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Chronic Fatigue Syndrome at Age 16 Years

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Short title: Chronic Fatigue Syndrome at Age 16 Years

Abbreviations: Avon Longitudinal Study of Parents and Children (ALSPAC); Chronic Fatigue Syndrome (CFS); Myalgic Encephalomyelitis (ME); Family Adversity Index (FAI); Strengths and Difficulties Questionnaire (SDQ); Short Moods and Feelings Questionnaire (SMFQ); National Institute for Health and Care Excellence (NICE); Chalder Fatigue Questionnaire (CFQ); National Pupil Database (NPD); Key Stage 2 (KS2).

Key words: ALSPAC; chronic fatigue syndrome; adolescent health

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Conflict of Interest: Dr. Crawley is a medical advisor for the Association of Young People with ME (AYME) and the Sussex & Kent ME/CFS Society. The remaining authors have indicated they have no potential conflicts of interest to disclose.

What's Known on This Subject: The prevalence of pediatric chronic fatigue syndrome (CFS) is unclear and is likely to be underestimated in clinical settings. Family adversity is associated with chronic disabling fatigue in 13 year olds, but its relationship with CFS in older children is unknown.

What This Study Adds: The prevalence of CFS at age 16 years is 1.9%, of which 0.6% is in children without high levels of depressive symptoms. CFS including depressive symptoms is more prevalent in girls and in children who have experienced family adversity.

Contributors' Statement:

Dr Collin analyzed the data, wrote the first draft, revised the manuscript, and approved of the final version.

Drs Nuevo and Norris provided methodological input, analyzed the data, revised the manuscript, and approved of the final version.

Dr Joinson provided methodological input, interpreted the results, revised the manuscript, and approved of the final version.

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Dr Crawley conceived the study, interpreted the results, revised the manuscript, and approved of the final version.

ABSTRACT

BACKGROUND: In the Avon Longitudinal Study of Parents and Children [ALSPAC] birth cohort, chronic disabling fatigue lasting ≥6 months affected 1.3% of 13-year-olds, was equally common in boys and girls, and became more prevalent with increasing family adversity.

METHODS: ALSPAC data were used to estimate the prevalence of chronic fatigue syndrome (CFS) at age 16 years, defined by parental report of unexplained disabling fatigue lasting ≥6 months. We investigated gender and a composite 14-item family adversity index as risk factors. School absence data were obtained from the National Pupil Database. Multiple imputation was used to address bias caused by missing data. RESULTS: The prevalence of CFS was 1.86% (95% confidence interval [CI]: 1.47 to 2.24). After excluding children with high levels of depressive symptoms, the prevalence was 0.60% (95% CI: 0.37 to 0.84). Authorized school absences were much higher (mean difference: 35.6 [95% CI: 26.4 to 44.9] half-day sessions per academic year) and reported depressive symptoms were much more likely (odds ratio [OR]: 11.0 [95% CI: 5.92 to 20.4]) in children with CFS than in those without CFS. Female gender (OR: 1.95 [95% CI: 1.33 to 2.86]) and family adversity (OR: 1.20 [95% CI: 1.01 to 1.42] per unit family adversity index) were also associated with CFS.

CONCLUSIONS: CFS affected 1.9% of 16-year-olds in a UK birth cohort and was positively associated with higher family adversity. Gender was a risk factor at age 16 years but not at age 13 years or in 16-year-olds without high levels of depressive symptoms

INTRODUCTION

Chronic fatigue syndrome (CFS) in children and young people is a debilitating disease which has a major impact on the lives of children and their families.[1-3] CFS, also known as myalgic encephalomyelitis (ME) or, more recently, systemic exertion intolerance disease (SEID),[4] has been defined by various diagnostic criteria.[5] UK National Institute for Health and Care Excellence (NICE) guidelines state that diagnosis of CFS should be made after 3 months of persistent or recurrent fatigue which is not the result of ongoing exertion, not substantially alleviated by rest, has resulted in a substantial reduction in activities, and has no other known cause.[6] CDC diagnostic criteria require 6 months' duration of fatigue.[7]

Chronic fatigue of at least 3 months' duration affects 2-3% of children and young people age 8 to 18 years.[8-10] Population-based studies in the UK and USA have reported a prevalence of 1.3% for fatigue of ≥6 months' duration.[8, 9, 11] Although clinician-verified CFS appears to be less prevalent (0.1-0.5%),[12-14] this discrepancy is almost certainly a consequence of referral pathways and barriers to accessing clinical services.[15] Recognition of CFS as a relatively common, highly debilitating, and potentially long-term pediatric disease has improved in recent years,[16, 17] but it is important that uncertainties about the population prevalence of pediatric CFS are resolved.

