Chronic Fatigue Syndrome at Age 16 Years

Simon M. Collin, PhD,a,b Tom Norris, PhD,a,b Roberto Nuevo, PhD,a,b Kate Tilling, PhD,a Carol Joinson, PhD,a,b Jonathan A.C. Sterne, PhD,a Esther Crawley, BMBCh, PhD a,b

abstract

BACKGROUND: In the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, chronic disabling fatigue lasting $\geq$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 $\geq$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.

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 at age 13 years, but its relationship with CFS in older children is unknown.

WHAT THIS STUDY ADDS: The prevalence of CFS at age 16 years was 1.9%, 0.6% of which occurred 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.
Chronic fatigue syndrome (CFS) in children and young people is a debilitating disease that has a major impact on the lives of children and their families.\textsuperscript{1–3} CFS, also known as myalgic encephalomyelitis (ME) or, more recently, systemic exertion intolerance disease,\textsuperscript{4} has been defined by using various diagnostic criteria.\textsuperscript{5} Guidelines from the UK National Institute for Health and Care Excellence state that the diagnosis of CFS should be made after 3 months of persistent or recurrent fatigue that 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.\textsuperscript{6} The diagnostic criteria of the Centers for Disease Control and Prevention require 6 months’ duration of fatigue.\textsuperscript{7}

Chronic fatigue of at least 3 months’ duration affects 2\% to 3\% of children and young people aged 8 to 18 years.\textsuperscript{8–10} Population-based studies in the United Kingdom and the United States have reported a prevalence of 1.3\% for fatigue of ≥6 months’ duration.\textsuperscript{8,9,11} Although clinician-verified CFS seems to be less prevalent (0.1\%–0.5\%),\textsuperscript{12–14} this discrepancy is almost certainly a consequence of referral pathways and barriers to accessing clinical services.\textsuperscript{15} Recognition of CFS as a relatively common, highly debilitating, and potentially long-term pediatric disease has grown in recent years,\textsuperscript{16,17} but it is important that the uncertainties regarding the population prevalence of pediatric CFS are resolved.

We previously reported 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.\textsuperscript{8} In this earlier study, we were unable to confirm a diagnosis of CFS because we had only parental report of fatigue; hence, chronic disabling fatigue was defined as the study outcome. In the present study, parental and child report of fatigue were combined to identify adolescents with CFS. We estimated the prevalence of CFS at age 16 years and investigated the relationships of CFS with gender, family adversity at age 8 to 10 years, and with school attendance, depressive symptoms, and life difficulties at age 16 years.

**METHODS**

**Participants**

The ALSPAC (Avon Longitudinal Study of Parents and Children) is a population-based study that aims to investigate a wide range of influences on the health and development of children.\textsuperscript{18} Pregnant women residing in the former Avon Health Authority in southwest England who had an estimated date of delivery between April 1, 1991, and December 31, 1992, were invited to participate, resulting in a cohort of 14,541 pregnancies and 13,978 children alive at 1 year of age (excluding triplets and quadruplets). The primary source of data for the present study was parent-completed questionnaires administered at 4 time points during the antenatal period and then at regular intervals after birth. The ALSPAC study Web site 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**

