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Use of nutritional supplements in youth with medicated and unmedicated attention-deficit/hyperactivity disorder

Running title: Nutritional supplement use in ADHD youth

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ABSTRACT

Objective: To find out whether use of nutritional supplements (NUS) differs between children and adolescents with ADHD (medicated or unmedicated), as compared to those without the disorder.

Methods: We used cross-sectional data from the population-based I.Family study conducted between 2013–2014 in eight European countries. Parents completed questionnaires and participated in interviews, e.g., on health and medical history of their child. Data from 5,067 children and adolescents aged 5–17 years were included. Exposures were medicated (with ADHD-approved medication) and unmedicated ADHD. The outcome was the use of NUS, measured by use of any or multiple different NUS. Multivariable logistic regression adjusted for socio-demographics and health determinants was used to find ADHD-depending differences.

Results: The study sample comprised 4,490 children and adolescents without ADHD and 51 medicated and 76 unmedicated subjects with ADHD. Regarding the use of any NUS, no statistically significant differences were found between children and adolescents without ADHD (18%) and those with medicated (18%) or unmedicated ADHD (22%). However, discrepancies appear when considering multiple use of NUS, which was not reported for any medicated ADHD subject but remarkably often for unmedicated ADHD subjects (13%), resulting in an adjusted odds ratio of 2.6 (95% confidence interval, 1.2–5.6) when compared to those without ADHD (5%).

Conclusion: Children and adolescents who were not using medication for treating ADHD potentially took NUS as oral remedies. Given the potential for a delay of indicated treatments and for use of NUS which have no proven effectiveness, pediatricians should actively explore whether NUS have been used to treat ADHD core symptoms, and families should be informed that the average effect size has to be considered small.

Key words: Attention Deficit Disorder with Hyperactivity; Dietary Supplements; Child; Adolescent; Drug Therapy.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with a worldwide prevalence of 3.4% in children and adolescents (Polanczyk et al. 2015). Apart from pharmacological treatments with stimulants, nutritional supplements, categorized as "complementary and alternative treatments", are also commonly used (Chan et al. 2003; Sinha and Efron 2005). Until recently, clinical guidelines on attention-deficit/hyperactivity disorder (ADHD) either did not explicitly mention complementary and alternative medicine, such as nutritional supplements, or reported a lack of evidence for their use (American Academy of Pediatrics 2011; Pliszka et al. 2007; Taylor et al. 2004). However, since 2016, the ADHD guideline by the British National Institute for Health and Care Excellence (NICE) clearly has advised against use of dietary polyunsaturated fatty acids supplementation for treating ADHD (NICE 2018). Research published after this update of the NICE guideline suggests that polyunsaturated fatty acids—particularly omega-3 fatty acids from fish oil—might be effective in reducing the dosage of the ADHD medication (Königs and Kiliaan 2016; Lange et al. 2017). Additionally, zinc, iron, and magnesium might assist in alleviating ADHD symptoms in children with deficiencies in any of these minerals or with an increased risk thereof (Bloch and Mulqueen 2014; Lange et al. 2017). Also, results from a randomized controlled trial indicate that children with ADHD and comorbid emotional dysregulation may benefit from certain vitamin-mineral supplementation by improving emotional regulation, aggression, and general functioning (Rucklidge et al. 2018). Nevertheless, more studies in this area are needed before the efficacy of these supplements can be properly measured.

The lack of evidence is contrary to the high popularity of complementary and alternative medicine indicated by previous studies. At the end of the 1990s, more than half of 114 US parents of children with ADHD in one clinic had reported using complementary and alternative medicine for their child during the past year (Chan et al. 2003) and in 2003, about

two thirds of parents in Australia reported ever having used complementary and alternative medicine to treat their ADHD-affected children (Sinha and Efron 2005). Nutritional supplements were among the most common interventions used. However, these studies did not have a comparison group and used clinical samples usually representing more severely affected ADHD patients. Results from the 1999–2002 US National Health and Nutrition Examination Surveys (NHANES) indicated that adolescents with ADHD were more likely to use nutritional supplements than those without ADHD (Gardiner et al. 2008). Use of nutritional supplements was generally more common in those who used prescription drugs. As the study did not focus on ADHD patients, the influence of using ADHD medication on the results remained unclear. Further, only participants aged eleven years and above were included. That age is beyond the typical ADHD onset and differences might be more pronounced when younger children are also included. Moreover, most evidence regarding fish oil as an omega-3 containing nutritional supplement to treat ADHD only emerged starting in the mid-2000s (Heilskov Rytter et al. 2015). Additionally, advertisements broadly formulating the beneficial effects of such nutritional supplements on ADHD symptoms might have led to an increased use since the publication of the NHANES data. In fact, use of omega-3 fatty acid supplements among US children and adolescents increased between 2003 to 2004 and 2013 to 2014 from 0.4% to 2.3% (Qato et al. 2018).

