# Etiology of Chronic Fatigue Syndrome: Testing Popular Hypotheses Using a National Birth Cohort Study

SAMUEL B. HARVEY, MRCPSYCH, MICHAEL WADSWORTH, PHD, SIMON WESSELY, MD, AND MATTHEW HOTOPF, PHD

**Objective:** To review the etiology of chronic fatigue syndrome (CFS) and test hypotheses relating to immune system dysfunction, physical deconditioning, exercise avoidance, and childhood illness experiences, using a large prospective birth cohort. **Methods:** A total of 4779 participants from the Medical Research Council's National Survey of Health and Development were prospectively followed for the first 53 years of their life with >20 separate data collections. Information was collected on childhood and parental health, atopic illness, levels of physical activity, fatigue, and participant's weight and height at multiple time points. CFS was identified through self-report during a semistructured interview at age 53 years with additional case notes review. **Results:** Of 2983 participants assessed at age 53 years, 34 (1.1%, 95% Confidence Interval 0.8–1.5) reported a diagnosis of CFS. Those who reported CFS were no more likely to have suffered from childhood illness or atopy. Increased levels of exercise throughout childhood and early adult life and a lower body mass index were associated with an increased risk of later CFS. Participants who later reported CFS continued to exercise more frequently even after they began to experience early symptoms of fatigue. **Conclusions:** Individuals who exercise frequently are more likely to report a diagnosis of CFS in later life. This may be due to the direct effects of this behavior or associated personality factors. Continuing to be active despite increasing fatigue may be a crucial step in the development of CFS. **Key words:** chronic fatigue syndrome, fatigue, myalgic encephalomyelitis, exercise, atopy.

**CFS** = chronic fatigue syndrome; **BMI** = body mass index.

## INTRODUCTION

Chronic fatigue syndrome (CFS) is a condition characterized by persistent severe fatigue accompanied by a number of somatic and cognitive symptoms (1). Despite significant amounts of research and multiple theories on causation, the etiology of CFS has remained unclear (2,3).

The increased rates of CFS after certain viral infections has led to speculation that dysfunction of the immune system may be involved in the etiology of persistent fatigue symptoms (4,5). Although a consistent pattern of immunological dysfunction is yet to be identified, a number of studies have reported abnormal levels of T cells, natural killer cells, and cytokines in those individuals with CFS (6). A hypothesis has emerged which suggests chronic fatiguing illnesses may be the result of a systematic shift in the immune Th1/Th2 balance toward a Th2 pattern of activation (7,8). A number of case-control and cross-sectional studies have found increased rates of atopic illnesses, such as allergies and asthma, in those with CFS (9). Atopic illnesses, also associated with activation of Th2 cells, have been seen as indirect evidence for immune system involvement in the etiology of CFS. However, increased levels of atopy among those with CFS have not been found consistently (10–13), and previous studies investigating this association have all been retrospective or cross-sectional in nature. Therefore, it has not been clear whether any immunological abnormality precedes fatigue symptoms or whether these abnormalities are occurring as a consequence of the disturbances in sleep and physical conditioning associated with CFS.

A further area of controversy in CFS has been the role of exercise and physical deconditioning (14,15). Graded exercise therapy, which has proven to be beneficial in those with CFS, is based on a hypothesis of fatigue being maintained by an avoidance of activity and physical deconditioning (14,16,17). However, patients with CFS do not seem to have an exercise phobia (18), with clinical experience suggesting that many patients with CFS describe themselves as being very active before they developed CFS symptoms. To our knowledge, no studies have ever investigated the level of physical activity undertaken in those with CFS as adults before the occurrence of their fatigue symptoms.

An alternative view of CFS is that it represents one of a cluster of functional somatic syndromes, which all share similar psychosocial etiological and maintaining factors (19,20). Previous studies have found that particular childhood illness experiences, such as persistent abdominal pain (21,22), frequent headaches (23), and parental illness (22) are associated with an increased risk of medically unexplained illnesses as adults. One study has examined similar childhood factors in relationship to CFS and found that underactive children and those with a limiting medical condition in childhood were at increased risk of CFS at age 30 years, but that parental illness was not a risk factor (24).