We reported previously that 1.3% of 13 year-olds in a UK birth cohort had chronic disabling fatigue of ≥6 months' duration, and that higher levels of family adversity increased the risk of chronic disabling fatigue at this age.[8] In this earlier study we were unable to confirm a diagnosis of CFS because we had only parental report of fatigue hence, we defined chronic disabling fatigue as our outcome. In the present study, we have combined parental and child report of fatigue to identify adolescents with CFS. We estimate the prevalence of CFS at age 16 years, and we investigate the relationships of CFS with sex, family adversity at age 8-10 years, and with school attendance, depressive symptoms, and life difficulties at age 16 years.

METHODS

Participants

ALSPAC is a population-based study which aims to investigate a wide range of influences on the health and development of children.[18] Pregnant women residing in the former Avon Health Authority in south-west England who had an estimated date of delivery between 1 April 1991 and 31 December 1992 were invited to take part, resulting in a cohort of 14,541 pregnancies and 13,978 children alive at 12 months of age (excluding triplets and quads). The primary source of data for the present study was parent-completed questionnaires administered at four time-points during the antenatal period then at regular intervals following birth. The ALSPAC study website contains details of all the data that are available through a fully searchable data dictionary (www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee (IRB00003312) and the Local Research Ethics Committees.

Classification of CFS at age 16 years

We used data from parent- and child-completed questionnaires in a two-stage process to classify children as having CFS. In the first stage, parent-reported data were used to classify presence/absence of CFS using criteria similar to the definition of chronic disabling fatigue in children in this cohort at age 13 years.[8] Parents received a "Your son/daughter 16+ years on" questionnaire (at median age 16.6, IQR 16.5 to 16.8 years) which included questions on whether their 'teenager' had been "feeling tired or felt she/he had no energy" over the last month (yes/no) and, if so: how long the tiredness/lack of energy had lasted (<3 months, between 3 and 5 months, between 6 months and 5 years, or >5 years); how many days (in the past year) their child had been off school/college because of tiredness/lack of energy; and whether the tiredness/lack of energy had prevented the child from taking part in hobbies,

sport or leisure activities (not at all; only a little; quite a lot; a great deal). The questionnaire asked whether the parent thought that the tiredness/lack of energy was due to: i) illness; ii) problems with sleep; iii) playing a lot of sport; iv) stress or worry; v) other reason (free text question). We classified children as having CFS (by parental report) if they had fatigue lasting ≥6 months that had stopped them from taking part in activities "quite a lot" or "a great deal", that was not due to playing too much sport, and that had resulted in any absence from school/college in the past year due to tiredness or lack of energy. Children who met these criteria, but who were reported by parents to have had problems with alcohol or drugs (crack, solvents, heroin, or cocaine) during the previous year, or a diagnosis of anorexia nervosa, were classified as not having CFS. We analysed CFS of ≥3 months' duration as a secondary outcome, in accordance with UK (NICE) guidelines.

In the second stage, we used child-reported data to classify children as not having CFS if they had a Chalder Fatigue Questionnaire (CFQ)[19] score below 19 (out of 33), including children who had been classified as having CFS by parental report, i.e. children classified as having CFS by parental report were re-classified as not having CFS. The CFQ was incorporated into a "Life of a 16+ teenager" questionnaire, which was completed by participants at age 16 (median 16.7, IQR 16.5 to 17.1) years. The CFQ asked about "problems you have had with feeling tired, weak or lacking in energy in the last month". No data were collected from the child regarding duration of fatigue. A cut-off score of 19/33 has a sensitivity of 82.4% and a specificity of 86.4% for CFS in adolescence.[20] Children were classified as having CFS if they met the criteria by parental report but CFQ data were missing, under the assumption that children with CFS would be less likely to have completed the "Life of a 16+ teenager" questionnaire. For the purpose of sensitivity analysis, we estimated the prevalence of CFS if all children with both CFS and depressive symptoms (SMFQ score ≥11) were recoded as not

having CFS, on the basis that chronic fatigue in these children might be secondary to depression.

