

Your article (# 2005-2307) from Pediatrics is available for download

=====

Dear Dr. van de Putte,

Proofs for your Pediatrics article are now available to be downloaded off the World Wide Web. In an effort to improve our editing process and better serve the needs of Pediatrics authors, we have moved to electronic delivery of all proofs. This allows faster dissemination of proofs and also provides you with the ability to access your proofs from home, the office, a laptop, or anywhere else you have access to the Internet.

Please be aware that, unless we receive an explicit request for traditional delivery, you will no longer receive paper copies in the mail

DOWNLOADING YOUR PROOFS

To download your proofs please click on the link below (or copy and paste the URL into your Web browser if the software you read e-mail with does not support hypertext linking).

<http://rapidproof.cadmus.com/RapidProof/retrieval/index.jsp>

LOGIN: Your e-mail address

PASSWORD: ----

Please find a single PDF file that includes a copy of your typeset proofs in addition to a reprint order form, instructions on marking your proofs, and a survey to let us know what you think about our copyediting.

You will need Adobe Acrobat® Reader software to read these files. This is free software that can be downloaded from the Adobe Web site if you do not already have it installed on your computer:

<http://www.adobe.com/products/acrobat/readstep.html>

If you are unable to access your proofs please contact me at the below telephone number or e-mail address immediately.

REVIEWING YOUR PROOFS

After downloading the PDF file to your computer, please print them out. You may also wish to save the PDF to your computer's hard drive for future reference.

Please read your proofs carefully and thoroughly as this will be your last chance to make changes or corrections! Pay particular attention to tables, equation, and Greek characters to make sure they have been typeset correctly. Please make sure to answer all author queries.

You may either write out your answers to author queries and explain any changes in an e-mail, OR you may mark your answers and corrections directly on the proof. If you mark changes on the proof, we have appended a list of proofreading marks to your proofs to assist you.

RETURNING YOUR PROOFS

We ask that you return your proof revisions **WITHIN 48 HOURS** in order to meet our tight production schedule. Failure to return proofs within 48 hours may result in your article being bumped to a subsequent issue of Pediatrics.

If you anticipate difficulty meeting this deadline, please contact me immediately to make alternate

arrangements.

Proofs may be returned by e-mail, fax, or express mail. All proofs should be returned to my attention at the address or fax number below.

ORDERING REPRINTS

Included in your proofs is a reprint order form. Indicate the number of reprints you wish to order and the method of payment. Please be aware that as the corresponding author you are the only author of your article that will receive this reprint order form. If other authors of your paper wish to order reprints, you will either need to order reprints for them, or forward this reprint order form to them so that they may order reprints themselves.

Please return this reprint order form to our Charlotte, NC office as noted on the form. Reprint orders received after your article is published will be subject to higher reprint costs.

Return all proofs and copyediting surveys to me.

Sincerely,
Kristin Wye-Rodney
Journal Production Manager, Pediatrics
Cadmus Professional Communications
8621 Robert Fulton Dr.
Suite 100
Columbia, MD 21046
USA

Tel: 410-691-6419
Fax: 410-691-6236
E-mail: we-rodneyk@cadmus.com

Proofreader's Marks

MARK	EXPLANATION	EXAMPLE
	TAKE OUT CHARACTER INDICATED	Your proof.
^	LEFT OUT, INSERT	Your proof. ^
#	INSERT SPACE	# Your proof. ^
9	TURN INVERTED LETTER	Your p ^o oof. ^
X	BROKEN LETTER	X Your p ^r oof.
	EVEN SPACE	# A good proof.
○	CLOSE UP: NO SPACE	Your pro ^o gf.
<i>tr</i>	TRANSPOSE	<i>tr</i> A proof ^o oof
<i>wf</i>	WRONG FONT	<i>wf</i> Your proof.
<i>lc</i>	LOWER CASE	<i>lc</i> Your proof.
	CAPITALS	Your proof. <i>caps</i> <u>Your</u> proof.
<i>ital</i>	ITALIC	Your proof. <i>ital</i> <u>Your</u> proof.
<i>rom</i>	ROMAN, NON ITALIC	<i>rom</i> Your <u>proof</u> .
	BOLD FACE	Your proof. <i>bf</i> <u>Your</u> proof.
..... <i>stet</i>	LET IT STAND	Your proof. <i>stet</i> Your proof.
<i>out sc.</i>	DELETE, SEE COPY	<i>out sc.</i> She <u>Our</u> proof.
<i>spell out</i>	SPELL OUT	<i>spell out</i> Queen <u>(Eliz.)</u>
#	START PARAGRAPH	# read. [Your
<i>no #</i>	NO PARAGRAPH: RUN IN	<i>no #</i> marked. → # Your proof.
└	LOWER	└ [Your proof.]

MARK	EXPLANATION	EXAMPLE
┌	RAISE	┌ [Your proof.]
┐	MOVE LEFT	┐ Your proof.
└	MOVE RIGHT	└ Your proof.
	ALIGN TYPE	┐ Three dogs. Two horses.
==	STRAIGHTEN LINE	== Your <u>p</u> roof.
⊙	INSERT PERIOD	⊙ Your proof. ^
;/	INSERT COMMA	;/ Your proof. ^
:/	INSERT COLON	:/ Your proof. ^
;/	INSERT SEMICOLON	;/ Your proof. ^
∨	INSERT APOSTROPHE	∨ Your m ^a n's proof. ^
∨∨	INSERT QUOTATION MARKS	∨∨ Marked it proof. ^ ^
=/	INSERT HYPHEN	=/ A proofmark. ^
!	INSERT EXCLAMATION MARK	! Prove it. ^
?	INSERT QUESTION MARK	? Is it right. ^
Ⓚ	QUERY FOR AUTHOR	Ⓚ <i>was</i> Your proof read by ^
[/]	INSERT BRACKETS	[/] The Smith girl ^ ^
(/)	INSERT PARENTHESES	(/) Your proof. ^ ^
1/m	INSERT 1-EM DASH	1/m Your proof. ^
□	INDENT 1 EM	□ Your proof
▢	INDENT 2 EMS	▢ Your proof.
▣	INDENT 3 EMS	▣ Your proof.