Data from parent- and child-completed questionnaires were used in a 2-stage process to classify children as having CFS. In the first stage, parent-reported data were used to classify the presence or absence of CFS by using criteria similar to the definition of chronic disabling fatigue in children in this cohort at age 13 years.\textsuperscript{8} Parents received a “Your son/daughter 16+ years on” questionnaire (at a median age of 16.6 years [interquartile range: 16.5–16.8]). This questionnaire 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, sports, or leisure activities (not at all, only a little, quite a lot, or a great deal). The questionnaire asked whether the parent thought that the tiredness/lack of energy was due to: (1) illness; (2) problems with sleep; (3) playing a lot of sports; (4) stress or worry; and (5) other reason (free-text question). Children were classified as having CFS (according to 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 being too involved in sports, 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 (eg, crack cocaine, solvents, heroin, cocaine) during the previous year, or a diagnosis of anorexia nervosa, were classified as not having CFS. CFS of ≥3 months’ duration was analyzed as a secondary outcome, in accordance with the guidelines of the UK National Institute for Health and Care Excellence.
In the second stage, child-reported data were used to classify children as not having CFS if they had a Chalder Fatigue Questionnaire (CFQ) score <19 (of 33), including children who had been classified as having CFS according to parental report (ie, children classified as having CFS by parental report were reclassified as not having CFS). The CFQ was incorporated into a “Life of a 16+ teenager” questionnaire, which was completed by participants at age 16 years (median: 16.7 years [interquartile range: 16.5–17.1]). 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 cutoff score of 19 (of 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 according to 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, gender and family adversity (measured at age 8–10 years) were considered to be a priori risk factors for CFS at age 16 years. This assumption was based on our earlier study of family adversity as a risk factor for chronic disabling fatigue in children at age 13 years8 and on the gender-related difference in CFS prevalence in adults.21 Psychological problems, life difficulties, and school attendance (all measured at age 16 years) were considered 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 to 10 years old regarding the following 9 factors, comprising 14 items in total: (1) age of mother at first pregnancy; (2) housing, comprising adequacy, basic amenities, defects, damp, and infestation; (3) mother’s and father’s low educational attainment; (4) financial difficulties; (5) relationship with partner, comprising lack of affection, cruelty, and lack of support; (6) social network, comprising lack of emotional support and 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 >1 questionnaire. The pregnancy FAI was coded as missing if any item was missing. The age 8 to 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-item Mood and Feelings Questionnaire.25 The SMFQ correlates well with other measures of depression and has good test–retest reliability.26,27 A cutoff score of ≥11 was used to indicate high levels of depressive symptoms at age 16 years. This threshold has high sensitivity, specificity, and negative predictive power for a diagnosis of depression (according to the International Classification of Diseases, 10th Revision) 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 behavioral 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, and prosocial behavior). Each item is coded on a Likert scale of 0 to 2 (from not true to certainly true), yielding a range of 0 to 10 for each subscale. A “total difficulties” score is calculated by adding scores for the first 4 subscales (excluding prosocial behavior), yielding a total score with a range of 0 to 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
RESULTS

A total of 13,978 ALSPAC children were alive at 1 year of age (excluding triplets and quadruplets). At 16 years of age, questionnaires were sent to 9523 parents and 9510 children, with returns of 54.8% (5495 of 9523) and 48.8% (4901 of 9510), respectively. Parent- and child-reported fatigue data were available for 4962 and 4847 children. These data allowed us to classify the presence or absence of CFS in 5756 children (Fig 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 of 5372) answered “yes,” with more girls (40.8% [1016 of 2492]) than boys (30.6% [759 of 2483]) affected. Based on parent-reported data only, the proportions of children experiencing CFS of ≥3 and ≥6 months’ duration were 4.17% (207 of 4962) and 2.76% (137 of 4962), respectively (Fig 1). Prevalence of CFS of ≥6 months’ duration was higher among girls (3.58% [89 of 2485]) than among boys (1.94% [48 of 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 of 2485]) than in boys (2.87% [71 of 2477]), a

Statistical Analysis

The prevalence of CFS was estimated among those children for whom sufficient data were available to define this outcome. Performing only complete case analyses (ie, omitting children with any missing data) can result in bias and will inflate SEs compared with analyses with no missing data. If missingness is dependent only on observed data (ie, if data are missing at random), multiple imputation can then be used to correct such bias. We generated 75 imputed data sets, separately for boys and girls, based on the outcome variable (ie, 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 the child; FAI at age 8 to 10 years; maternal psychopathology at child’s age 8 to 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; and 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 SE of the coefficient being estimated, with the number of imputations being increased incrementally until the Monte Carlo error achieved a value that was <10% of the SE of the estimate.

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 a twin. The data under a logistic regression model were imputed by using an imputation sampling method (implemented in Stata’s uvis command), which incorporates all sources of variability and uncertainty in the imputed values. Imputed estimates were combined by using Rubin’s rules. We investigated the relationships of our primary outcome (CFS of ≥6 months’ duration) with gender, family adversity, mood problems, life difficulties, and school attendance by using linear and logistic regression models, which were fitted to the complete and imputed data sets. Analyses were performed by using Stata version 13 (Stata Corp, College Station, TX).
difference of 2.60% (95% CI: 1.50 to 3.72; \( P < .001 \)).