Auxiliary variables

Auxiliary variables were selected for the purposes of comparing family and individual characteristics of children with/without CFS, and imputing missing data. Of the family and individual characteristics, we considered sex and family adversity (measured at age 8-10 years) to be *a priori* risk factors for CFS at age 16 years, based on our earlier study of family adversity as a risk factor for chronic disabling fatigue in children at age 13 years,[8] and on the sex-related difference in CFS prevalence in adults.[21] We considered psychological problems, life difficulties and school attendance (all measured at age 16 years) to be potential risk factors for, or consequences of, CFS at age 16 years.[22, 23]

Family Adversity

The standard ALSPAC family adversity index (FAI) was adopted for consistency with previous ALSPAC studies. The FAI is derived from responses to questions asked during pregnancy and when the child was 8-10 years old about the following 9 factors, comprising 14 items in total: 1) age of mother at first pregnancy; 2) housing, comprising a) adequacy, b) basic amenities, c) defects, damp, infestation; 3) mother's and father's low educational attainment; 4) financial difficulties; 5) relationship with partner, comprising a) lack of affection, b) cruelty, c) lack of support; 6) social network, comprising a) lack of emotional support, b) lack of practical support; 7) substance abuse; 8) being in trouble with the police; and 9) psychopathology of the mother (anxiety, depression or suicide attempts). Each of the 14 items is assigned a value of 1 if an adversity is present and 0 if it is not present hence, the FAI has a theoretical range of 0 to 14. Questions pertaining to the FAI items were distributed across more than one questionnaire. The pregnancy FAI was coded as missing if any item was missing. The age 8-10 years FAI was coded as missing if ≥10 items were missing; if <10

items were missing, missing responses were assumed to indicate absence of adverse circumstances for that particular question.

Psychological problems

Children completed the Short Moods and Feelings Questionnaire (SMFQ)[24] at age 16 years. Parents completed the SMFQ when the child was 13 years old as part of the "My Teenage Son/Daughter at 157 Months" questionnaire. The SMFQ is a 13-item scale derived from the 33-items Mood and Feelings Questionnaire.[25] The SMFQ correlates well with other measures of depression and has good test–retest reliability.[26, 27] We used a cut-off score of ≥11 to indicate high levels of depressive symptoms at age 16 years. This threshold has high sensitivity, specificity and negative predictive power for an ICD-10 diagnosis of depression at age 18 years in the ALSPAC cohort.[28]

Life difficulties

Life difficulties were quantified by means of the Strengths and Difficulties Questionnaire (SDQ),[29, 30] which was completed by parents as part of the "My Teenage Son/Daughter at 157 Months" (age 13 years) and "Your son/daughter 16+ years on" questionnaires. The SDQ is a behavioural screening questionnaire designed to assess 25 attributes in children up to 16 years old. The SDQ comprises five 5-item subscales (emotional symptoms, conduct problems, hyperactivity inattention, peer relationships problems, prosocial behaviour). Each item is coded on a 0-2 Likert scale (from Not True to Certainly True), yielding a range of 0 – 10 for each subscale. A 'total difficulties' score is calculated by adding scores for the first four subscales (excluding prosocial behaviour), yielding a total score with a range of 0 – 40. The SDQ is a widely used, valid and reliable screening questionnaire for mood disorders in children.[31]

School attendance and academic attainment

The total number of authorized and unauthorized school absences during the Year 11 school year (age 15-16 years) were obtained via linkage to the National Pupil Database (NPD). NPD is a pupil level longitudinal database which matches pupil and school characteristics to pupil level attainment in England (www.gov.uk/government/collections/national-pupil-database). Schools are required to take attendance registers twice a day: once at the beginning of the morning session and once during the afternoon session. In their register, schools are required to distinguish whether pupils are present, engaged in an approved educational activity or are absent. Where a day pupil of compulsory school age is absent, schools have to indicate in their register whether the absence is authorized by the school or is unauthorised. Authorised absence is absence with school permission, including instances of absences for which a satisfactory explanation has been provided, for example, for a hospital appointment. Unauthorised absence is absence without permission from a teacher or other authorized representative of the school, including all unexplained absences. Arriving late for school (without permission), after the register has closed, is recorded as unauthorised absence. We measured academic attainment using NPD data to calculate a mean Key Stage 2 (KS2) point score, from the results of tests in English, Mathematics and Science which were conducted during school Year 6 (age 10-11 years).