Pediatrics 2006

This is your reprint order form or pro forma invoice

(Please keep a copy of this document for your records.)

Reprint order forms and purchase orders or prepayments must be received 2 weeks before publication either by mail or by fax at 410-820-9765. It is the policy of Cadmus Reprints to issue one invoice per order. Please print clearly.

Author Name _____
Title of Article _____
Issue of Journal _____ Manuscript # 3084690 Publication Date _____
Number of Pages _____ Article # 2005-2307 Symbol PEDIAT
Color in Article? Yes / No (Please Circle)

Please include the symbol and reprint number or manuscript number on your purchase order or other correspondence.

Reprint Costs (Please see page 2 of 2 for reprint costs/fees.)

_____ number of reprints ordered \$ _____
Add color in reprints: \$80 per 100 copies
up to 500 copies \$ _____
_____ number of color reprints ordered for
articles that are published on the **internet**. \$ _____
_____ number of covers ordered, \$80 per first
100 copies plus \$10 for each add'l 100 copies \$ _____
Subtotal \$ _____
Taxes \$ _____

(Add appropriate sales tax for Virginia, Maryland,
Pennsylvania, and the District of Columbia or Canadian GST
to the reprints if your order is to be shipped to these locations.)
Add \$32 for each additional ship location \$ _____

Publication Fees

Color in journal: per quote \$ _____

Total Amount Due \$ _____
(Reprint Costs and Publication Fees)

Ordering Details

Invoice Address

Name _____
Institution _____
Department _____
Street _____
City _____ State _____ Zip _____
Country _____
Phone _____ Fax _____
E-mail Address _____
Purchase Order No. _____

Enclosed:

Personal Check _____
Institutional Purchase Order _____
Credit Card Payment Details _____
Checks must be paid in U.S. dollars and drawn on a U.S. Bank.

Shipping Address (cannot ship to a P.O. Box)

Name _____
Institution _____
Street _____
City _____ State _____ Zip _____
Country _____
Quantity _____ Fax _____
Phone: Day _____ Evening _____

Additional Shipping Address* (cannot ship to a P.O. Box)

Name _____
Institution _____
Street _____
City _____ State _____ Zip _____
Country _____
Quantity _____ Fax _____
Phone: Day _____ Evening _____
* Add \$32 for each additional shipping address

Credit Card Payment Details

Credit Card: ___ VISA ___ Am. Exp. ___ MasterCard
Card Number _____
Expiration Date _____
Please complete invoice address as it appears on credit card statement
Name: _____
Address: _____

Signature _____
**Cadmus will process credit cards and Cadmus Journal
Services will appear on the credit card statement.**

Please send your order form and purchase order or prepayment made payable to:

Cadmus Reprints
P.O. Box 751903
Charlotte, NC 28275-1903

Note: Do not send express packages to this location.

FEIN #: 54-1274108

Signature _____ Date _____
Signature is required. By signing this form, the author agrees to accept the responsibility for the payment of reprints and/or all charges described in this document.

Pediatrics 2006

Reprint and Publication Charges

Reprint Order Forms and Purchase Orders or prepayments must be received 2 weeks before publication.

Please return this form even if no reprints are ordered.

Black and White Reprint Prices

Domestic (USA only)					
# of Pages	100	200	300	400	500
1-4	\$143	\$151	\$163	\$177	\$188
5-8	\$232	\$253	\$276	\$300	\$323
9-12	\$318	\$351	\$389	\$405	\$461
13-16	\$400	\$449	\$497	\$546	\$595
17-20	\$485	\$546	\$609	\$669	\$731

International (includes Canada and Mexico)					
# of Pages	100	200	300	400	500
1-4	\$162	\$185	\$211	\$232	\$259
5-8	\$265	\$312	\$357	\$406	\$452
9-12	\$364	\$433	\$507	\$575	\$648
13-16	\$457	\$552	\$648	\$743	\$839
17-20	\$557	\$675	\$798	\$916	\$1,030

Minimum order is 100 copies. For orders larger than 500 copies or longer than 20 pages, please consult Cadmus Reprints at 800-407-9190.

Color in Reprints

Add \$80.00 per 100 copies (up to 500 copies) to the cost of reprints if the article contains any color in addition to black for articles that appear in the journal. For color articles appearing only on the internet, please refer to the "Color Prices for Internet -only articles" price grid above.

Reprint Covers

For reprint covers (black text printed on white cover), add \$80 for first 100 copies, plus \$10 for additional 100 copies.

Articles Published with Color

If your article contains color illustrations, you were informed of the cost for this service by the Editorial Office. Please state the exact color charge on the reverse side and add to your payment or purchase order accordingly.

Shipping

Shipping costs are included in the reprint prices. Domestic orders are shipped via UPS Ground service. Foreign orders are shipped via an expedited air service. The shipping address printed on an institutional purchase order always supercedes.

Multiple Shipments

Orders can be shipped to more than one location. Please be aware that it will cost \$32 for each additional location.

