10-16

Grant JE, Odlaug BL, Suck WK (2009) N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. Archives of General Psychiatry 66: 756-763. doi:10.1001/archgenpsychiatry.2009.60

Grimaldi BL (2002) The central role of magnesium deficiency in Tourette's syndrome: causal relationships between magnesium deficiency, altered biochemical pathways and symptoms relating to Tourette's syndrome and several reported comorbid conditions. *Medical hypotheses* 58(1): 47-60. Doi: 10.1054/mehy.2001.1447

Gorman DA, Zhu H, Anderson GM, Davies M and Peterson BS (2006) Ferritin levels and their association with regional brain volumes in Tourette's syndrome. *American Journal of Psychiatry,* 163(7), 1264–72. DOI: 10.1176/ajp.2006.163.7.1264

Himle MB, Woods DW, Piacentini JC and Walkup JT (2006) Brief review of habit reversal training for Tourette syndrome. *Journal of Child Neurology* 21(8): 719-725.

Horton JR and Yates AJ.(1987) The effects of long-term high and low refined-sugar intake on blood glucose regulation, mood, bodily symptoms and cognitive functioning. *Behaviour research and therapy* 25(1): 57-66. DOI: 10.1016/0005-7967(87)90115-X

Kompoliti K, Fan W and Leurgans S (2009) Complementary and alternative medicine use in Gilles de la Tourette syndrome. *Movement Disorders* 24(13): 2015-2019. DOI: 10.1002/mds.22724

Jankovic, J (1982) Treatment of hyperkinetic movement disorders with tetrabenazine: A double- blind crossover study. *Annals of neurology* 11(1): 41-47.

Johnson RJ, Gold MS, Johnson DR, Ishimoto T, Lanaspa MA, Zahniser NR and Avena, NM (2011) Attention-deficit/hyperactivity disorder: Is it time to reappraise the role of sugar consumption?. *Postgraduate medicine* 123(5): 39-49. DOI: 10.3810/pgm.2011.09.2458

Joshi K, Lad S, Kale M, Patwardhan B, Mahadik SP, Patni B. Chaudhary A, Bhave,S and Pandit A (2006). Supplementation with flax oil and vitamin C improves the outcome of Attention Deficit Hyperactivity Disorder (ADHD). *Prostaglandins, Leukotrienes and Essential Fatty Acids* 74(1): 17-21. DOI: 10.1016/j.plefa.2005.10.001

Laires MJ, Monteiro CP and Bicho M (2004) Role of cellular magnesium in health and human disease. *Frontiers in Bioscience* 9(262): 76.

Lanzi G, Zambrino CA, Termine C, Palestra M, Ginevra OF, Orcesi S, Manfredi P and Beghi E (2004) Prevalence of tic disorders among primary school students in the city of Pavia, Italy. *Archives of disease in childhood,89*(1): 45-47.

Latif A, Heinz P and Cook R (2002) Iron deficiency in autism and Asperger syndrome. *Autism* 6(1): 103-114. DOI: 10.1177/1362361302006001008

Liang H, Sun X, Ma A and Liu Y (2015) Evaluation of dietary behavior and nutrient intake in patients with Tourette Syndrome. *The FASEB Journal* 29(1): 911-16.

Mantel, B. J., Meyers, A., Tran, Q. Y., Rogers, S., & Jacobson, J. S. (2004). Nutritional supplements and complementary/alternative medicine in Tourette syndrome. Journal of Child & Adolescent Psychopharmacology, 14(4), 582-589. 10.1089/cap.2004.14.582

Marcks BA, Woods DW, Teng EJ and Twohig MP (2004) "What do those who know, know? Investigating providers' knowledge about Tourette's syndrome and its treatment." *Cognitive and Behavioural Practice* 11(3): 298-305. DOI: 1016/S1077-7229(04)80044-0

Millward C, Ferriter M, Calver SJ and Connell-Jones GG (2008) Gluten-and casein-free diets for autistic spectrum disorder. *The Cochrane Library*. DOI: 10.1002/14651858.CD003498.pub3

Mousain-Bosc M, Roche M, Polge A, Pradal-Prat D, Rapin J and Bali JP (2006) Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. *Magnesium Research* 19(1): 53-62.

Müller‐Vahl KR, Buddensiek N, Geomelas M and Emrich HM (2008) The influence of different food and drink on tics in Tourette syndrome. *Acta Paediatrica* 97(4): 442-446. DOI: 10.1111/j.1651-2227.2008.00675.x

Planells E, Lerma A, Sanchez-Morito N, Aranda P and Llopis J (1997) Effect of magnesium deficiency on vitamin B2 and B6 status in the rat. *Journal of the American College of Nutrition* 16(4): 352-356. DOI: 10.1080/07315724.1997.10718697

Pringsheim T, Ho J, Sarna JR, Hammer T and Patten S (2017) Feasibility and Relevance of Antipsychotic Safety Monitoring in Children With Tourette Syndrome:

A Prospective Longitudinal Study. *Journal of Clinical Psychopharmacology* 37(5): 498-504. DO1: 10.1097/JCP.0000000000000760

Pringsheim T, Panagiotopoulos C, Davidson J, Ho J and Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline group (2011) Evidence-based recommendations for monitoring safety of second-generation antipsychotics in children and youth. *Paediatrics & child health*: 16(9), 581-589.