The Medical Research Council's National Survey of Health and Development is a large British national birth cohort that was established in 1946. Because of its size and the prospective collection of data across many years, it provides a unique opportunity to test a number of the hypotheses relating to the etiology of CFS. It also allows the temporal relationships between potential risk factors and the development of symptoms to be examined across the life span. We aimed to test the hypotheses that those with self-reported CFS would have increased rates of atopic illness, decreased levels of physical

From the Institute of Psychiatry (S.B.H., S.W., M.H.), King's College London, London, UK; Medical Research Council's National Survey of Health and Development (M.W.), Department of Epidemiology and Public Health, Royal Free and UCL Medical School, London, UK. M.W. is now retired.

Authors' Contributions: M.H. and S.B.H. conceptualized and planned this study. M.W. coordinated the data collection and retrieval. S.B.H. and M.H. carried out the statistical analysis. S.B.H. wrote this paper with M.H., S.W., and M.W. providing detailed comments on early drafts.

Address correspondence and reprint requests to Samuel Harvey, Weston Education Centre, 10 Cutcombe Road, London, UK SE5 9RJ. E-mail: s.harvey@iop.kcl.ac.uk

The Medical Research Council's National Survey of Health and Development is funded by the Medical Research Council. M.H. and S.W. are partially funded by the South London and Maudsley NHS Foundation Trust/Institute of Psychiatry NIHR (National Institute of Health Research) Biomedical Research Centre.

Received for publication May 1, 2007; revision received November 12, 2007.

DOI: 10.1097/PSY.0b013e31816a8dbc



0033-3174/08/7003-0001

exercise, and increased childhood experiences of illness before the onset of their fatiguing illness.

## METHODS

### Sample

The Medical Research Council's National Survey of Health and Development is based on a random social class stratified sample of 5362 participants selected from all single, legitimate births occurring in England, Wales, and Scotland in 1 week of March 1946. This sample has been prospectively followed with >20 separate data collections up to the age of 53 years. The sampling procedure and follow-up have been described elsewhere (25).

### Childhood Exposures

Participants' childhood experience of illness was assessed in various ways. Data were available on all childhood illnesses that had led to a hospital admission. In addition, participants' parents and physicians were asked about specific symptoms such as abdominal pain, coughs, heart murmurs, vomiting, and convulsions at various assessments between the ages of 6 and 15 years. Participants' level of school absence between the ages of 6 and 10 years were available from school records. In terms of childhood atopy, participants' mothers were asked if their children suffered from asthma when the participants were aged 6, 11, and 15 years.

The perceived level of illness in participants' families during childhood was also assessed. When participants were aged 6 years, their mothers were asked if other members of the family suffered from frequent colds. When the participants were aged 15 years, their mothers were also asked to rate their own health and their husband's health.

### Atopic Illness as an Adult

At age 36 years, participants were visited at home and a trained nurse conducted a semistructured interview. During this interview, participants were asked if either they or their parents had ever suffered from asthma, hay fever, or skin trouble such as eczema or psoriasis. At age 43 years, they were again visited at home and a similar interview was conducted, although with the addition of a question relating to any personal or family history of allergies. These responses were combined to classify participants as having either any or no personal and/or family history of atopic illness.

### Physical Activity

Participants' level of physical activity was ascertained at several points throughout their life. Teachers were asked to rate the participants' energy level and their ability in sports when they were 13 years old. At age 31 years, participants were asked to describe how often they engaged in various physical activities, such as swimming, cycling, squash, tennis, badminton, fitness classes, or other activities. Using the frequencies of these various activities, we were able to estimate how often participants would engage in any exercise, and whether or not this occurred more than once a week. At age 31 years, participants were also asked to rate their perceived level of fitness. At age 36 years, participants were again asked about various activities; although on this occasion, they were asked to rate both the frequency and total time in the last month they had spent on numerous different forms of physical activity. We inquired about a total of 27 different sports and recreational activities, together with the level of physical activity at work, the amount of cycling/walking, and ten different heavy gardening and do-it-yourself (DIY) tasks. Participants' responses for each of these four broad types of exercise were divided into inactive, less active, and most active according to detailed criteria previously published (26). A combined estimate of overall physical activity at age 36 years was made according to the following classification: "Inactive"—inactive in three or more of the four broad types of exercise; "Less Active"—less active in two or three types of exercise or more active in one category; "More Active"—more active in two types or less active in all four; "Very Active"—more active in at least three of the four types of exercise. At ages 43 and 53 years, participants were asked to estimate how many times in the previous 4 weeks they had taken part in sports, exercise, or vigorous leisure activities.