Child-reported data showed that 10.2% (496 of 4847) of children had an CFQ score \( \geq 19 \). Children deemed to have CFS according to parental report were more likely to have missing CFQ data: these were missing for 34.3% (47 of 137) of children with parent-reported CFS of \( \geq 6 \) months’ duration, compared with 27.1% (1306 of 4825) of children not classified according to parental report only because 38.7% (53 of 137) of the participants classified with CFS according to parental report were reclassified 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 of 4962) of children who had been classified according to parental report. CFS of \( \geq 3 \) months’ duration was more prevalent among girls (2.39% [72 of 3014])

**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Children With Data to Define CFS at Age 16 Years (N = 5756)</th>
<th>Children Without Data to Define CFS at Age 16 Years (N = 8222)</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>52.4% (3014/5756)</td>
<td>45.5% (5744/8222)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FAI score during mother’s pregnancy (range: 0–14)</td>
<td>0.92 (0.89 to 0.96), ( n = 4870 )</td>
<td>1.45 (1.40 to 1.49), ( n = 5286 )</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FAI score at age 10 y (range: 0–14)</td>
<td>0.99 (0.95 to 1.02), ( n = 4617 )</td>
<td>1.17 (1.11 to 1.22), ( n = 2895 )</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SMFQ total score at age 13 y (range: 0–26)</td>
<td>2.21 (2.12 to 2.30), ( n = 4882 )</td>
<td>2.78 (2.69 to 2.85), ( n = 2051 )</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SDQ total score at age 13 y (range: 0–40)</td>
<td>6.39 (6.26 to 6.52), ( n = 4869 )</td>
<td>7.76 (7.50 to 8.01), ( n = 1853 )</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of authorized school absences</td>
<td>16.1 (15.6 to 16.5), ( n = 4461 )</td>
<td>21.1 (20.6 to 21.7), ( n = 6991 )</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of unauthorized school absences</td>
<td>2.51 (2.19 to 2.82), ( n = 4461 )</td>
<td>8.64 (8.04 to 9.25), ( n = 6440 )</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean KS2 test score (range: 0–100)</td>
<td>64.0 (63.5 to 64.4), ( n = 4569 )</td>
<td>55.7 (55.3 to 56.1), ( n = 6191 )</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Scores and school absences are summarized as mean (95% CI). School absences are half-day sessions from a typical total of 390 sessions during the year 11 school year (age 15–16 years) obtained via linkage to the NPD. KS2 is the mean test score for English, mathematics, and science (tests conducted at 11 years of age).

\( a \) The \( \chi^2 \) test was used for proportions, and Student’s \( t \) test was used for means.
than among boys (1.60% [44 of 2742]), a difference of 0.78% (95% CI: 0.06 to 1.50; P < .001). CFS of ≥6 months’ duration was also more prevalent among girls (1.79% [54 of 3014]) than among boys (1.09% [30 of 2742]), a difference of 0.70% (95% CI: 0.08 to 1.31; P = .03).

Multiple imputation to correct biases caused by missing data increased the overall prevalence estimates for CFS of ≥3 months’ duration from 2.02% (95% CI: 1.68 to 2.41) to 2.50% (95% CI: 2.04 to 2.96), and for CFS of ≥6 months’ duration from 1.46% (95% CI: 1.18 to 1.80) to 1.86% (95% CI: 1.47 to 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 absences (Table 3). After imputation, depressive symptoms (SMFQ score ≥11) were reported by 67.4% of children with CFS, compared with 15.3% in those without CFS, and children with CFS had 11-fold higher odds of depressive symptoms (odds ratio [OR]: 11.0 [95% CI: 5.92 to 20.4]), compared with children without CFS. 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% (95% CI: 0.60 to 1.20) and 0.60% (95% CI: 0.37 to 0.84), respectively (Table 2).