In this study, we aimed to assess differences in use of nutritional supplements among children and adolescents with ADHD compared to those without the disorder in a population-based sample. The research question was stimulated by the results of the NHANES study, where adolescents with ADHD had a slightly higher (10%) use of any nutritional supplement than other adolescents (Gardiner et al. 2008). The study also showed that adolescents who used prescription drugs were significantly more likely (37%) to use any nutritional supplement (Gardiner et al. 2008). As compared to the NHANES study, our data enabled us to estimate

the effect of use of prescription drugs without considering medication to treat ADHD. Furthermore, they allowed us to ask a more specific research question: Is the use of nutritional supplements in children and adolescents with ADHD dependent on whether they are treated with ADHD medication or not?

METHODS

Setting

Data were used from the European I.Family study conducted between 2013 and 2014 in eight countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, and Sweden). The study can be regarded as the second follow-up examination of a community-based field study on "Identification and prevention of Dietary- and lifestyle-induced health Effects In Children and infantS" (IDEFICS) (Ahrens et al. 2011). Examination modules comprised several questionnaires, physical examinations, and biological samples. The cohort profile has been described in detail elsewhere (Ahrens et al. 2017).

Ethical considerations

Each participating center obtained ethical approval from the local responsible authorities. Informed consent from the children and their parents was required before any data collection and they were free to reject single examination modules and questionnaires.

Study design and recruitment

An initial baseline examination (T0) in the context of the above-mentioned IDEFICS study—the data of which were not used for this study as use of nutritional supplements was not recorded—took place from 2007–2008, followed by a first follow-up examination (T1) from

2009–2010, in at least two local not randomly selected communities per country. All children aged 2–9 years attending kindergarten and elementary school had been eligible. As part of the subsequent I.Family study—which provided the data for this study—children who participated in T0 and/or T1 of IDEFICS (hereafter referred to as index children) as well as their parents and siblings were invited for a second follow-up. Thus, between 2013 and 2014 data were provided from 6,167 families. For the present cross-sectional analysis, all 5- to 17-year-olds were eligible and we selected one member from each family using an algorithm described under "Exclusion criteria".

General information about the respondent or the family such as socio-demographic characteristics was given by at least one parent or legal guardian. Information on the medical history of the participants, including diseases, drug use, and the intake of nutritional supplements was obtained from at least one parent living in the main household using a computer-assisted personal or telephone interview.

Study measures

Participants were categorized as having ADHD depending on a parent-reported diagnosis and/or use of any of the following ADHD-approved medications: methylphenidate, atomoxetine, amfetamine, dexamfetamine, lisdexamfetamine. Centrally acting alpha-agonists (clonidine or guanfacine) were not approved for ADHD in Europe during the study years. Details about the diagnosis, drug use, and use of nutritional supplements within the last 14 days were collected using a questionnaire about chronic diseases diagnosed in the individual participant. A subject with ADHD was categorized as "medicated" if at least one of the above-mentioned ADHD-approved medications had been used.

The study outcome was *use of nutritional supplements*, measured by use of (a) any or (b) multiple different nutritional supplements (either simultaneously or sequentially) during the

last 14 days. The measure regarding multiple different nutritional supplements reflecting a more intensive intake was added post hoc to the protocol during the analysis, since we observed conspicuously high rates of the differently classified nutritional supplements (e.g., omega-3 fatty acids, vitamin D, and so on) in unmedicated subjects with ADHD. In addition to given categories of nutritional supplements, parents could specify additional products, which interviewers entered as free text. Free text records were allocated to the respective categories; e.g., brand names from omega-3 products were assigned to "omega-3 fatty acids". A pharmacist carried out the allocation using blinded records, i.e., without information on the ADHD diagnosis. This was reviewed by one person from each participating country.