Participants' heights and weights were also measured by nursing staff during home visits when they were aged 36 and 43 years, thus allowing their body mass index (BMI) to be calculated and the interaction between exercise levels, weight, and CFS to be examined. Weight measurements were also available from birth and at age 7 years.

### Sociodemographic Details

Sociodemographic details including gender, father's social class (in 1961), participant's social class (at age 53 years), and participant's educational level were also obtained. Social class was derived from the participant's occupation using the Registrar General's classification (27); the participant's highest education level achieved was coded, using the Burnham classification (28).

### Outcome

At age 53 years, participants were again interviewed at home by trained nurses. During this semistructured interview, they were asked if they had ever been diagnosed with CFS or myalgic encephalomyelitis (ME). ME is an alternative term for CFS that is often preferred by patient groups within the UK. If a diagnosis was reported, they were asked at what age this problem had first begun. Hospital records were reviewed for all participants who reported suffering CFS. If these records indicated any psychotic or serious medical disorder which may explain the fatigue, then these patients were excluded from further analysis. Individuals with a psychotic mental disorder were also excluded from the control group. As we aimed to specifically investigate predisposing factors, we included only exposure data collected before the age that participants reported their CFS beginning. For example, participants who reported CFS symptoms beginning before the age of 44 years were excluded from the analysis of measures collected at the age of 43 years. When the participants were 36 and 43 years old, trained nurses administered a 40-item version of the Present State Examination (29) and the Psychiatric Symptom Frequency scale (30), respectively. In each of these scales, there are questions related to energy levels and fatigue. This provided an additional measure of fatigue to ensure that the exposures and behaviors being examined were occurring before the development of any fatigue symptoms.

### Statistical Analysis

Statistical analysis was performed using STATA computer software (Stata Corporation, College Station, Texas) (31). Differences between those with CFS and the remainder of the sample interviewed at age 53 years were initially explored, using univariable analysis. The $\chi^2$ tests were used for categorical variables, whereas the $t$ tests were used for continuous variables, such as weight and BMI. Multivariable logistic regression analysis was then used to calculate odds ratios (ORs) corrected for sociodemographic confounders. Missing data were accounted for by utilizing list-wise deletions within each individual regression analysis.

### Ethical Approval

The London area multicenter research ethics committee gave ethical approval for the data collection when the participants were 53 years old. Cohort members gave their informed consent for each assessment. Ethical approval and consent procedures at earlier ages conformed to contemporary best practice.

## RESULTS

Of the 5362 individuals initially recruited, 583 (10.9%) participants were permanent refusers and did not provide any exposure information at any of the child or adult follow-ups. The remaining 4779 participants comprised the risk set followed prospectively in this study. At age 53 years, 3035 participants were interviewed, 2983 (62.4% of the original risk set) of whom provided a valid answer when asked about a diagnosis of CFS. Analysis reported elsewhere has shown that the sample taken when the participants were aged 53

years remained representative of the national population (25). Despite this, male participants, those who achieved lower educational standards, and those whose fathers had manual occupations were less likely to be followed up. Participants with atopy were more likely to be followed up whereas those who had a chronic illness or low energy levels as a child were less likely. Individuals lost to follow-up also tended to have higher BMI at age 36 years. There were no differences in adult levels of physical activity between participants who were followed up and those who were not.