Statistical analysis

We estimated the prevalence of CFS among those children for whom sufficient data were available to define this outcome. Performing only complete-case analyses (omitting children with any missing data) can result in bias, and will inflate standard errors compared to analyses with no missing data. If missingness is dependent only on observed data, i.e. if data are missing at random (MAR), then multiple imputation can be used to correct such bias. We

generated 75 imputed datasets, separately for boys and girls, based on the outcome variable, i.e. CFS of ≥3 or ≥6 months' duration at age 16 years, and the following auxiliary variables: chronic disabling fatigue of ≥3 months' duration at age 13 years; FAI during mother's pregnancy; mother's age at birth of child; FAI at age 8-10 years; maternal psychopathology at age child's age 8-10 years (anxiety, depression or suicide attempts); SDQ score at age 11, 13 and 16 years; SMFQ score at age 13 and 16 years; NPD authorized absences, KS2 mean test score. These variables were included because of their strong hypothesized association with CFS and their relatedness to the missingness of the outcome. The number of imputations required to achieve convergence of parameter estimates was determined by checking the estimate of the Monte Carlo error in relation to the standard error of the coefficient being estimated, with the number of imputations being increased incrementally until the Monte Carlo error achieved a value which was <10% of the standard error of the estimate.[32] The sample after imputation was 13,978, which represents those ALSPAC children who were alive at 1 year and who were either a singleton or twin. We imputed the data under a logistic regression model using an imputation sampling method (implemented in Stata's *uvis* command),[33] which incorporates all sources of variability and uncertainty in the imputed values. We combined imputed estimates using Rubin's rules.[34] We investigated the relationships of our primary outcome (CFS of ≥6 months' duration) with sex, family adversity, mood problems, life difficulties, and school attendance using linear and logistic regression models, which were fitted to the complete and imputed datasets. Analyses were performed using Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

RESULTS

13978 ALSPAC children were alive at one year of age (excluding triplets and quads). At 16 years of age, questionnaires were sent to 9523 parents and 9510 children, with returns of 54.8% (5495/9523) and 48.8% (4901/9510), respectively. Parent- and child-reported fatigue data were available for 4962 and 4847 children, respectively. These data allowed us to classify presence/absence of CFS in 5756 children (**Figure 1**). These 5756 children were more likely to be female, had fewer school absences and higher academic attainment, lower SMFQ and SDQ scores at age 13 years, and were from families with lower levels of family adversity (**Table 1**).

Prevalence of CFS at age 16 years

Of the 5372 parents who answered the initial question asking whether their child had been "feeling tired or felt she/he had no energy" (over the last month), 41.0% (2201/5372) answered "yes", with more girls (40.8% (1016/2492)) than boys (30.6% (759/2483)) affected. Based on parent-reported data only, the proportions of children experiencing CFS of ≥3 and ≥6 months' duration were 4.17% (207/4962) and 2.75% (137/4962), respectively (**Figure 1**). Prevalence of CFS of ≥6 months' duration was higher among girls (3.58% (89/2485)) than among boys (1.94% (48/2477)), a difference of 1.64% (95% CI 0.73% to 2.55%). Similarly, CFS of ≥3 months' duration was more prevalent in girls (5.47% (136/2485)) than in boys (2.87% (71/2477)), a difference of 2.60% (95% CI 1.50% to 3.72%), P<0.001).

Child-reported data showed that 10.2% (496/4847) of children had a Chalder Fatigue Questionnaire score ≥19. Children deemed to have CFS by parental report were more likely to have missing CFQ data: these were missing for 34.3% (47/137) of children with parent-

reported CFS of ≥6 months' duration, compared with 27.1% (1306/4825) of children not classified by parental report as having CFS (P=0.06).