As covariates, we included characteristics shown by former studies to be either associated with ADHD and/or use of nutritional supplements or that we hypothesized to be associated with any form of dietary intervention (e.g., food intolerance). Use of prescription drugs (other than ADHD medications) during the last 14 days was assessed from free text records on medication that were processed as described for the nutritional supplements. The following parent-reported chronic diseases of the child were included: food intolerance (e.g., to lactose, fish and crustaceans, fruits and vegetables), serious infection requiring hospitalization, and allergic diseases (e.g., eczema, hay fever). Regarding parental psychiatric disorders the interviewer asked about psychological/psychiatric problems. The highest parental education level was coded according to the 2011 International Standard Classification of Education and further categorized into low (0–2), medium (3–5), and high (6–8) (United Nations Educational, Scientific and Cultural Organisation 2011). Income level was categorized into five groups by linking the income to the average country-specific net household income.

Exclusion criteria

Subjects were excluded from the analysis if a completed questionnaire on health and medical history was not available. Moreover, to avoid any effects of familial clustering, we excluded siblings using the following algorithm: participants who had been diagnosed with ADHD were identified first and their siblings without ADHD excluded. From families without any or more than one ADHD subject, non-index children were excluded. If more than one index child was eligible, we randomly selected one.

Statistical analyses

Using descriptive statistics, sample characteristics and use of nutritional supplements were shown for each of the three groups, namely children and adolescents without ADHD (1) and those with ADHD who were unmedicated (2) or medicated (3). Two multivariable logistic regressions were used to identify group-dependent differences: First, a partially adjusted model, controlling for the demographic variables age, sex, and country, and second, a fully adjusted model, taking also into account education level, income level, serious infections, allergic diseases, food intolerance, and parental psychiatric disorders. When considering education and income level as confounders, missing values for these variables were treated as separate categories and taken into account as dummy variables in the regression models. An additional analysis was conducted to compare all subjects with ADHD—independently of medication status—with non-ADHD peers to evaluate the comparability of our estimates (fully adjusted) with those obtained from the NHANES data. Additionally, although parent-reported ADHD diagnoses have shown convergent validity (Visser et al. 2013), we attempted to corroborate the parent-reported ADHD diagnoses in our study. Using the *t*-test, we compared subjects with and without ADHD regarding mean differences in a score for impulsiveness based on survey items. Higher scores indicate more impulsive behavior of a subject according to the negative urgency subscale of the UPPS Impulsive Behaviour Scale (Cyders et al. 2007).

For all statistical programming, the analysis software SAS 9.3 (SAS Institute, Cary, NC, USA) was used. For each parameter estimate, we calculated raw (two-sided) p-values and 95% confidence limits. However, since the main focus of this study was based on four hypotheses regarding the influence of ADHD (medicated/unmedicated vs. non-ADHD) on the use of any nutritional supplement (yes/no) and the use of multiple different nutritional supplements, the (Bonferroni-corrected) significance level was considered to be $\alpha = 0.05/4$, i.e., a null hypothesis was rejected for each $p \leq 0.0125$.

RESULTS

After excluding siblings, 127 children and adolescents with ADHD (51 medicated and 76 unmedicated) and 4,940 without ADHD were included in the cohort (Fig. 1).

Sample characteristics

The male-to-female sex ratio was 4.5:1 in all ADHD subjects and higher in those medicated (Table 1). For both unmedicated and medicated children and adolescents with ADHD, there was a five-year interval (mean) since the onset of ADHD. Use of non-ADHD prescription drugs was higher in ADHD subjects.

Use of nutritional supplements

Any nutritional supplement use was reported by 20% (26/127) of those with ADHD and by 18% (877/4,940) of those without ADHD (Table 1). Unmedicated subjects with ADHD (*n* = 76) had the highest percentages in almost all categories of nutritional supplements. In both groups, with and without ADHD, multivitamin/multimineral complex products were most frequently used. Use of at least two different nutritional supplements was 5% among those without ADHD and 13% among unmedicated ADHD subjects, while none of the 51

medicated ADHD subjects had use of multiple nutritional supplements. In unmedicated subjects with ADHD who used multiple different nutritional supplements (n = 10), omega-3 fatty acids and vitamin D were most frequently used. In subjects without ADHD who used multiple different nutritional supplements (n = 235), vitamin C was most frequently used (54%). No melatonin use was reported as a nutritional supplement. This was expected as—in contrast to the US—melatonin is rather uncommon as a nutritional supplement in Europe; a 2 mg preparation is even approved as a prescription drug by the European Medicines Agency.