At age 53 years, 37 (1.2%) of the sample reported a diagnosis of CFS. Twenty-two (65%) of these participants reported that a doctor had made this diagnosis. Hospital records for these participants revealed that two had serious medical conditions (meningitis and chronic active hepatitis) and one had a psychotic disorder (schizophrenia) that required them to be excluded from further analysis. After these exclusions, the prevalence estimate for CFS was 1.1% (95% Confidence Interval (CI) = 0.8–1.5). The age that participants reported their fatigue symptoms beginning varied between 41 and 53 years. Table 1 shows the associations between sociodemographic factors and a reported diagnosis of CFS. Women were more likely to report a diagnosis of CFS with an unadjusted OR of 2.34 (95% CI = 1.22–4.91), but neither social class nor educational levels were associated with the diagnosis.

The various measures of childhood illness and their associations with a reported diagnosis of CFS in adulthood are displayed in Table 2. There is no indication of any increased reporting of CFS in those who were exposed to illness in their childhood. There was also no association between the perceived health of participant's parents and later self-reporting of a diagnosis of CFS. The relationship between prior atopic illness and a later diagnosis of CFS is demonstrated in Table 3. Neither a personal history nor a family history of any atopic illness was associated with any increased risk of later self-reported CFS.

Table 4 demonstrates the relationships between self-reported CFS and prior physical activity levels. At every assessment of participants' exercise levels between the ages of 13 years and 43 years, there was a clear trend toward those with higher levels of exercise being at increased risk of later CFS. There were significant correlations between the measures of physical activity at different ages, suggesting that individuals tended to maintain their relative level of activity throughout their life. Spearman's correlation coefficients for the various self-reported adult physical activity measures at different ages varied between 0.16 and 0.35 ($p < .001$ for all correlations). Of the 182 participants who reported engaging in sport or fitness activities on a weekly basis at age 31years, 102 (56.0%) were still undertaking weekly sport or vigorous leisure time activity at the age of 43 years. When compared with the remainder of the sample, these persistently active individuals were at significantly greater risk of later reporting a diagnosis of CFS, with an adjusted OR of 10.80 (95% CI = 2.66–43.79; $p = .001$). Because of the correlation between the independent variables in each of the analyses reported in Table 4, corrections for multiple comparisons were not appropriate.

At the age of 36 years, there was no significant difference in the levels of fatigue reported by participants who were later to suffer from CFS compared to the rest of the sample. However, by the age of 43 years, participants who were to report a diagnosis of CFS at the age of 53 years were beginning to report significantly more fatigue than the rest of the sample (OR adjusted for gender = 2.62; 95% CI = 1.1.5–5.96; $p = .02$). However, despite this, those who were later to report a diagnosis of CFS were still persisting in exercising more frequently than those who did not go on to report CFS. Figure 1 shows that, by the age of 53 years, once the patient is diagnosed with CFS, the frequency of exercise undertaken by individuals with CFS reverts to the level maintained by the rest of the population.

Table 5 demonstrates the relationships between weight, BMI, and a later diagnosis of CFS. Those who were later to report a diagnosis of CFS had significantly lower BMIs at ages 36 and 43 years. This may provide some indirect but objective evidence of increased levels of activity at these ages,

**TABLE 1. Univariable Associations Between Sociodemographic Variables and a Self-Reported Diagnosis of Chronic Fatigue Syndrome (CFS) at Age 53 Years**

| Variable | CFS, *n* (%) | No CFS, *n* (%) | Significance |
|---|---|---|---|
| Gender | | | |
| Male | 10 (29.4) | 1446 (49.4) | $\chi^2 = 5.35$, $p = .02$ |
| Female | 24 (70.6) | 1484 (50.6) | |
| Father's social class (when participants aged 15 years) | | | |
| Manual | 16 (47.1) | 1558 (55.6) | $\chi^2 = 0.99$, $p = .32$ |
| Nonmanual | 18 (52.9) | 1245 (44.4) | |
| Subject's social class (aged 53 years) | | | |
| Manual | 8 (29.6) | 889 (32.5) | $\chi^2 = 0.10$, $p = .75$ |
| Nonmanual | 19 (70.4) | 1847 (67.5) | |
| Subject's educational level | | | |
| Below 'O' level[a] | 16 (50.0) | 1220 (44.1) | $\chi^2 = 0.45$, $p = .51$ |
| 'O' level or above[a] | 16 (50.0) | 1546 (55.9) | |

[a] 'O' level = Ordinary Level Exam, an examination usually taken at age 16 years, which is required to continue further education.