Complete-data prevalence estimates for CFS of ≥3 and ≥6 months' duration based on combined parent- and child-reported data were 2.02% (119/5756; 1.68% to 2.41%) and 1.46% (84/5756; 1.18% to 1.80%), respectively. These estimates are lower than those by parental report only because 38.7% (53/137) of the participants classified with CFS by parental report were re-classified as not having CFS. The child-reported data also added 1042 participants without CFS (CFQ score <19) to the denominator. CFQ scores were available for 73% (3609/4962) of children who had been classified by parental report. CFS of ≥3 months' duration was more prevalent among girls (2.39% (72/3014)) than among boys (1.60% (44/2742)), a difference of 0.78% (95% CI 0.06% to 1.50%, P<0.001), as was CFS of ≥6 months' duration: girls (1.79% (54/3014)); boys (1.09% (30/2742)), a difference of 0.70% (95% CI 0.08% to 1.31%, P=0.03).

Multiple imputation to correct biases caused by missing data increased the overall prevalence estimates for CFS of ≥3 months' duration from 2.02% (1.68%, 2.41%) to 2.50% (2.04%, 2.96%), and for CFS of ≥6 months' duration from 1.46% (1.18%, 1.80%) to 1.86% (1.47%, 2.24%) (**Table 2**).

Characteristics of children with CFS at age 16 years

Children with CFS had higher levels of psychological problems, life difficulties and school absence (**Table 3**). After imputation, depressive symptoms (SMFQ score ≥11) were reported by 67.4% of children with CFS, compared to 15.3% in those without CFS, and children with CFS had 11-fold higher odds of depressive symptoms (OR 11.0 (5.92, 20.4)), compared with children without CFS (**Table 3**). The imputed prevalence of CFS of ≥3 and ≥6 months'

duration, if all children with depressive symptoms were classified as not having CFS, was 0.90% (0.60%, 1.20%) and 0.60% (0.37%, 0.84%), respectively (**Table 2**).

Total SDQ scores (range 0 to 40) were higher in children with CFS (difference in means = 6.16 points (5.09 to 7.23 points)) (**Table 3**), a difference which complete data analysis suggests was mainly due to higher emotional symptoms scores in children with CFS (difference in means = 3.44 points (3.03 to 3.84 points)) (**Supplementary Table 1**).

Authorized school absences were much higher among children with CFS (**Table 3**). Children with CFS had an average 53.9 (95% CI 42.9, 64.9) half-day absences per academic year, compared with 18.3 (17.9, 18.7) in the group without CFS, a difference of 34.8 (25.4, 44.1) sessions (representing approximately 3 – 4 weeks off school per year).

Similar results were obtained if children with CFS of ≥3 months' duration were compared with children without CFS, namely: 10-fold higher odds of depressive symptoms (OR 9.70 (5.42, 17.4)); a 6-point difference in total SDQ score (6.12 (5.13 to 7.11) points); and 28.1 (20.5 to 35.8) more half-day absences.

Risk factors for CFS at age 16 years

In imputed data analysis, girls had almost double the odds of CFS at age 16 years compared with boys (odds ratio (OR) 1.95 (1.33, 2.86)), and the odds of CFS increased by 20% for each unit increase in the ALSPAC family adversity index (OR 1.20 (1.01, 1.42)) (**Table 4**). If children with depressive symptoms were classified as not having CFS, sex and family adversity were not associated with CFS (**Table 4**). Associations of female sex (OR 1.84 (1.30, 2.60)) and family adversity (OR 1.18 (1.01, 1.37)) with CFS of ≥3 months' duration were similar to those with CFS of ≥6 months' duration.

DISCUSSION

This study estimated the prevalence of CFS among 16 year-olds in a large population-based birth cohort as 1.86% (1.47% to 2.24%) using a 6 months' criterion, or 2.50% (95% CI 2.04% to 2.96%) using a 3 months' duration criterion. Excluding children with high levels of depressive symptoms reduced the ≥6 months' prevalence to 0.60% (0.37%, 0.84%), and the ≥3 months' prevalence to 0.90% (0.60%, 1.20%). Higher levels of family adversity were associated with an increased risk of CFS in children at age 16, as was observed at age 13. CFS was more common in girls than in boys, a sex-related difference not seen at age 13 years in the same cohort. Neither of these associations were evident if children with depressive symptoms were excluded. CFS in 16 year-olds was accompanied by greater life difficulties than in unaffected children, and was associated with much higher levels of school absence. Similar associations were observed if fatigue of ≥3 months' duration was used to define CFS, although with a slightly reduced effect on school absence.