ADHD-dependent differences in using nutritional supplements

Compared to those without ADHD, unmedicated ADHD subjects were more likely to use multiple different nutritional supplements (fully adjusted odds ratio [OR], 2.6; 95% confidence interval [CI], 1.2–5.6; Table 2). Participants who used non-ADHD prescription drugs (both ADHD and non-ADHD subjects) were more likely to use any and multiple nutritional supplements.

Additional analyses

Regarding the comparison of all ADHD subjects with non-ADHD peers, we found odds ratios similar to those from the NHANES data (Gardiner et al. 2008). The OR regarding ADHD in our study was 1.2; 95% CI, 0.7–2.0 compared to 1.1; 95% CI, 0.8–1.5 in Gardiner et al. (2008) and the OR regarding use of prescription drugs was 1.6; 95% CI, 1.2–2.1 compared to 1.4; 95% CI, 1.1–1.7, respectively.

The comparison of subjects with and without ADHD regarding impulsive behavior revealed that of those with an available score, subjects with ADHD (n = 45) had higher scores ($p < 0.05$) than those without (n = 1,989).

DISCUSSION

This population-based study found a higher use of multiple different nutritional supplements in unmedicated children and adolescents with ADHD compared to medicated ones and those without ADHD. An increased use of any nutritional supplement was not statistically significant for both medicated and unmedicated ADHD subjects. Gardiner and colleagues also used population-based survey data to estimate prevalence of and common factors for use of any nutritional supplement (Gardiner et al. 2008). As in our study, not ADHD, but use of prescription drugs was strongly associated with use of any nutritional supplement. Similar to our study, multivitamins and vitamin C were most commonly used underlining the comparability of our results with those from the NHANES data analyzed by Gardiner and colleagues (2008). The overall prevalence of use of any nutritional supplement was, however, higher in their study. This might be because they enquired about use in the prior month, compared to the last two weeks in our study.

We hypothesized that the suggested association between ADHD and use of nutritional supplements may depend on ADHD medication treatment, since use of prescription drugs in general was a predictor of use of any nutritional supplement (Gardiner et al. 2008). In our sample, the point estimate indicated that subjects with medicated ADHD were 50% more likely to use any nutritional supplement; however, due to the small number of children with medicated ADHD, the corresponding wide confidence interval does not allow any reliable conclusions.

Interestingly, we found that use of multiple different nutritional supplements in ADHD subjects occurred only in those who were not taking ADHD medication. Consequently, we added this variable as a second measure for the primary outcome, thereby enhancing the reflection of utilization habits. On the one hand, the observed association between use of

multiple nutritional supplements and unmedicated ADHD was surprising as using prescription drugs in general was a predictor for use of any nutritional supplement. On the other hand, this finding is in line with results from Sinha and Efron (2005). They showed that "*additional* benefit to doctor's treatment" was one of the main reasons (70%) to use complementary and alternative medicine in children with ADHD, however, a "benefit *in place* of doctor's treatment" was still indicated in 30% of the surveyed parents (Sinha and Efron 2005). It is possible that we identified—for the first time in a population-based sample—such a subgroup of children and adolescents with ADHD who received parent-initiated self-care interventions with multiple different nutritional supplements in place of medication. At first glance, the proportion of 13% of unmedicated children and adolescents with ADHD who potentially received this intervention appears relatively small. However, given both the epidemiology of ADHD as well as its correlates and sequelae, it is a notable amount from a public health point of view. Assuming that ADHD medication would have been indicated in these subjects, this therapeutic attempt should be assessed critically.

Unmedicated children and adolescents with ADHD who used multiple different nutritional supplements in our study mainly took omega-3 fatty acids and vitamin D. The NICE committee concluded that omega-3 fatty acids had no clinically important benefits for ADHD and, due to lack of data on side effects, that harm could not be excluded (NICE 2018). A later systematic review aimed to examine effects of omega-3 supplementation on cognition in the general population and in those with neurodevelopmental disorders. The authors concluded that there is no evidence for an effect on cognition in both population groups and that advertisement claims of cognitive benefits should be narrowed (Cooper et al. 2015). The same authors concluded in another review that the possibility of moderate to large effects on reducing emotional dysregulation, oppositional behavior and conduct problems (which commonly accompany ADHD) by omega-3 fatty acid supplementation can be ruled out