Color Prices for Internet-only articles.

Domestic (USA only)					
# of Pages	100	200	300	400	500
1-4	\$670	\$685	\$698	\$712	\$725
5-8	\$1,229	\$1,254	\$1,284	\$1,315	\$1,344
9-12	\$1,826	\$1,864	\$1,906	\$1,944	\$1,986
13-16	\$2,294	\$2,360	\$2,406	\$2,493	\$2,566
17-20	\$2,893	\$2,972	\$3,030	\$3,119	\$3,205

International (includes Canada and Mexico)					
# of Pages	100	200	300	400	500
1-4	\$700	\$728	\$764	\$794	\$828
5-8	\$1,272	\$1,336	\$1,400	\$1,468	\$1,534
9-12	\$1,891	\$1,979	\$2,079	\$2,166	\$2,263
13-16	\$2,378	\$2,515	\$2,629	\$2,786	\$2,932
17-20	\$2,997	\$3,161	\$3,309	\$3,483	\$3,653

Delivery

Your order will be shipped within 2 weeks of the journal print date. Allow extra time for delivery.

Tax Due

Residents of Virginia, Maryland, Pennsylvania, and the District of Columbia are required to add the appropriate sales tax to each reprint order. For orders shipped to Canada, please add 7% Canadian GST unless exemption is claimed.

Ordering

Prepayment or a signed institutional purchase order is required to process your order. Please reference journal name and reprint number or manuscript number on your purchase order or other correspondence. You may use the reverse side of this form as a proforma invoice. Please return your order form and purchase order or prepayment to:

Cadmus Reprints
P.O. Box 751903
Charlotte, NC 28275-1903

*Note: Do not send express packages to this location.
FEIN #:541274108*

Please direct all inquiries to:

Anna Sobotor
800-407-9190 (toll free number)
410-819-3996 (direct number)
410-820-9765 (FAX number)
SobotorA@cadmus.com



Dear Author:

The staff of *Pediatrics* is conducting a periodic survey of the accuracy and clarity of our interactions with you during the proofing process of articles. Please answer the following questions and return this form with your corrected page proofs to the address below. You may respond via e-mail or fax if it would be more convenient. Thank you for your time.

In your responses, please indicate the appropriate number from the following scale for each category:

5 = Excellent 4 = Very good 3 = Good 2 = Fair 1 = Unacceptable

CATEGORIES

Copy editing (grammar, style, consistency, and meaning):

Quality: _____ Accuracy: _____

Typesetting (fonts/typefaces, page layout, and presentation):

Quality: _____ Accuracy: _____

Tables (title, column headings, and spacing):

Quality: _____ Accuracy: _____

COMMENTS

Instructions. Were the instructions in this packet easily understood? If not, please tell us what could be better.

Accuracy. Were any errors introduced into your article between its submission and the proofs you just received? If so, please tell us what types of errors (typographic, formatting, attribution, references, etc.).

Reprint order form. Was the reprint order form easy to use? If not, what was confusing?

Yours sincerely,

Kristin Wye-Rodney
Editorial Production Services
Cadmus Professional Communications--Baltimore
8621 Robert Fulton Dr., Suite 100 / Columbia, MD 21046
(410) 691-6419 / (410) 691-6236 fax
wye-rodneyk@cadmus.com

ARTICLE

Mirrored Symptoms in Mother and Child With Chronic Fatigue Syndrome

Elise M. van de Putte^a, Lorenz J. P. van Doornen^b, Raoul H. H. Engelbert^c, Wietse Kuis^a, Jan L. L. Kimpen^a, Cuno S. P. M. Uiterwaal^d

Departments of ^aPediatrics and ^cPediatric Physical Therapy and Pediatric Exercise Physiology, Wilhelmina Children's Hospital, University Medical Center, Utrecht, Netherlands; ^bDepartment of Health Psychology, University Utrecht, Utrecht, Netherlands; ^dJulius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, Netherlands

AQ: A

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

AQ: B

OBJECTIVE. Our aim with this study was to assess the relation between chronic fatigue syndrome in adolescents and fatigue and associated symptoms in their fathers and mothers, more specifically the presence of chronic fatigue syndrome-like symptoms and psychologic distress.

METHOD. In this cross-sectional study, 40 adolescents with chronic fatigue syndrome according to the Centers for Disease Control and Prevention criteria were compared with 36 healthy control subjects and their respective parents. Questionnaires regarding fatigue (Checklist Individual Strength), fatigue-associated symptoms, and psychopathology (Symptom Checklist-90) were applied to the children and their parents.

RESULTS. Psychologic distress in the mother corresponds with an adjusted odds ratio of 5.6 for the presence of CFS in the child. The presence of fatigue in the mother and dimensional assessment of fatigue with the Checklist Individual Strength revealed odds ratios of, respectively, 5.29 and 2.86 for the presence of chronic fatigue syndrome in the child. An increase of 1 SD of the hours spent by the working mother outside the home reduced the risk for chronic fatigue syndrome in their child with 61%. The fathers did not show any risk indicator for chronic fatigue syndrome in their child.