This is, to our knowledge, the largest population-based study investigating CFS in children. We used 6 and 3 months' duration of fatigue to define CFS, enabling us to estimate prevalence in accordance with standard definitions of CFS in the USA (6 months) and UK (3 months).[6, 7] We used multiple imputation to correct for potential bias in prevalence estimates caused by differential losses to follow up. Imputed estimates were higher than those derived from complete data, which is consistent with children who were lost to follow-up being more likely to have chronic fatigue or the risk factors associated with it. For example, the ALSPAC cohort has higher losses to follow-up among families which have higher levels of family adversity.[18]

Our criteria for classifying children as having CFS used both parent- and child-reported data. Our previous study used only parent-reported data, which limited us to classifying 13 year-

olds as having 'chronic disabling fatigue'.[8] In the present study we were able to use stricter criteria, by classifying as not having CFS those children who had CFQ scores <19. This threshold has a sensitivity of 82.4% and a specificity of 86.4% for CFS in adolescence,[20] and CFQ scores were available for 73% of children who had been classified by parental report. The CFQ data showed that classification by parental report would over-estimate occurrence of CFS, with almost 40% of children classified with CFS by parental report being re-classified as not having CFS when child-reported data were used. Our decision to rely on parental report when child-reported data were missing was based on the assumption that, in conditions such as CFS, being ill may be associated with non-return of data. This assumption was supported by our finding that child-reported data were more likely to be missing for children whose parents had identified the child as having fatigue.

The children in this population-based study were not assessed by a doctor, and our classification was not subject to clinical verification. It is therefore possible that parents and children reported significant levels of disabling fatigue which was caused by another disorder. The most likely alternative diagnosis in this group is depression. We found that 67% of children with CFS exceeded the SMFQ threshold for depressive symptoms. Among clinical cohorts, which excluded depression as a primary diagnosis, the proportion of children with CFS who also had probable depression (>9 on the Hospital Anxiety & Depression Scale) was 29% (95% CI 25% to 33%).[35] However, this HADS threshold classifies only 2% of UK school children as having depression,[36] compared with 15% of children without CFS in our cohort who had an SMFQ score ≥11. This discrepancy suggests that HADS and SMFQ classifications are not directly comparable, and that the SMFQ threshold has much lower specificity. However, other studies have reported high levels of depression (50%)[37] and psychiatric problems (72%)[38] in pediatric CFS, and the prevalence estimates from our

sensitivity analyses (in which we excluded all children with high levels of depressive symptoms) are almost certainly too low.

The increase in prevalence between ages 13 and 16 years appeared to be entirely due to a large increase in prevalence in girls (from 1.19% at age 13 to 2.46% at age 16), whereas the prevalence in boys remained almost unchanged (1.40% at age 13, 1.28% at age 16), based on estimates from our previous study of chronic disabling fatigue (of ≥6 months' duration).[8] A sex gap in depression also begins to emerge in early to mid-adolescence,[39] with a dramatic rise in rates of depression in girls, whilst rates remain relatively constant in boys.[40] Various physical, psychological, and environmental explanations have been proposed, including hormonal changes that accompany puberty.[41] Different cognitive styles or coping strategies with stress have been also suggested as possible explanations: Mezulis *et al* found that adolescent girls display greater negative brooding in response to negative life events;[42] Rood *et al* found that this effect could be associated with specific domains, because females had higher responses of a negative cognitive style to stressors involving physical appearance or body-image.[43] The sex-related difference that we found in prevalence of CFS disappeared if children with CFS and depressive symptoms were re-classified as not having CFS, showing that the increase in prevalence of CFS in girls is accompanied by an increase in depressive symptoms in the same children, as they grow towards adulthood.

Indeed, our age 16 prevalence estimates were consistent with estimates from a recent review of studies of the prevalence of CFS in adults: we estimated a ≥3 months' prevalence of 0.90% (0.60% to 1.20%) excluding children with depressive symptoms, compared with a pooled prevalence of 0.76% (0.23% to 1.29%) for CFS/ME by clinical assessment; and we estimated a prevalence of 2.50% (2.04% to 2.96%) by combined parental- and child-report, including children with depressive symptoms, compared with a pooled prevalence of 3.48% (2.36% to 4.60%) for self-reported CFS/ME.[44] These comparisons show that self-reported data will

over-estimate CFS prevalence in children and adults, and suggest that much of the over-reporting can be attributed to depression (which would be excluded in a clinical assessment).