Total SDQ scores (range: 0–40) were higher in children with CFS (difference in means: 6.16 points [95% CI: 5.09 to 7.23]) (Table 3). Complete data analysis suggests this difference was mainly due to higher emotional symptom scores in children with CFS (difference in means: 3.44 points [95% CI: 3.03 to 3.84]) (Supplemental Table 5).

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

---

**TABLE 2** Prevalence of CFS Among the ALSPAC Birth Cohort at Age 16 Years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence (95% CI), Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CFS of ≥3 months’ duration</strong></td>
<td></td>
</tr>
<tr>
<td>Overall Complete data</td>
<td>2.02% (1.68 to 2.41), 116/5756</td>
</tr>
<tr>
<td>Imputed*</td>
<td>2.50% (2.04 to 2.96), 349/13978</td>
</tr>
<tr>
<td>Imputed, reclassified depressive symptoms*</td>
<td>0.90% (0.60 to 1.20), 125/13978</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td></td>
</tr>
<tr>
<td>Complete data</td>
<td>1.60% (1.20 to 2.15), 44/2742</td>
</tr>
<tr>
<td>Imputed*</td>
<td>1.80% (1.26 to 2.34), 130/7220</td>
</tr>
<tr>
<td>Imputed, reclassified depressive symptoms*</td>
<td>0.95% (0.55 to 1.42), 71/7220</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
</tr>
<tr>
<td>Complete data</td>
<td>2.39% (1.90 to 3.00), 72/3014</td>
</tr>
<tr>
<td>Imputed*</td>
<td>3.24% (2.57 to 3.92), 219/13978</td>
</tr>
<tr>
<td>Imputed, reclassified depressive symptoms*</td>
<td>0.80% (0.37 to 1.23), 54/13978</td>
</tr>
<tr>
<td><strong>CFS of ≥6 months’ duration</strong></td>
<td></td>
</tr>
<tr>
<td>Overall Complete data</td>
<td>1.46% (1.18 to 1.80), 84/5756</td>
</tr>
<tr>
<td>Imputed*</td>
<td>1.85% (1.47 to 2.24), 259/13978</td>
</tr>
<tr>
<td>Imputed, reclassified depressive symptoms*</td>
<td>0.60% (0.37 to 0.84), 84/13978</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td></td>
</tr>
<tr>
<td>Complete data</td>
<td>1.09% (0.77 to 1.56), 30/2742</td>
</tr>
<tr>
<td>Imputed*</td>
<td>1.28% (0.85 to 1.72), 85/7220</td>
</tr>
<tr>
<td>Imputed, reclassified depressive symptoms*</td>
<td>0.66% (0.33 to 0.99), 47/7220</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
</tr>
<tr>
<td>Complete data</td>
<td>1.79% (1.37 to 2.33), 54/3014</td>
</tr>
<tr>
<td>Imputed*</td>
<td>2.46% (1.89 to 3.04), 167/13978</td>
</tr>
<tr>
<td>Imputed, reclassified depressive symptoms*</td>
<td>0.55% (0.20 to 0.88), 37/13978</td>
</tr>
</tbody>
</table>

* Data sets imputed separately for male and female subjects by 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 to 10 years; maternal psychopathology at child’s age 8 to 10 years; SDQ score at ages 11 and 13 years; NPD-authorized absences during school year 11 (age 15–16 years); and KS2 mean test score. Exclusionary criterion for depressive symptoms was an 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)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No CFS</th>
<th>CFS (≥6 Months)</th>
<th>Effect Measure (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological problems at age 16 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMFQ total score (range: 0–26)</td>
<td>5.67 (5.51 to 5.83)</td>
<td>14.4 (12.5 to 16.4)</td>
<td>Difference in means: 8.15 (6.21 to 10.1)</td>
</tr>
<tr>
<td>Depressive symptoms (SMFQ score ≥11)</td>
<td>15.3% (14.4 to 16.3)</td>
<td>67.4% (58.6 to 75.2)</td>
<td>OR: 11.0 (5.92 to 20.4)</td>
</tr>
<tr>
<td>Life difficulties at age 16 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDQ total score (range: 0–40)</td>
<td>6.62 (6.49 to 6.75)</td>
<td>13.0 (11.8 to 14.2)</td>
<td>Difference in means: 6.16 (5.08 to 7.23)</td>
</tr>
<tr>
<td>School attendance at age 15–16 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of authorized absences</td>
<td>18.3 (17.9 to 18.7)</td>
<td>53.9 (42.8 to 64.3)</td>
<td>Difference in means: 34.8 (25.4 to 44.1)</td>
</tr>
</tbody>
</table>