(Cooper et al. 2016). However, omega-3 fatty acids might be used as an adjunct therapy to ADHD medication to reduce the dosage (Königs and Kiliaan 2016; Lange et al. 2017), for subjects with sub-clinical symptoms (Sonuga-Barke 2015), or by families who decline other psychopharmacological options (Bloch and Qawasmi 2011). There is hypothetical evidence for the efficacy of vitamin D supplementation in patients with psychiatric disorders on improving brain functions (Patrick and Ames 2015). However, clinical evidence is only available for the effect of vitamin D supplementation on improving ADHD evening symptoms when it is used adjunctively to methylphenidate but not as monotherapy (Mohammadpour et al. 2016). In addition to the limited evidence on the effectiveness of nutritional supplements in unmedicated ADHD patients, consumers in the countries participating in this study usually have to pay for nutritional supplements as they are normally not reimbursed by health insurances. This might result in a potentially unnecessary financial burden for families who have a child with ADHD. These families already have a high burden due to the effects of ADHD on family life (Le et al. 2014). Undoubtedly, the generally smaller effect size (Faraone et al. 2015; Sonuga-Barke et al. 2013; Stevenson et al. 2014) of a single administered nutritional supplement to treat ADHD, if proven ineffective, should not lead to attempts of enhancing the effect with additional supplements. As an alternative to combining single conventional nutritional supplements, e.g., omega-3 fatty acids with vitamin D as in our study, there is a growing base of literature suggesting that carefully balanced, highly bioavailable multi-vitamin/mineral supplements may be beneficial at least for some comorbid children with ADHD (Rucklidge et al. 2018). A recent—first and yet to be confirmed—randomized placebo-controlled study indicated reduction of debilitating symptoms such as emotional dysregulation and aggression by a 48-ingredient micronutrient formula (Rucklidge et al. 2018).

In reviewing the literature, it can be assumed that at least one of three parents does not inform their pediatrician about child's use of complementary and alternative medicine (Chan et al. 2003; Sinha and Efron 2005) and a delay in ADHD treatment due to its use is reportedly common (Hurt and Arnold 2014; Vohra et al. 2009). Research has shown an increased willingness to use medical and psychosocial interventions to treat ADHD among parents and adolescents who felt knowledgeable and among those who considered the treatments acceptable and helpful (Bussing et al. 2012). Hence, the clinical implication of our findings is that pediatricians should actively explore whether parents/patients favor orally administered nutritional supplements over medication to treat ADHD core symptoms and, if necessary, emphasize that based on current evidence the average effect size of ADHD medication is larger. In case that families decline psychopharmacological options and prefer nutritional supplements, recommendations should optimally be given according to best available evidence.

The main strength of our study lies in the large population-based approach, avoiding clinical sampling biases and improving the statistical certainty of our findings. Another strength is that our data allowed us to differentiate between subjects with medicated and unmedicated ADHD. However, our study has some limitations. First, we did not have information on psychosocial interventions such as behavioral therapy and therefore could only focus on oral remedies (i.e., ADHD medication and nutritional supplements). Second, we did not know when the patient had last visited the pediatrician and whether a nutrient deficiency existed possibly justifying use of multiple different nutritional supplements. Third, we were not able to assess the severity of ADHD. Fourth, the calculated prevalence of ADHD in the included sample is somewhat lower than the worldwide prevalence reported in the meta-analysis by Polanczyk and colleagues (2015). Reasons might be that our prevalence can be considered as an administrative prevalence (reported diagnosis), unwillingness to admit a psychiatric

disorder in one's child by a parent to the interviewer, and generally lower prevalence rates according to the criteria of the International Classification of Diseases (ICD)—which is more common in Europe—than according to the Diagnostic and Statistical Manual of Mental Disorders (Döpfner et al. 2008). As the sample of children and adolescents with ADHD is rather small, our interpretations need to be treated with care. Fifth, parents were only asked for current use of medication. Hence, we do not know whether children who were unmedicated at the time of the study had been medicated in the past. ADHD medication might have not been effective/tolerated and therefore alternative treatments could have been chosen. Additionally, we do not know whether unmedicated subjects in our sample benefitted from nutritional supplements. Finally, as the study was conducted in several countries, our data were structured hierarchically. Typically, multilevel logistic regression models should be used to counteract false inferences. Our model did not converge for the outcome "use of multiple nutritional supplements". Therefore, we decided on a conventional logistic regression model. However, both models resulted in equivalent findings with the outcome "any nutritional supplement" and research suggests that, given a small number of countries, and when interested in the effect of characteristics on the individual level as in our study, the hierarchical structure can be ignored (Austin et al. 2003; Bryan and Jenkins 2016).