**TABLE 2. Childhood Illness Measures and Adjusted Odds Ratios (95% Confidence Intervals) for a Later Reported Diagnosis of Chronic Fatigue Syndrome (CFS)**

| Age Measured (years) | Variable | Number of Subjects | CFS Diagnosed as Adult (%)[a] | Adjusted Odds Ratio (95% CI)[b] | *p* |
|---|---|---|---|---|---|
| 0–15 | Any chronic illness | | | | |
| | No | 2503 | 1.12 | 1.00 | |
| | Yes | 461 | 1.30 | 1.20 (0.49–2.92) | .69 |
| 6 | Cough (without a cold) | | | | |
| | No | 2190 | 1.32 | 1.00 | |
| | Yes | 442 | 0.68 | 0.72 (0.21–2.42) | .59 |
| | Fits or convulsions | | | | |
| | No | 2616 | 1.22 | NA | |
| | Yes | 16 | 0.00 | | .66[c] |
| 6–15 | Persistent abdominal pain | | | | |
| | No | 2258 | 1.20 | NA | .43[c] |
| | Yes | 51 | 0.00 | | |
| 6–15 | Ever had heart murmur | | | | |
| | No | 2529 | 1.03 | 1.00 | |
| | Yes | 248 | 2.42 | 2.03 (0.69–6.02) | .20 |
| 7 | Recurrent vomiting | | | | |
| | No | 2264 | 1.15 | 1.00 | |
| | Yes | 194 | 0.52 | 0.61 (0.08–4.55) | .63 |
| 6–10 | Weeks of school absence | | | | |
| | 0–2 | 635 | 1.10 | 1.00 | |
| | 3–4 | 536 | 1.49 | 1.17 (0.41–3.36) | .28 (linear trend) |
| | 5–8 | 629 | 0.79 | 0.58 (0.17–2.00) | |
| | ≥9 | 467 | 1.07 | 0.59 (0.15–2.30) | |
| 6 | Other family members suffering frequent colds | | | | |
| | No | 1594 | 1.00 | 1.00 | |
| | Yes | 1023 | 1.56 | 1.84 (0.82–4.14) | .14 |

[a] Expressed as a percentage of the relevant exposure group.
[b] Adjusted for gender, father's social class, participant's social class and highest level of education.
[c] $\chi^2$ test.

especially as this difference had resolved by the age of 53 years.

## DISCUSSION

### Principal Findings

The use of a large, prospective, population-based cohort allowed us to examine the relationship between self-reported CFS and a number of proposed etiological factors across the life span. Our results show that those who report CFS were more likely to be active and less likely to be overweight before their fatigue symptoms developed. Individuals between the ages of 31 and 43 years who persistently engaged in physical activity on at least a weekly basis were around ten times more likely to report CFS later in life. We found no evidence of increased levels of atopy or childhood illness experiences in those who reported CFS.

### Strengths and Limitations

The strengths of this study include its large size and its prospective nature. The collection of data throughout the first 53 years of participants' lives provided a unique opportunity to analyze behavior and potential risk factors across the life span without recall bias. However, a limitation of this type of research is the potential for attrition bias. In this study, we attempted to reduce the number of participants lost to follow-up by maintaining regular contact with participants through annual birthday cards and regular written communication (32). This resulted in good follow-up rates, given the time length of the study. Despite this, there were significant numbers of individuals who were not able to be followed up, with the greatest attrition rates occurring in the early adult years (25). Those followed up to the end of our study were not totally representative of the sample taken at the beginning. In particular, males, those from poorer families, and those who suffered ill health as children were less likely to be followed up. This attrition bias must be considered when assessing our results, especially in regard to our negative findings relating to childhood illness experiences. There was no evidence of any attrition bias in relation to participants' levels of physical activity as young adults.