CONCLUSIONS. Mothers of adolescents with chronic fatigue syndrome exhibit fatigue and psychologic symptoms similar to their child in contrast with the fathers. The striking difference between the absent association in fathers and the evident association in mothers suggests that the shared symptom complex of mother and child is the result of an interplay between genetic vulnerability and environmental factors.

www.pediatrics.org/cgi/doi/10.1542/peds.2005-2307

doi:10.1542/peds.2005-2307

Key Words

chronic fatigue syndrome, familial aggregation, family health, risk, psychopathology

Abbreviations

CFS—chronic fatigue syndrome
CDC—Centers for Disease Control and Prevention
CIS-20—Checklist Individual Strength
SCL-90-R—revised Symptom Checklist
CDI—Children's Depression Inventory
OR—odds ratio
95% CI—95% confidence interval

Accepted for publication Nov 22, 2005

Address correspondence to Elise M. van de Putte, KE04.133.1, Wilhelmina Children's Hospital, University Medical Center Utrecht, PO Box 85090, 3508 AB Utrecht, Netherlands.
E-mail: e.vandeputte@wkz.azu.nl

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2006 by the American Academy of Pediatrics

A MAJOR CONSENSUS in modern pediatric practice is that a child's health is profoundly influenced by family structure, family dynamics, and family functioning.¹ Nevertheless, remarkably little is known about family health and about how families develop illness-promoting or illness-preventing strategies.² Especially in unexplained illnesses, these family factors could elucidate part of the complex multifactorial etiology. Chronic fatigue syndrome (CFS) is such an illness and is characterized by chronic disabling fatigue, pain, sleep difficulties, and cognitive impairment. CFS is not restricted to adults but is increasingly recognized in adolescents and children.³

Fatigue seems to aggregate in families. In a large study of twins aged over 50, Hickie found that familial aggregation of fatigue of at least 1 month's duration seemed to be largely the result of genetic factors with a 2.5 times higher concordance rate in monozygotic twins than in dizygotic twins.⁴ These results resemble those of a child twin study, in which the parents' reports of disabling fatigue of 1 month's duration in their children revealed a concordance rate of 0.75 in monozygotic twins versus 0.47 in dizygotic twins.⁵

Not only fatigue but also CFS aggregates in families. Buchwald performed a large twin study on chronic fatigue and CFS, and revealed a concordance rate for CFS of 0.55 in monozygotic and 0.19 in dizygotic twins,⁶ confirming the familial aggregation of CFS and suggesting that genes may play a role. In a family history study of CFS, results based on subjects' reports of illness in first-degree relatives suggested that relatives of patients with CFS had significantly higher rates of CFS than relatives of a patient with another chronic illness.⁷ Garalda⁸ found more health problems in a cross-sectional study in the families of adolescents with a history of CFS than in the families of healthy control subjects, but it is not clear whether these health problems were CFS-like. Several years earlier, Bell⁹ estimated from a cluster of 21 pediatric cases of CFS that familial CFS is a major risk factor for pediatric CFS.

All these findings suggest a familial predisposition for CFS of varying intensities but do not discriminate between a distinct incidence for the fatigue symptoms in fathers or mothers.

Because fatigue is necessarily associated with other somatic symptoms¹⁰ and often is accompanied by depression and anxiety,¹¹ a family survey should deal with this cluster of symptoms.

The aim of this study was to assess the relation between CFS in adolescents and fatigue and associated symptoms in fathers and mothers, more specifically the presence of CFS-like symptoms and psychologic distress.

METHODS

Population

A total of 70 adolescents (aged 12–18 years) was referred with severe fatigue to a specific CFS clinic of the Uni-

versity Medical Center Utrecht between June 2003 and September 2004. All patients were investigated by a pediatrician and the final diagnosis of CFS was established by 1 pediatrician (E.v.d.P.) in 47 adolescents after medical and psychologic examinations using specific Dutch questionnaires for anxiety and depression in combination with an interview of both child and parent. Additional to the Centers for Disease Control and Prevention (CDC) exclusion criteria, patients with somatic comorbidity interfering with fatigue were excluded ($N = 4$ [1 hyperhomocysteinemia, 1 celiac disease, 1 irritable bowel syndrome, and 1 delayed-phase sleep syndrome]). One patient was excluded because of severe depression requiring pharmaceutical treatment. Two adolescents refused to participate. Of the remaining 40 included adolescents, 36 fulfilled all criteria for CFS of the CDC.¹⁰ Four patients had <4 side symptoms but were nevertheless included. The mean number of the 8 CDC side symptoms was 5.2 (SD: 1.6). Forty mothers and 34 fathers participated. The remaining 6 fathers lost contact with their child after a divorce.

As a reference group, 102 adolescents aged 12 to 18 years from a secondary school were invited to participate with their parents. Families with an adoptive child or a child with a chronic illness were excluded ($n = 3$). From the remaining 99 adolescents, 36 adolescents (37%) agreed to participate, including 4 pairs of siblings. Two fathers and 2 mothers refused to participate, leaving 30 mothers and 30 fathers for participation.

Self-Report Measures

Fatigue was assessed dimensionally in all participants with the Checklist Individual Strength (CIS-20), which asks about fatigue in the 2 weeks before the assessment. There are 4 subscales: subjective experience of fatigue, concentration, motivation, and physical activity, each item scored on a Likert scale (scored 1–7). A high score indicates a high level of subjective fatigue and concentration problems and a low level of motivation and physical activity. The internal consistency is high as is the discriminative validity for CFS.¹²

The revised Symptom Checklist (SCL-90-R), a 90-item self-report scale, was used to assess current psychologic distress in parents on 9 subscales: somatization, obsession, interpersonal sensitivity, depression, anxiety, aggression, phobia, paranoia, psychoticism, and additional items.^{13–15} The questionnaire asks about the presence of a symptom in the preceding week, including the day of assessment, on a 5-point Likert scale (range: 1–5). The higher the score, the more psychologic distress.