Even after excluding depressive symptoms, CFS was more common in our population cohort compared to a Dutch study which relied on medical diagnosis, and which reported a prevalence of 0.11%.[13] This discrepancy might be a consequence of the limitations of our methods for classifying CFS, but it could also have occurred because not all children with CFS visit their doctor, or visit a doctor but are not diagnosed or offered treatment.[23] Despite the limitations of our study, we would argue that pediatricians need to consider the possibility of CFS in children who are not attending school full-time. This is particularly so for children from disadvantaged backgrounds, because families that experience early family adversity may be less likely to overcome barriers to accessing specialist care.[15] Awareness needs to be raised to ensure that families of children affected by CFS access specialist medical care, and that pediatricians and those looking after children are trained in the identification and management of CFS. Future research should examine the type of fatigue experienced by children, and its different phenotypes, and investigate potentially important etiologic factors that might explain the association of fatigue with family adversity. Further research is also needed to investigate the extent to which psychological problems and life difficulties pre-date or follow CFS.[45] This aspect of adolescent CFS, in particular the role of depression, requires in-depth analysis using repeated measures of mood and fatigue from childhood through to early adulthood.

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Table 1: Characteristics of ALSPAC participants for whom fatigue-related data were available *versus* missing at age 16 years[†]

	Children with data to define CFS at age 16 years (N=5756)	Children without data to define CFS at age 16 years (N=8222)	P-value*
Sex (female)	52.4% (3014/5756)	45.5% (3744/8222)	<0.001
FAI score during mother's pregnancy (range 0 – 14)	0.92 (0.89, 0.96), n=4870	1.45 (1.40, 1.49), n=5266	<0.001
FAI score at age 10 years (range 0 – 14)	0.99 (0.95, 1.02), n=4617	1.17 (1.11, 1.22), n=2895	<0.001
SMFQ total score at age 13 (range 0 – 26)	2.21 (2.12, 2.30), n=4882	2.76 (2.59, 2.93), n=2051	<0.001
SDQ total score at age 13 (range 0 – 40)	6.39 (6.26, 6.52), n=4869	7.76 (7.50, 8.01), n=1853	<0.001
Number of authorized school absences	16.1 (15.6, 16.6), n=4461	21.1 (20.6, 21.7), n=6091	<0.001
Number of unauthorized school absences	2.51 (2.19, 2.82), n=4461	8.64 (8.04, 9.25), n=6440	<0.001
Mean KS2 test score (range 0 – 100)	64.0 (63.5, 64.4), n=4369	55.7 (55.3, 56.1), n=6191	<0.001

[†] Scores and school absence summarized as mean (95% CI); FAI = Family Adversity Index; SMFQ = Short Moods and Feelings Questionnaire; SDQ = Strengths and Difficulties Questionnaire; school absences are half-day sessions out of a typical total of 390 sessions during the 'Year 11' school year (age 15-16 years) obtained via linkage to the National Pupil Database (NPD); KS2 = Key Stage 2 mean test score for English, Mathematics and Science (tests conducted at age 11 years)

* Chi-squared test for proportions, Student's *t* test for means

Table 2: Prevalence of CFS among the ALSPAC birth cohort at age 16 years

	Prevalence (95% CI), fraction
CFS of ≥3 months' duration	
Overall	
Complete data	2.02% (1.68%, 2.41%), 116/5756
Imputed‡	2.50% (2.04%, 2.96%), 349/13978
Imputed, re-classified depressive symptoms‡	0.90% (0.60%, 1.20%), 125/13978
Boys	
Complete data	1.60% (1.20%, 2.15%), 44/2742
Imputed‡	1.80% (1.26%, 2.34%), 130/7220
Imputed, re-classified depressive symptoms‡	0.99% (0.55%, 1.42%), 71/7220
Girls	
Complete data	2.39% (1.90%, 3.00%), 72/3014
Imputed‡	3.24% (2.57%, 3.92%), 219/6758
Imputed, re-classified depressive symptoms‡	0.80% (0.37%, 1.23%), 54/6758
CFS of ≥6 months' duration	
Overall	
Complete data	1.46% (1.18%, 1.80%), 84/5756
Imputed‡	1.86% (1.47%, 2.24%), 259/13978
Imputed, re-classified depressive symptoms‡	0.60% (0.37%, 0.84%), 84/13978
Boys	
Complete data	1.09% (0.77%, 1.56%), 30/2742
Imputed‡	1.28% (0.85%, 1.72%), 93/7220
Imputed, re-classified depressive symptoms‡	0.66% (0.33%, 0.99%), 47/7220
Girls	
Complete data	1.79% (1.37%, 2.33%), 54/3014
Imputed‡	2.46% (1.89%, 3.04%), 167/6758
Imputed, re-classified depressive symptoms‡	0.55% (0.20%, 0.89%), 37/6758