CONCLUSIONS

The results of this study suggest that a notable proportion of unmedicated children and adolescents with ADHD—or presumably rather their parents—prefer a treatment strategy of using multiple different nutritional supplements rather than ADHD medication. As all studied nutritional supplements had to be taken orally, this subgroup obviously did not avoid oral remedies in general. The findings in this study add to a growing body of literature on

complementary and alternative medicine use in children and adolescents with ADHD suggesting that nutritional supplements are potentially taken inappropriately as treatment for ADHD. This study confirmed this fact, for the first time, in a population-based sample and by including a comparison group. Pediatricians should actively enquire in routine care about parent-initiated self-care interventions with nutritional supplements at an early stage and provide both the patient and the parent/caregiver with evidence-based patient information about pharmacological and other non-pharmacological ADHD treatments.

CLINICAL SIGNIFICANCE

This is the first study that showed differences in use of nutritional supplements depending on ADHD and medication status in a population-based sample. Unmedicated ADHD children and adolescents are more likely to use multiple different nutritional supplements compared to medicated and non-ADHD peers. This finding suggests that a notable proportion of children and adolescents with ADHD or their parents prefer a treatment strategy of taking multiple nutritional supplements instead of ADHD medication.

DISCLOSURES

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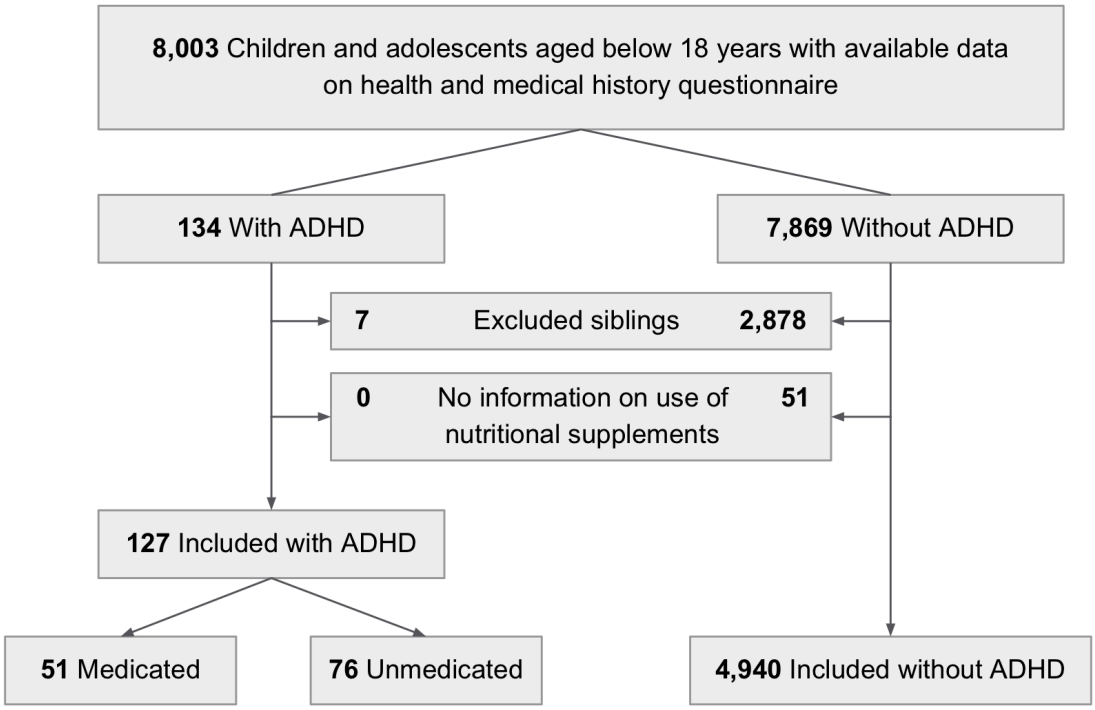
8,003 Children and adolescents aged below 18 years with available data on health and medical history questionnaire
134 With ADHD
7,869 Without ADHD
7 Excluded siblings 2,878
0 No information on use of nutritional supplements 51
127 Included with ADHD
51 Medicated
76 Unmedicated
4,940 Included without ADHD