A general questionnaire was applied to all parents regarding demographic data (eg, age, household size), hours of paid work, and current presence of fatigue and the 8 CDC symptoms for CFS (yes/no).

A sleep questionnaire was applied to all participants to measure sleep in the 2 weeks before the assessment

with 14 dichotomic scored items. The total score is a measure of sleep quality; the higher the score, the poorer the quality.¹⁶

Depression in adolescents was measured with a validated Dutch translation of the Children's Depression Inventory (CDI).^{17,18} The CDI quantifies depressive symptoms in the past 2 weeks and consists of 27 items rated on a 3-point scale (range: 0–2).

Assessment of trait anxiety in adolescents was performed with a Dutch translation of the Spielberger State-Trait Anxiety Inventory for Children.^{19,20} The Spielberger State-Trait Anxiety Inventory for Children consists of 20 statements on a 3-point scale that assess the level of anxiety a person reports as generally characteristic of himself or herself (disposition).

Somatic complaints were assessed with a validated Dutch translation of the Children's Somatization Inventory), a self-report questionnaire rating the presence of each of 35 somatic symptoms in the preceding 2 weeks using a 5-point Likert scale ranging from "not at all" to "a whole lot" (range: 0–4).^{21,22}

All questionnaires were completed individually in separate rooms in a university building in May through August 2004. The adolescents completed the questionnaires on average in 30 minutes and the parents in 20 minutes.

The medical ethics committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from both adolescents and parents.

Statistical Analysis

Of the relevant variables, group-specific means and SDs or proportions were calculated for descriptive purposes.

The data were analyzed with linear regression using the variable of interest as dependent variable and a group indicator (patient, 1; control, 0) as independent variable to explore group differences. Results are pre-

sented as linear regression coefficients representing mean differences between the adolescents with CFS and the healthy control subjects for the investigated parameter with their corresponding 95% confidence intervals (CIs). The same models were used to adjust for possible confounding factors.

The magnitude of the associations between parental risk indicators and CFS in their offspring was quantified by estimating odds ratios (ORs) and respective 95% CIs using binary logistic regression with CFS (yes/no) as the dependent variable and the factors of interest as the independent variable. These factors were transformed into z scores to obtain relative risks per SD difference. The adjusted OR was quantified in the same model by adding possible confounding factors as covariates (age and gender of the child and the age of the parent concerned).

To account for possible differential nonresponse of the control group, we checked for the presence of fatigue and past or present psychologic treatment in the nonresponding parents (63 families) and adolescents (results from the Fatigue in Teenagers-I study 2002).²³

RESULTS

Table 1 shows that both adolescent groups had the same gender composition, but the CFS adolescents were slightly younger (16 vs 16.8 years). Both groups came from a high percentage of intact families with exactly the same number of siblings.

Evidently, the patients with CFS showed a higher score on all the subscales of the CIS-20 than the healthy adolescents. Sleeping problems were more prominent in the CFS group as were somatic complaints. Anxiety was more manifest in the adolescents with CFS just like depression. The mean CDI score for depression in the adolescents with CFS (11.7) is below that for a depressive disorder, which is 22.8 in a Dutch and Belgian reference sample of 18 children with a depressive disorder.

TABLE 1 Characteristics of Adolescents With CFS and Healthy Control Subjects

	CFS (n = 40)	Healthy (n = 36)	Difference (95% CI)	P	Adjusted Difference (95% CI) ^a	P
Mean symptom duration (SD), mo	23.4 (11.3)	NA				
Age, mean (SD), y	16.0 (1.5)	16.8 (1.4)	0.8 (–1.5 to –0.1)	0.019		
Gender, % girls	78	67	11 (–10 to 31)	0.298		
Intact families, %	82	93	–9 (–27 to 5)	0.185		
Household size (No. of children), mean (SD)	2.5 (0.8)	2.5 (0.8)	0 (–0.3 to 0.3)	0.954		
Fatigue assessment, mean (SD)						
Total score CIS-20 (20 items; 20–140)	101.8 (17.8)	48.0 (18.8)	53.9 (45.5 to 62.2)	0.0001	50.8 (42.4 to 59.2)	.0001
Score subjective fatigue subscale (8 items; 8–56)	46.9 (7.4)	19.4 (10.0)	27.5 (23.5 to 31.5)	0.0001	26.0 (21.9 to 30.0)	.0001
Sleep problems (14 items; 0–14)	6.2 (3.2)	2.8 (2.9)	3.4 (2.0 to 4.8)	0.0001	3.4 (1.9 to 4.9)	.0001
Somatic complaints (CIS 35 items; 0–140)	35.6 (20.1)	13.0 (9.3)	22.6 (15.5 to 29.7)	0.0001	19.9 (12.6 to 27.1)	.0001
Psychologic adjustment, mean (SD)						
Anxiety disposition (Spielberger State-Trait Anxiety Inventory for Children; 20 items; 20–60)	36.9 (7.8)	30.3 (6.4)	6.6 (3.3 to 9.9)	0.0001	5.9 (2.5 to 9.3)	.001
Depression disposition (CDI; 27 items; 0–54)	11.7 (6.1)	5.6 (4.4)	6.1 (3.7 to 8.5)	0.0001	6.1 (3.5 to 8.7)	.0001

^a Adjusted for age and gender.

der.²⁴ A cutoff score of ≥ 16 is proposed as predictive of a depressive disorder.²⁴ In our study, only 1 of the healthy adolescents scored ≥ 16 compared with 6 of the adolescents with CFS.

All differences between the healthy adolescents and the adolescents with CFS were statistically significant, and adjusting for age and gender did not influence the results.