**TABLE 3. Prior Atopic Illness and Adjusted Odds Ratios (95% Confidence Intervals (CI)) for a Later Reported Diagnosis of Chronic Fatigue Syndrome (CFS)**

| Age Measured (years) | Variable | Number of Subjects | CFS Diagnosed After This Age (%)[a] | Adjusted Odds Ratio (95% CI)[b] | *p* |
|---|---|---|---|---|---|
| 6–15 | Any childhood asthma | | | | |
| | No | 2694 | 1.15 | | |
| | Yes | 83 | 0.00 | NA | .32[c] |
| 36–43 | Any adult asthma | | | | |
| | No | 2711 | 1.18 | 1.00 | |
| | Yes | 173 | 1.16 | 1.31 (0.31–5.63) | .72 |
| | Ever had hay fever | | | | |
| | No | 2366 | 1.18 | 1.00 | |
| | Yes | 518 | 1.16 | 1.30 (0.52–3.30) | .58 |
| | Any skin trouble such as eczema or psoriasis | | | | |
| | No | 2284 | 1.14 | 1.00 | |
| | Yes | 600 | 1.33 | 1.44 (0.60–3.45) | .42 |
| 43 | Any allergies | | | | |
| | No | 2195 | 1.00 | 1.00 | |
| | Yes | 567 | 0.88 | 1.05 (0.38–2.90) | .92 |
| 6–43 | Lifetime atopic illness | | | | |
| | No | 1646 | 1.15 | 1.00 | |
| | Yes | 1307 | 1.15 | 1.38 (0.63–3.00) | .42 |
| | Any family history of atopic illness | | | | |
| | No | 2258 | 1.24 | 1.00 | |
| | Yes | 611 | 0.98 | 1.01 (0.40–2.56) | .98 |

[a] Expressed as a percentage of the relevant exposure group.
[b] Adjusted for gender, father's social class, participant's social class and highest level of education.
[c] $\chi^2$ test.

The other main limitation of this study is its reliance on self-report of CFS. Due to the nature and scope of the Medical Research Council's National Survey of Health and Development, individual examinations or investigations for specific diagnoses were not possible. However, medical records were accessed allowing the exclusion of any participants who suffered from a psychotic illness or who had a likely medical explanation for their fatigue. In addition, participants provided an estimate of the age at which their fatigue symptoms began which, together with objective measures of fatigue at ages 36 and 43 years, allowed us to establish the temporal nature of any associations. The use of self-reported CFS may provide some additional benefits. Fatigue is a subjective experience that is difficult to define and therefore difficult to measure (33). Any attempt to use structured diagnostic interviews may have led to a failure to capture the phenomena of patients who complain of fatigue in a clinical setting. A post hoc analysis was performed, using only those participants who had received their diagnosis of CFS from a doctor. This analysis confirmed that the associations between adult exercise levels and a later diagnosis of CFS remained in this subgroup, although with some reduced significance, due to a loss of statistical power. The strong association between persistent high frequency exercise (between ages 31 and 43 years) and later reporting of CFS was unchanged in this post hoc analysis (adjusted OR for physician-diagnosed CFS = 10.80; 95% CI = 2.66–43.79; $p = .001$).

Prior estimates of the prevalence of CFS have varied. Population-based studies using a two-stage approach of telephone interviews followed by clinical examinations have produced prevalence estimates of 0.4% and 0.2% (34,35). Other questionnaire-based studies have suggested higher rates of more broadly defined CFS, with prevalence estimates of between 1.4% and 2.4% (36,37). Although the number of individuals who reported a diagnosis of CFS was broadly in line with previous prevalence estimates of self-reported fatigue, the fact that CFS is a relatively rare outcome meant the number of participants reporting CFS was relatively small. This will have reduced the statistical power of this study and increased the chance of Type 2 errors, although the fact we were able to find a series of relatively strong associations suggests this was not a major problem.