Table 1. Sample characteristics and nutritional supplement use by group.

	no ADHD	ADHD		
		unmedicated	medicated	all cases
	(*n* = 4,940)	(*n* = 76)	(*n* = 51)	(*n* = 127)
Age in years, mean (SD)	11.6 (1.94)	11.7 (2.59)	11.4 (2.06)	11.6 (2.39)
Male sex, *n* (%)	2,454 (49.7)	61 (80.3)	43 (84.3)	104 (81.9)
Years since onset[a], mean (SD)	NA	5 (3.2)	5 (3.2)	5 (3.2)
Use of non-ADHD prescription drugs, *n* (%)	441 (8.9)	10 (13.2)	8 (15.7)	18 (14.2)
Use of any nutritional supplement within 14 days, *n* (%)	877 (17.8)	17 (22.4)	9 (17.6)	26 (20.5)
Omega-3 fatty acids, *n* (%)	145 (2.9)	5 (6.6)	1 (2.0)	6 (4.7)
Vitamin C, *n* (%)	267 (5.4)	5 (6.6)	1 (2.0)	6 (4.7)
Vitamin D, *n* (%)	161 (3.3)	6 (7.9)	0 (0.0)	6 (4.7)
Vitamin B, *n* (%)	20 (0.4)	1 (1.3)	0 (0.0)	1 (0.8)
Multivitamin complex, *n* (%)	162 (3.3)	2 (2.6)	2 (3.9)	4 (3.1)
Multivitamin/multimineral complex[b], *n* (%)	257 (5.2)	7 (9.2)	4 (7.8)	11 (8.7)
Other mineral, *n* (%)	138 (2.8)	4 (5.3)	0 (0.0)	4 (3.1)
Other nutritional supplement, *n* (%)	37 (0.7)	2 (2.6)	1 (2.0)	3 (2.4)
Use of multiple different nutritional supplements from above[c], *n* (%)	235 (4.8)	10 (13.2)	0 (0.0)	10 (7.9)

[a] Based on those unmedicated (*n* = 68) and medicated (*n* = 30) with available information.

[b] More than one vitamin and more than one mineral.

[c] Either simultaneously or sequentially within 14 days. In unmedicated subjects with ADHD who used multiple different nutritional supplements (*n* = 10), omega-3 fatty acids and vitamin D were most frequently used.

ADHD, attention-deficit/hyperactivity disorder; SD, standard deviation; NA, not applicable.

Table 2. Estimated odds ratios for use of nutritional supplements in children and adolescents.

		Use of any nutritional supplement within 14 days					**Use of multiple different nutritional supplements within 14 days**				
	n	%	Partially adjusted OR (95% CI)[a]	p-value	Fully adjusted OR (95% CI)[b]	p-value	%	Partially adjusted OR (95% CI)[a]	p-value	Fully adjusted OR (95% CI)[b]	p-value
no ADHD	4,940	17.8	Ref.	NA	Ref.	NA	4.8	Ref.	NA	Ref.	NA
ADHD											
unmedicated	76	22.4	1.2 (0.7–2.3)	.53	1.1 (0.6–2.1)	.76	13.2	2.9 (1.4–6.1)	.005	2.6 (1.2–5.6)	.01
medicated	51	17.6	1.5 (0.7–3.3)	.28	1.5 (0.7–3.3)	.33	0.0	NA	NA	NA	NA
Use of non-ADHD prescription drugs											
No	4,608	17.4	Ref.	NA	Ref.	NA	4.6	Ref.	NA	Ref.	NA
Yes	459	21.8	1.7 (1.3–2.3)	<.001	1.6 (1.2–2.1)	<.001	7.0	2.0 (1.3–3.1)	<.001	2.0 (1.3–3.0)	.002

[a] Based on a logistic regression model, adjusted for age, sex, and country.

[b] Based on a logistic regression model, adjusted for age, sex, country, as well as education level, income level, serious infections, allergic diseases, food intolerance, and parental psychiatric disorders; the analyses of ADHD cases were adjusted for the use of non-ADHD prescription drugs (and vice versa).

ADHD, attention-deficit/hyperactivity disorder; OR, odds ratio; CI, confidence interval; NA, not applicable.