The comparisons of the characteristics of the mothers and the fathers are shown separately in Table 2 and Table 3, respectively. Mothers of adolescents with CFS differed from mothers of healthy adolescents in all measurements of fatigue and fatigue-associated symptoms, including sleep. Nine mothers even fulfilled CDC criteria for CFS.¹⁰ The presence of fatigue in the mother and dimensional assessment of fatigue with the CIS-20 revealed an OR of, respectively, 5.3 (95% CI: 1.3 to 21.2) and 2.9 (95% CI: 1.4 to 5.8) for the presence of CFS in the child. Self-reported psychologic distress was significantly higher, especially in the subscales somatization, depression, and anxiety. Psychologic distress in the mother corresponded with a 5.6 times higher chance for the presence of CFS in the child (95% CI: 1.9 to 16.8) with depression as the main risk factor.

An increase of 1 SD of the hours spent by the working mother outside the home reduced the risk for CFS in their child with 61% (OR: 0.39; 95% CI: 0.20 to 0.75). None of the ORs of the same variables of the fathers were different from 1.

The nonresponding mothers ($n = 63$) of the control group mentioned fatigue in 19% and psychologic treatment in 13% (compared with, respectively, 17% and 13% of the responding mothers in this study). The nonresponding adolescents were more fatigued (CIS-20 score: 55.7) than the responding adolescents, leading to a nonsignificant difference in the CIS-20 score of -7.7 (95% CI: -15.7 to 0.2 ; $P = .06$).

DISCUSSION

This is the first study comparing families with a physician-diagnosed CFS proband with healthy families. Our study revealed a shared symptom complex of fatigue, fatigue-associated symptoms, and psychologic distress between adolescents with CFS and their mothers. A similar association between adolescents with CFS and their fathers was not found.

Associated emotional distress and psychopathology are commonly reported in adults and children with CFS.²⁵⁻²⁷ The origin of this psychologic morbidity in CFS has not yet been clarified. Possibly it shares a common etiology with CFS or one is the result of the other. It is remarkable, however, that in our study, the same symptom complex is uncovered in both mother and child. The striking difference between the absent association in fathers and the evident association in mothers suggests that the shared symptom complex of mother and child is the result of an interplay between genetic susceptibility and environmental factors. It may point to a gene-environment interaction in which the child not only inherits the genetic characteristics of the mother, but these maternal characteristics also function as environmental factors for the child.

There is evidence for genetic factors to play a role in the cause of CFS. All twin studies on CFS or less strictly defined fatigue reveal a higher concordance rate among monozygotic twins.⁴⁻⁶ Female gender is a risk factor for CFS as is clear from prevalence studies and from the twin studies. If CFS is assumed to be a multifactorial illness, monogenetic inheritance will be unlikely. The twin study of Hickie et al revealed independent genetic factors for fatigue only (44%) and common genetic factors for psychologic distress and fatigue.⁴ Accordingly, mothers and children may share a genetic tendency for fatigue and psychologic distress and a genetic susceptibility to environmental influences both beyond and within the family. The nature of this susceptibility is

TABLE 2 ORs for Characteristics of Mothers and the Presence of CFS in the Adolescent

	CFS ($n = 40$)	Healthy ($n = 30$)	OR _{uni} (95% CI)	P	OR _{adj} ^a (95% CI)	P
Age, mean (SD), y	45.1 (4.9)	47.4 (3.1)	0.6 (0.3 to 1.0)	.041	0.8 (0.4 to 1.6)	.533
Measures of psychologic distress						
SCL-90, mean (SD)	128.1 (29.4)	111.9 (16.1)	2.5 (1.2 to 5.2)	.016	5.6 (1.9 to 16.8)	.002
Depression, mean (SD)	20.2 (6.0)	16.5 (3.0)	3.0 (1.4 to 6.6)	.006	8.4 (2.2 to 31.6)	.002
Anxiety, mean (SD)	13.1 (3.8)	11.6 (2.0)	1.9 (0.9 to 3.6)	.074	3.0 (1.1 to 8.0)	.034
Somatization, mean (SD)	18.7 (6.5)	15.7 (3.7)	2.0 (1.0 to 3.9)	.037	3.1 (1.3 to 7.4)	.010
Measures of fatigue and fatigue-related symptoms						
Subjective fatigue, mean (SD)	28.5 (13.4)	19.2 (7.7)	2.0 (1.2 to 3.5)	.015	2.2 (1.2 to 4.2)	.015
CIS-20, mean (SD)	60.7 (27.6)	43.1 (12.4)	2.5 (1.3 to 4.7)	.004	2.9 (1.4 to 5.8)	.004
Fatigue present, n (%)	45 (50)	17 (38)	4.1 (1.3 to 12.9)	.016	5.3 (1.3 to 21.2)	.019
No. of CDC criteria present (SD)	2.4 (2.4)	1.0 (1.7)	1.4 (1.1 to 1.9)	.016	1.5 (1.1 to 2.2)	.020
Sleep score, mean (SD)	4.2 (3.7)	2.3 (2.7)	1.9 (1.1 to 3.4)	.027	2.2 (1.2 to 4.3)	.015
Daily work outside the home, mean (SD), h/wk	14.3 (13.0)	24.5 (8.6)	0.4 (0.2 to 0.7)	.002	0.4 (0.2 to 0.8)	.005

^aOR_{adj} was adjusted for age and gender of the child and age of the parent.