**TABLE 4. Prior Physical Activity and Adjusted Odds Ratios (95% Confidence Intervals (CI)) for a Later Reported Diagnosis of Chronic Fatigue Syndrome (CFS)**

| Age Measured (years) | Variable | Number of Subjects | CFS Diagnosed After This Age (%)[a] | Adjusted Odds Ratio (95% CI)[b] | *p* |
|---|---|---|---|---|---|
| 13 | Energy levels (reported by teacher) | | | | |
| | Always tired | 111 | 0.00 | NA | |
| | Normal | 2227 | 0.99 | 1.00 | |
| | Extreme | 192 | 3.13 | 3.58 (1.29–9.93) | .006[c] |
| | Ability at sport (reported by teacher) | | | | |
| | Below average | 355 | 0.28 | 1.00 | |
| | Average | 1702 | 1.12 | 2.79 (0.37–21.26) | |
| | Above average | 458 | 1.75 | 3.40 (0.39–29.46) | .29[c] |
| 31 | Sports or keep fit activities | | | | |
| | Less then weekly | 1120 | 0.89 | 1.00 | |
| | More than weekly | 182 | 2.75 | 3.52 (0.99–12.50) | .05 |
| | Self-rating of fitness | | | | |
| | Not very | 530 | 0.75 | 1.00 | |
| | Fairly | 1762 | 1.19 | 1.23 (0.41–3.72) | |
| | Very | 221 | 2.26 | 2.86 (0.70–11.66) | .19[c] |
| 36 | Physical activity (sports, cycling, walking, work, heavy gardening, or DIY) | | | | |
| | Inactive | 183 | 1.09 | 1.00 | |
| | Less active | 1183 | 0.85 | 1.24 (0.15–10.04) | |
| | More active | 820 | 1.10 | 1.76 (0.22–14.26) | |
| | Very active | 451 | 2.22 | 3.17 (0.39–25.71) | .06[c] |
| 43 | Sports or vigorous leisure activity | | | | |
| | None | 1429 | 0.63 | 1.00 | |
| | 1–4 times a month | 420 | 1.19 | 2.81 (0.74–10.67) | |
| | 4+ times a month | 929 | 1.40 | 4.41 (1.52–12.75) | .006[c] |
| 31–43 | Persistent sport or vigorous physical activity at least oncea week | | | | |
| | No | 1197 | 0.67 | 1.00 | |
| | Yes | 102 | 3.92 | 10.80 (2.66–43.79) | .001 |

[a] Expressed as a percentage of the relevant exposure group.
[b] Adjusted for gender, father's social class, participant's social class and highest level of education.
[c] The *p* value for linear trend.
DIY = do-it-yourself tasks.

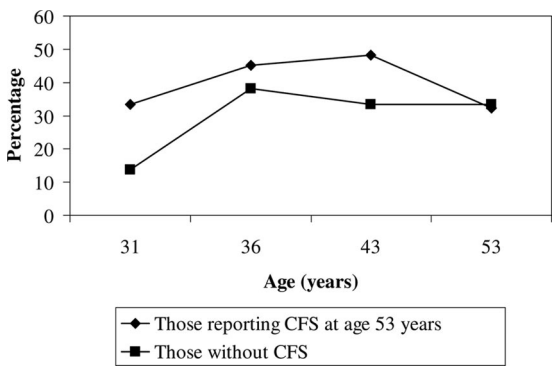


Figure 1. Percentage of participants engaging in exercise more often than weekly. CFS = chronic fatigue syndrome.

Another potential limitation of this study is that our findings are restricted to those who reported CFS at a relatively older age. The majority of those who reported CFS in our sample were female. Although this may reflect a general increase in the prevalence of fatiguing illnesses among females, it may also be due to the additional household and occupational burden encountered by some females in the cohort. Given that we inquired about CFS when the participants were aged 53 years, some of the symptoms reported may also relate to menopause and therefore not be relevant to males or other age groups.

### Exercise and CFS

The increased levels of physical activity seen in those who later went on to report CFS was unexpected and is in contrast

**TABLE 5. Weight and Body Mass Index (BMI) at Various Ages and the Association With a Later Self Reported Diagnosis of Chronic Fatigue Syndrome (CFS)**

| Age | Variable | Mean (SD) in Those With CFS at Age 53 Years | Mean (SD) in Those Without CFS at Age 53 Years | Significance |
|---|---|---|---|---|
| Birth | Weight (g) | 3426 (473) | 3393 (505) | $t$ (2952) = −0.37, $p$ = .71 |
| 7 years | Weight (kg) | 22.4 (3.6) | 22.8 (3.1) | $t$ (2465) = 0.68, $p$ = .50 |
| 36 years | BMI | 22.6 (1.9[a]) | 23.9 (3.6[a]) | $t$ (31.6) = 3.79, $p < .001$ |
| 43 years | BMI | 23.6 (2.8[a]) | 25.1 (4.1[a]) | $t$ (25.0) = 2.78, $p$ = .01 |
| 53 years | BMI | 26.4 (3.6[a]) | 27.4 (4.8[a]) | $t$ (32.2) = 1.59, $p$ = .12 |