* Data are presented as mean or proportion (95% CI). Data sets were imputed separately for male and female subjects by 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 to 10 years; maternal psychopathology at child’s age 8 to 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); and KS2 mean test score.

* Differences in means and ORs obtained from linear and logistic regression, respectively, adjusted for gender and family adversity at age 8 to 10 years.
TABLE 4 Factors Associated With CFS of ≥6 Months’ Duration at Age 16 Years (Imputed Data)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No CFS</th>
<th>CFS (≥6 Months)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>48.0% (47.2 to 52.8)</td>
<td>64.3% (55.6 to 73.0)</td>
<td>1.95 (1.33 to 2.86)</td>
</tr>
<tr>
<td>FAI score at age 8–10 y (range: 0–14)</td>
<td>1.12 (1.09 to 1.15)</td>
<td>1.51 (1.12 to 1.88)</td>
<td>1.20 (1.01 to 1.42)</td>
</tr>
<tr>
<td>Excluding children with depressive symptomsb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>48.4% (47.5 to 49.2)</td>
<td>43.6% (22.4 to 64.8)</td>
<td>0.82 (0.35 to 1.92)</td>
</tr>
<tr>
<td>FAI score at age 8–10 y (range: 0–14)</td>
<td>1.13 (1.10 to 1.16)</td>
<td>1.15 (0.59 to 1.72)</td>
<td>1.00 (0.75 to 1.35)</td>
</tr>
</tbody>
</table>

Data are presented as mean or proportion (95% CI). Data sets were imputed separately for male and female subjects by using data on: chronic disabling fatigue of ≥3 months’ duration at age 15 years; FAI during mother’s pregnancy; mother’s age at birth of child; FAI at age 8 to 10 years; maternal psychopathology at child’s age 8 to 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); and KS2 mean test score.

a Adjusted for gender and total FAI score.

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 to 17.4]); 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 the imputed data analysis, girls had almost double the odds of CFS at age 16 years compared with boys (OR: 1.95 [95% CI: 1.33 to 2.86]), and the odds of CFS increased by 20% for each unit increase in the ALSPAC FAI (OR: 1.20 [95% CI: 1.01 to 1.42]) (Table 4). If children with depressive symptoms were classified as not having CFS, gender and family adversity were not associated with CFS. Associations of female gender (OR: 1.84 [95% CI: 1.30 to 2.60]) and family adversity (OR: 1.18 [95% CI: 1.01 to 1.37]) with CFS of ≥3 months’ duration were similar to those with CFS of ≥6 months’ duration.

**DISCUSSION**

The present study estimated the prevalence of CFS among 16-year-olds in a large population-based birth cohort as 1.86% (95% CI: 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% (95% CI: 0.37 to 0.84) and the ≥3 months’ prevalence to 0.90% (95% CI: 0.60 to 1.20). Higher levels of family adversity were associated with an increased risk of CFS in children at age 16 years, as was observed at age 13 years. CFS was more common in girls than in boys, a gender-related difference not seen at age 13 years in the same cohort. Neither of these associations was 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.

The present study is, to our knowledge, the largest population-based investigation of 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 United States (6 months) and the United Kingdom (3 months). Multiple imputation was used 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 with higher levels of family adversity.