TABLE 3 ORs for Characteristics of Fathers and the Presence of CFS in the Adolescent

	CFS (n = 40)	Healthy (n = 30)	OR _{uni} (95% CI)	P	OR _{adj} (95% CI) ^a	P
Age, mean (SD), y	48.2 (4.7)	50.3 (3.3)	0.6 (0.3 to 1.0)	.060	0.6 (0.3 to 1.2)	.147
Measures of psychologic distress						
SCL-90, mean (SD)	112.0 (23.8)	112.7 (18.5)	1.0 (0.6 to 1.6)	.896	1.1 (0.6 to 1.9)	.794
Measures of fatigue and fatigue-related symptoms						
Subjective fatigue, mean (SD)	21.1 (10.8)	20.3 (17.7)				
CIS-20, mean (SD)	49.2 (20.5)	48.9 (28.4)	1.0 (0.6 to 1.7)	.955	1.2 (0.7 to 2.2)	.465
Fatigue present, n (%)	24 (43.1)	26 (44)	0.9 (0.3 to 2.7)	.831	1.1 (0.3 to 4.1)	.891
No. of CDC criteria present, mean (SD)	1.1 (1.4)	1.0 (1.5)	1.0 (0.7 to 1.4)	.940	1.2 (0.8 to 1.7)	.476
Sleep score, mean (SD)	2.0 (2.9)	1.4 (1.6)	1.3 (0.8 to 2.3)	.328	1.4 (0.8 to 2.5)	.314
Daily work outside the house, mean (SD), h/wk	34.4 (12.6)	31.9 (17.8)	1.2 (0.7 to 2.1)	.548	1.2 (0.6 to 2.3)	.606

^a OR_{adj} was adjusted for age and gender of the child and age of the parent.

unknown and genetic research is hampered by the lack of a possible biologic substrate, an endophenotype, for the symptoms of CFS. Occasionally, one causal biologic factor for CFS has been explored, like homozygosity for the serine allele of the CBG gene.²⁸

Potential shared environmental factors beyond the family are infections, like Epstein-Barr virus and other enteroviruses and herpesviruses, or intolerance to certain chemicals.²⁹⁻³¹ However, these external environmental factors are potentially harmful for all family members and do not explain the difference in risk indicators between fathers and mothers, which means that other risk factors are necessarily involved for developing CFS.

Shared environmental factors within the family are illness attitudes, illness beliefs, and illness behavior. It has been shown that parental reinforcement of illness behavior is higher in children with CFS compared with children with juvenile rheumatoid arthritis. The parent (not explicitly the mother or the father) of teens with CFS experienced more concern and behaved in a more protective fashion with their teens, thereby reinforcing their illness behavior.³² Viewed in this respect, the striking lower amount of working hours in mothers with an adolescent with CFS, with consequently more time to spend within the family with their ill child, could be quite relevant.

Another explanation for the shared symptom complex between mother and child is the possibility that the symptoms seen in the child are a reaction to a primary illness of the mother. The cross-sectional design of our study makes causal inference from the results impossible. However, we know from other studies in depressed mothers that their children are at increased risk for a series of behavioral disorders and depression through different mechanisms, like reduction of parental tolerance, social problem-solving, and coping skills.^{33,34} However, a recently published longitudinal study on risk factors for CFS did not reveal preceding maternal psychopathology or parental illness (measured with the General Health Questionnaire) as risk factors for the

lifetime prevalence of self-reported CFS.²⁷ The time interval between the measurement of maternal psychopathology (at age 10 and 15 of the child) and that of lifetime prevalence of CFS (at the age of 30) was large. A smaller time interval is perhaps necessary to reveal these maternal symptoms as risk factors for CFS in their children.

Finally, the established symptoms in the mothers of adolescents with CFS may constitute a reaction of the mother to the illness of the child. From other chronic illnesses in children, we know that a reactive pattern predominated by depressive symptoms of the mother is possible, especially at the start of the illness.³⁵ From this study, we cannot conclude whether the health symptoms in the mother of an adolescent with adolescent are specific or also apply to mothers of children with other chronic illnesses. A recent study of Rangel suggests that the pattern of emotional reactions and health problems is quite specific for the parents of the child with CFS in comparison with juvenile rheumatoid arthritis and emotional disorders.³⁶ She found more psychopathology in CFS families than in families with a child with juvenile rheumatoid arthritis. A distinction between the parents was not made. The CFS families exhibited a pattern of emotional overinvolvement compared with the parents of a child with juvenile rheumatoid arthritis.³⁶ Another, retrospective study also established this maternal overprotectiveness in patients with CFS.³⁷

CONCLUSIONS

The clustering of symptoms in mother and child suggests genetic transfer and gene-environment interaction. The preferential choice of treatment for CFS at this time is cognitive behavioral therapy. A randomized, controlled trial in adolescents established a recovery rate of ~60%.³⁸ It is not clear which factors influence this recovery rate. Purely behavioral models of treatment of the adolescents with CFS may neglect these risk indicators in the mother and thereby overlook these potentially important perpetuating factors.

ACKNOWLEDGMENTS

We thank the patients with chronic fatigue syndrome and the children of the secondary school De Breul in Zeist and their respective parents for their willingness to participate in this study.