[a] Nonequal variance confirmed with variance ratio test; therefore, $t$ test for unequal variance used.

to a previous study that examined childhood exercise levels (24). However, these findings are in keeping with historical accounts given by many patients in a clinical setting. The tendency toward increased risk of later CFS among the most active individuals was also consistent across numerous different measures of physical activity throughout the life span. The finding of lower BMI measurements among those who later went on to develop CFS provides some objective endorsement of the self-reported activity levels. Taken together, these findings provide evidence for a life-long behavioral style of intense physical activity being a risk factor for the development of a chronic fatiguing illness. The effect sizes we report are relatively large, suggesting this association is likely to have some clinical significance.

The observation that those who went on to report a diagnosis of CFS continued to exercise more frequently, even after they had begun to report increased levels of fatigue, is of particular interest. It may be that this persistence of strenuous activity, despite subjective fatigue, is an important initial step in the emergence of a CFS state. Such observations are consistent with many of the patient testimonies reported in self-help literature on CFS, where statements such as "I forced myself to keep going" (38) and rest being "too little, far too late" (39) are common. The observation of continued overactivity, despite emerging fatigue, is also consistent with the current cognitive theories of CFS—in particular, the concept of a cycle of alternating ineffectual rest and frustrated effort (40).

If increased levels of physical activity have a role in the etiology of CFS, then some of the biological theories proposed for the overtraining syndrome (reported in athletes who continue to train in spite of fatigue) may be relevant (41). However, exercise is known to have numerous health benefits with overtraining syndrome being a rare problem. In addition, a limited number of clinical trials have shown exercise may have some benefits as an intervention to prevent fatigue (42,43). It may, therefore, not be the actual process of physical activity, but the associated personality factors and attitudes to health and fitness that are responsible for any link between exercise and CFS. Previous studies have found that various personality traits are associated with CFS (44–46), although these results have not been consistently replicated (47). Van Houdenhove and colleagues have been able to replicate findings of a premorbid "hyperactive" personality or "action-proneness" in individuals with CFS (48,49). They described this personality feature as an orientation toward direct action and achievement and suggested that this may cause individuals to be more prone to develop physical complaints after an incapacitating illness (49). It has been suggested that some individuals may use overactivity as a coping strategy to avoid painful emotions or to maintain self-esteem (50). Such individuals may be more prone to somatic attributions, especially at times when other factors, such as increasing age or recovery from a physical illness, limit their ability to exercise.

### Atopy and Childhood Illness

Our results show that those with atopy in childhood or early adulthood are not at any increased risk of later reporting CFS. This does not necessarily mean that immune system dysfunction has no role in CFS. However, it does provide evidence against chronic, life-long overactivity of the Th2 system, although abnormalities in the Th1/Th2 system may occur later as a consequence of fatigue and its associated symptoms. In contrast to those with medically unexplained symptoms (22), those who reported a diagnosis of CFS did not have increased levels of childhood or parental illness.

## CONCLUSIONS

Individuals who are physically active as children and young adults are more likely to report a diagnosis of CFS in later life. Premorbid childhood and atopic illness do not seem to convey any increased risk of CFS. It is unclear whether the association between increased levels of premorbid physical activity and self-reported CFS is due to the direct effects of this behavior or associated personality traits. The observed pattern of continuing to exercise, despite increasing fatigue, may be an important step in the development of CFS. These findings provide considerable evidence for and against a number of hypotheses relating to the etiology of CFS. A better understanding of these relationships may provide guidance on both the prevention and treatment of this disabling condition.

*We remained independent in our analysis and reporting of these results.*

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