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.” 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, and CFQ scores were available for 73% of children who had been classified according to parental report. The CFQ data showed that classification according to parental report would overestimate the occurrence of CFS, with ~40% of children classified with CFS according to parental report being reclassified 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 nonreturn 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 physician, and our classification was not subject to clinical verification. It is therefore possible that parents and children reported significant levels of disabling fatigue that 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 (score >9 on the Hospital Anxiety and Depression Scale [HADS]) was 29% (95% CI: 25 to 33). However, this HADS threshold classifies only 2% of UK schoolchildren as having depression, 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%) and psychiatric problems (72%) 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 seemed to be entirely due to a large increase in prevalence in girls (from 1.19% at age 13 years to 2.46% at age 16 years), whereas the prevalence in boys remained almost unchanged (1.40% at age 13 years and 1.28% at age 16 years), based on estimates from our previous study of chronic disabling fatigue (≥6 months’ duration). A gender gap in depression also begins to emerge in early to mid-adolescence, with a dramatic rise in rates of depression in girls, while rates remain relatively constant in boys. Various physical, psychological, and environmental explanations have been proposed, including hormonal changes that accompany puberty. Different cognitive styles or coping strategies with stress have been also suggested as possible explanations. Mezulis and Rudolph found that adolescent girls display greater negative brooding in response to negative life events, and Rood et al found that this effect could be associated with specific domains, because female subjects had higher responses of a negative cognitive style to stressors involving physical appearance or body image. The gender-related difference that we found in the prevalence of CFS disappeared if children with CFS and depressive symptoms were reclassified as not having CFS, illustrating that the increase in prevalence of CFS in girls is accompanied by an increase in depressive symptoms in the same children as they grow toward adulthood.

Indeed, our age 16 year 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% (95% CI: 0.60 to 1.20), excluding children with depressive symptoms, compared with a pooled prevalence of 0.76% (95% CI: 0.23 to 1.29) for CFS/ME by clinical assessment; and we estimated a prevalence of 2.50% (95% CI: 2.04 to 2.96) by combined parental- and child-report, including children with depressive symptoms, compared with a pooled prevalence of 3.48% (95% CI: 2.36 to 4.60) for self-reported CFS/ME. These comparisons show that self-reported data will overestimate CFS prevalence in children and adults, and they suggest that much of the overreporting 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 with a Dutch study that relied on medical diagnosis and which reported a prevalence of 0.11%. 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 physician, or they visit a physician but are not diagnosed or offered treatment. 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 finding is particularly true for children from disadvantaged backgrounds because families that experience early family adversity may be less likely to overcome barriers to accessing specialist care.

**CONCLUSIONS**

Awareness needs to be raised to ensure that families of children...
affected by CFS can 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 predate or follow CFS. 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.

ACKNOWLEDGMENTS

The authors are extremely grateful to all the families who participated in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. The UK Medical Research Council and the Wellcome Trust (grant reference 102215/2/13/2) and the University of Bristol provide core support for ALSPAC.

FUNDING: Supported by a Medical Research Council research grant (MR/K020289/1).

POTENTIAL CONFLICT OF INTEREST: Dr Crawley is a medical advisor for the Association of Young People with ME and the Sussex and Kent ME/CFS Society. The other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES


13. Nijhof SL, Majer K, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Adolescent chronic fatigue syndrome: prevalence, incidence, and

ABBREVIATIONS

ALSPAC: Avon Longitudinal Study of Parents and Children
CFS: chronic fatigue syndrome
CFQ: Chalder Fatigue Questionnaire
CI: confidence interval
FAI: Family Adversity Index
HADS: Hospital Anxiety and Depression Scale
KS2: Key Stage 2
ME: myalgic encephalomyelitis
NPD: National Pupil Database
OR: odds ratio
SDQ: Strengths and Difficulties Questionnaire
SMFQ: Short Moods and Feelings Questionnaire
morbidly. Pediatrics. 2011;127(5). Available at: www.pediatrics.org/cgi/content/full/127/5/e1169


33. Royston P. Multiple imputation of missing values: further update of ice, with an emphasis on interval censoring. Stata J. 2007;7:9


Chronic Fatigue Syndrome at Age 16 Years
Simon M. Collin, Tom Norris, Roberto Nuevo, Kate Tilling, Carol Joinson, Jonathan A.C. Sterne and Esther Crawley

*Pediatrics* 2016;137;
DOI: 10.1542/peds.2015-3434 originally published online January 25, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
[http://pediatrics.aappublications.org/content/137/2/e20153434](http://pediatrics.aappublications.org/content/137/2/e20153434)