‡ Datasets imputed separately for males and females using data on: chronic disabling fatigue of ≥3 months' duration at age 13 years; FAI during mother's pregnancy; mother's age at birth of child; FAI at age 8-10 years; maternal psychopathology at child's age 8-10 years; SDQ score at ages 11, 13 and 16 years; SMFQ score at ages 13 and 16 years; NPD authorized absences during school Year 11 (age 15-16 years), KS2 mean test score. Exclusionary criterion for depressive symptoms was SMFQ score ≥11 – children with CFS and depressive symptoms were classified as not having CFS.

Table 3: Psychological problems, life difficulties, and school attendance among children with and without CFS at age 16 years (imputed data)[†]

	No CFS	CFS (≥6 months)	Effect measure (95% CI)[‡]
Psychological problems at age 16 years:			
SMFQ total score (range: 0-26)	5.67 (5.51, 5.83)	14.4 (12.5, 16.4)	difference in means = 8.15 (6.21, 10.1)
Depressive symptoms (SMFQ score ≥11)	15.3% (14.4%, 16.3%)	67.4% (55.6%, 79.2%)	odds ratio = 11.0 (5.92, 20.4)
Life difficulties at age 16 years:			
SDQ total score (range: 0-40)	6.62 (6.49, 6.75)	13.0 (11.8, 14.2)	difference in means = 6.16 (5.09, 7.23)
School attendance at age 15-16 years:			
Total number of authorized absences	18.3 (17.9, 18.7)	53.9 (42.9, 64.9)	difference in means = 34.8 (25.4, 44.1)

[†] Values shown are mean or proportion (95% CI). Datasets were imputed separately for males and females using data on: chronic disabling fatigue of ≥3 months' duration at age 13 years; FAI during mother's pregnancy; mother's age at birth of child; FAI at age 8-10 years; maternal psychopathology at child's age 8-10 years; SDQ score at ages 11, 13 and 16 years; SMFQ score at ages 13 and 16 years; NPD authorized absences during school Year 11 (age 15-16 years), KS2 mean test score.

[‡] Differences in means and odds ratios obtained from linear and logistic regression, respectively, adjusted for sex and family adversity at age 8-10 years.

Table 4: Factors associated with CFS of ≥6 months' duration at age 16 years (imputed data)[†]

	No CFS	CFS (≥6 months)	Adjusted odds ratio (95% CI)[‡]
All children			
Sex (female)	48.0% (47.2%, 52.8%)	64.3% (55.6%, 73.0%)	1.95 (1.33, 2.86)
FAI score at age 8-10 years (range 0 – 14)	1.12 (1.09, 1.15)	1.51 (1.12, 1.89)	1.20 (1.01, 1.42)
Excluding children with depressive symptoms[*]			
Sex (female)	48.4% (47.5%, 49.2%)	43.6% (22.4%, 64.8%)	0.82 (0.35, 1.92)
FAI score at age 8-10 years (range 0 – 14)	1.13 (1.10, 1.16)	1.15 (0.59, 1.72)	1.00 (0.75, 1.35)

[†] Values shown are mean or proportion (95% CI). Datasets were imputed separately for males and females using data on: chronic disabling fatigue of ≥3 months' duration at age 13 years; FAI during mother's pregnancy; mother's age at birth of child; FAI at age 8-10 years; maternal psychopathology at child's age 8-10 years; SDQ score at ages 11, 13 and 16 years; SMFQ score at ages 13 and 16 years; NPD authorized absences during school Year 11 (age 15-16 years), KS2 mean test score.

[‡] Adjusted for sex and total FAI score.

[*] Exclusionary criterion for depressive symptoms was SMFQ score ≥11 – children with CFS and depressive symptoms were classified as not having CFS.

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