Pynnönen PA, Isometsä ET, Verkasalo MA, Kähkönen SA, Sipilä I, Savilahti E and Aalberg VA (2005) Gluten-free diet may alleviate depressive and behavioural symptoms in adolescents with coeliac disease: a prospective follow-up case-series study. *BMC psychiatry* 5(1): DOI: 10.1186/1471-244X-5-14

Robertson MM (2008) The prevalence and epidemiology of Gilles de la Tourette syndrome: Part 1: The epidemiological and prevalence studies. *Journal of psychosomatic research* 65(5): 461-472. DOI: 10.1016/j.jpsychores.2008.03.006

Robertson MM, Eapen V and Cavanna AE (2009) The international prevalence, epidemiology, and clinical phenomenology of Tourette syndrome: a cross-cultural perspective. *Journal of psychosomatic research* 67(6): 475-483. DOI: 10.1016/j.jpsychores.2009.07.010

Rodrigo L, Huerta M and Salas-Puig J (2015) Tourette Syndrome and Non-Coeliac Gluten Sensitivity. Clinical Remission with a Gluten-Free Diet: A Description Case.

Journal of Sleep Disorder Therapy 4(183): 2167-0277. DOI: 10.4172/2167-0277.100018

Scahill L, Erenberg G, Berlin CM, Budman C, Coffey BJ, Jankovic J, Kiessling L, King, RK, Kurlan R, Lang A, Mink J, Murphy T, Zinner S and Walkup J (2006) Contemporary assessment and pharmacotherapy of Tourette syndrome. *NeuroRx, 3*(2): 192-206.

Schaefer SM, Chow CA, Louis ED and Robakis D (2017) Tic exacerbation in adults with Tourette syndrome: a case series. *Tremor and Other Hyperkinetic Movements* 1-7. DOI: 10.7916/D8FF3Z1Q

Silva RR, Munoz DM, Barickman J and Friedhoff AJ (1995) Environmental factors and related fluctuation of symptoms in children and adolescents with TS. *Journal of Child Psychology and Psychiatry* 36(2): 305-312. DOI: 10.1111/j.1469-7610.1995.tb01826.x

Singer HS(2005) Tourette's syndrome: from behaviour to biology. *The Lancet Neurology* 4(3): 149-159. DOI: 10.1016/S1474-4422(05)01012-4

Wachs TD (2009) Models linking nutritional deficiencies to maternal and child mental health. *The American journal of clinical nutrition* 89*(3),* 935S-939S. DOI: 10.3945/ajcn.2008.26692B

Table 1: Main types of treatment for TS.

Treatments	Types of Treatments	How they work	Adverse effects
Self-help	The individual with TS can use a range of strategies to help alleviate tics.	•Avoiding stress, anxiety boredom and becoming too tired	Time consuming, few long term beneficial effects, more successful for less severe cases and in older children and adults.
Psychoeducation	Educating both the individual with TS and other people about the condition.	Learning about Tic Disorders and TS. Can include learning about the causes, the usual course of tics, and the types of co-occurring conditions that often occur in individuals with TS.	Time consuming, and not always clear how best to teach others about the syndrome. May help an individual with TS, to understand their condition more, but does not necessarily lead to an improvement in their symptoms.
Medication	First Generation Neuroleptics	Medications that inhibit dopamine reuptake	High rate of extrapyramidal side effects, including Tardive dyskinesia, rigidity, bradykinesia, dystonias,, tremor, and akathisia.
	Second Generation Neuroleptics		Lower risk of movement side effects. Associated with significant lipid and prolactin elevation, weight gain, and type II diabetes.
Behaviour Therapies	Habit Reversal Therapy (HRT)	•Tic-awareness training- to educate others about the condition

• Help the person to identify when tics occur and the types of urges felt before the tics.

•Helps to identify new responses to do when a person feels the urge to tic | Found to be less beneficial in individuals whose symptoms persist have a more chronic form of the disorder. Requires practice outside of the therapy sessions. Lack of therapists trained in HRT. |
| | Exposure and response prevention (ERP) | Teaches the person to suppress the growing feeling you need to tic until it subsides. Can be used to improve all the individuals tics at the same time. | Requires practice outside of the therapy sessions. Some individuals have reported 30-40% reduction in tics.

Can be very demanding on young children. |
| | Relaxation Training | Teaches the individual with TS, to cope with stress. | Not found to be very effective for more severe cases. |

		Involves deep breathing and tensing and relaxing muscles in the body.	
	Cognitive Behavioural Therapy	Usually offered in 8-12 weekly or fortnightly sessions with a therapist. Changes are made through cognitive restructuring, and through behavioral and physiological modifications	Dependent often upon an NHS referral.
Surgery	Deep brain stimulation	It has been used in only few severe cases Under anaesthetic, a small number of electrodes are placed in areas of bran associated with the tics. Thin wires run from the electrodes to a pulse generator, placed under the skin of your chest. This gives out an electric current to help regulate the signals in your brain and control your tics.	Uncertainties exist surrounding how effective and safe it is. Only been used in severe cases and in adults.

Table 2: Summary of research addressing diet and dietary interventions in TS

Author(s), year	Participants diagnosis, gender and age	Comorbid symptoms	Purpose	Method	Results
Observation and Case reports					
Bruun, 1984	TS (n=300) Not stated	Not stated	A review of 12 years of cases of TS	Clinical observations	Seasonal allergic responses or the ingestion of allergens in food
Davis, 1998	Normal Development with tics (n=2) no TS diagnosis of phonic or vocal tics reported. 11 and 13 year old male cousins Other than tics normal development	Not stated	To observe whether intake of caffeine would influence tics	3 year observational design	Tics exacerbated with consumption, and decreased with discontinuation, of caffeine-related products.
Rodrigo, Huerta, Salas-Puig (2015)	TS (N=1) 13yrs female	OCD, celiac disease*	To assess any clinical improvements in symptoms after the use of a gluten-free diet	Observation	Diminishment of tics 1 week after beginning diet. After 2.5 years is in complete remission from tics with only the occasional flare up

Parent and Self-report

Silva, Munoz, Barickman & Friedhoff, 1995	TS (n=14) 10 males, 4 females 6.6-14.5 years (mean, 10.3 ± 2.5) 8 participants assessed for tics using the Yale Global Tic severity scale by trained clinical rater. None of participants had ever received medication.	Not stated	To assess how 29 different environmental factors affected TS.	Self–report questionnaire	10 factors reported as having no impact on tics (alcohol, coffee, vitamins, foods, and special diets, cigarette smoking, exposure to hot cold weather and living away from home). 17 factors increased tics (e.g. anxiety, emotional trauma and fatigue, watching TV and social gatherings).
Mantel et al., 2004	TS (n=115) Both under and over 18 years (33 <10y; 51 11-18y; 19 >18y; and 12 unspecified). Means and sd not presented.	ADHD (78)* OCD (46)* Autism (4)* A breakdown of those with kidney disease, heart disease, allergies, asthma and aggression also reported.	To explore the use of supplements and CAM among TS patients	Parent and self-report survey	87.7% used 1 or more of 29 supplements to control symptoms. 33% reported improved benefit with the use of dietary modification
Muller-Vahl, Buddensiek 2008	TS (n=224) 5–72 years M=24.7 years SD: ±14.5	Not stated	To assess influence of food and drinks in TS	Parent and self-report survey	Tics increase following consumption of coke, coffee, black tea, preserving agents, refined white sugar and sweeteners. The use of algio-antigen and sugar free diet was found to significantly reduce tics.
Kompoliti, Wenquin & Leurgans, 2009,	TS (n=100) 76 males and 23 females (aged: 21.5 ± 13.5y) 39% patient, 27% parent/guardian and 24% both cases. TS diagnosis confirmed. CAMS TS users and TS non-users did not differ on gender, age, general health, tic severity, medication, income or educational level.	Made by a neurologist Comorbidity included ADHD (DSM-IV criteria), OCD (Leyton Inventory). Affective disorders (Depression: Hamilton Inventory; Anxiety DSM-IV criteria).	To monitor the use of Complementary and Alternative Medicine Use (CAMS)	Parent and self-report survey on CAMS	64% has used at least one CAMS 56% reported improvement with CAMS 15% used diet supplements 9% diet alterations

Experimental Placebo Designs

Gabbay et al., 2012	Thirty-three children and adolescents (aged 6–18yrs) with TS	OCD*	To examine the efficacy of O3FA in tic severity compared with a placebo (olive oil)	A placebo-controlled trial over 20 weeks	Some benefits of O3FA in ameliorating tic-related impairment, but not tics per se.
Bloch et al., 2006	Thirty-One children and adolescents (aged 8-17 yrs) with TS	Clinical evaluation involved psychiatric history, mental state, clinical assessment of past medication and behavioural treatment. DSM-IV criteria for diagnosis. Severity of Tics (Yale Global Tic Severity Scale YGTSS) and Premonitory Urges for TICS OCD (CY-BOCS)(*N=6*) ADHD (ADHD-RS)(*N=15*) Anxiety and Depression (MASC) Pharmacological treatment for tics (current and past use)(*N=22*) Current Pharmacological treatment for tics (*N=13*)	To examine the efficacy of N-Acetylcysteine (NAC) in treatment of tics in paediatric TS.	A double-blind, placbo control study over a 12 week period. Children were either assigned NAC or placebo.	Two-dropouts, one from each group. No significant differences between the two groups in the reduction of severity of premonitory urges associated with tics (PUTS), or in improving the severity of tics (YGTSS) No significant differences in reducing severity of comorbid symptoms, including OCD, ADHD and Anxiety. Depression symptoms increased in placebo.

*Simply based on parent and/or self report