REFERENCES

- Schor EL. Family pediatrics: Report of the Task Force on the Family. *Pediatrics*. 2003;111:1541–1571
- Eccleston C, Malleon P. Managing chronic pain in children and adolescents. We need to address the embarrassing lack of data for this common problem. *BMJ*. 2003;326:1408–1409
- Chalder T, Goodman R, Wessely S, Hotopf M, Meltzer H. Epidemiology of chronic fatigue syndrome and self reported myalgic encephalomyelitis in 5–15 year olds: cross sectional study. *BMJ*. 2003;327:654–655
- Hickie I, Kirk K, Martin N. Unique genetic and environmental determinants of prolonged fatigue: a twin study. *Psychol Med*. 1999;29:259–268
- Farmer A, Scourfield J, Martin N, Cardno A, McGuffin P. Is disabling fatigue in childhood influenced by genes? *Psychol Med*. 1999;29:279–282
- Buchwald D, Herrell R, Ashton S, et al. A twin study of chronic fatigue. *Psychosom Med*. 2001;63:936–943
- Walsh CM, Zainal NZ, Middleton SJ, Paykel ES. A family history study of chronic fatigue syndrome. *Psychiatr Genet*. 2001;11:123–128
- Garralda E, Rangel L, Levin M, Roberts H, Ukoumunne O. Psychiatric adjustment in adolescents with a history of chronic fatigue syndrome. *J Am Acad Child Adolesc Psychiatry*. 1999;38:1515–1521
- Bell KM, Cookfair D, Bell DS, Reese P, Cooper L. Risk factors associated with chronic fatigue syndrome in a cluster of pediatric cases. *Rev Infect Dis*. 1991;13(suppl 1):S32–S38
- Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med*. 1994;121:953–959
- Smith MS, Martin-Herz SP, Womack WM, Marsigan JL. Comparative study of anxiety, depression, somatization, functional disability, and illness attribution in adolescents with chronic fatigue or migraine. *Pediatrics*. 2003;111(4). Available at: www.pediatrics.org/cgi/content/full/111/4/e376
- Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res*. 1994;38:383–392
- Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol*. 1977;16:347–356
- Derogatis LR. *SCL-90-R Administration, Scoring & Procedures. Manual I. For the R(evised) Version and Other Instruments of the Psychopathology Rating Scale Series. Clinical Psychometric Research*. Baltimore, MD: John Hopkins University School of Medicine; 1977
- Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behav Sci*. 1974;19:1–15
- Verhelst MMR, Kerkhof GA, Schimsheimer RJ. Objective sleep quality versus subjective sleep quality in 332 patients. *J Sleep Res*. 2000;9(suppl 1):200
- Kovacs M. The Children's Depression Inventory (CDI). *Psychopharmacol Bull*. 1985;21:995–998
- Timbremont B, Braet C. Psychometrische evaluatie van de Nederlandstalige Children's Depression Inventory. *Gedrags therapie*. 2001;34:229–242
- Papay JP, Spielberger CD. Assessment of anxiety and achievement in kindergarten and first- and second-grade children. *J Abnorm Child Psychol*. 1986;14:279–286
- Houtman IL, Bakker FC. The anxiety thermometer: a validation study. *J Pers Assess*. 1989;53:575–582
- Walker LS, Garber J, Greene JW. Somatization symptoms in pediatric abdominal pain patients: relation to chronicity of abdominal pain and parent somatization. *J Abnorm Child Psychol*. 1991;19:379–394
- Meesters C, Muris P, Ghys A, Reumerman T, Rooijmans M. The Children's Somatization Inventory: further evidence for its reliability and validity in a pediatric and a community sample of Dutch children and adolescents. *J Pediatr Psychol*. 2003;28:413–422
- van de Putte EM, Engelbert RH, Kuis W, Sinnema G, Kimpen JL, Uiterwaal CS. Chronic fatigue syndrome and health control in adolescents and parents. *Arch Dis Child*. 2005;90:1020–1024
- Timbremont B, Braet C, Dreessen L. Assessing depression in youth: relation between the Children's Depression Inventory and a structured interview. *J Clin Child Adolesc Psychol*. 2004;33:149–157
- Garralda ME, Rangel L. Annotation: chronic fatigue syndrome in children and adolescents. *J Child Psychol Psychiatry*. 2002;43:169–176
- Rangel L, Garralda ME, Hall A, Woodham S. Psychiatric adjustment in chronic fatigue syndrome of childhood and in juvenile idiopathic arthritis. *Psychol Med*. 2003;33:289–297
- Viner R, Hotopf M. Childhood predictors of self reported chronic fatigue syndrome/myalgic encephalomyelitis in adults: national birth cohort study. *BMJ*. 2004;329:941
- Torpy DJ, Bachmann AW, Gartside M, et al. Association between chronic fatigue syndrome and the corticosteroid-binding globulin gene ALA SER224 polymorphism. *Endocr Res*. 2004;30:417–429
- Ablashi DV. Viral studies of chronic fatigue syndrome. *Clin Infect Dis*. 1994;18(suppl 1):S130–S133
- Cope H, David A, Pelosi A, Mann A. Predictors of chronic "postviral" fatigue. *Lancet*. 1994;344:864–868
- Bell IR, Baldwin CM, Schwartz GE. Illness from low levels of environmental chemicals: Relevance to chronic fatigue syndrome and fibromyalgia. *Am J Med*. 1998;105:74S–82S
- Brace MJ, Scott SM, McCauley E, Sherry DD. Family reinforcement of illness behavior: A comparison of adolescents with chronic fatigue syndrome, juvenile arthritis, and healthy controls. *J Dev Behav Pediatr*. 2000;21:332–339
- Kahn RS, Brandt D, Whitaker RC. Combined effect of mothers' and fathers' mental health symptoms on children's behavioral and emotional well-being. *Arch Pediatr Adolesc Med*. 2004;158:721–729
- Rutter M. Commentary: some focus and process considerations regarding effects of parental depression on children. *Dev Psychol*. 1990;26:60–67
- Kovacs M, Iyengar S, Goldston D, Obrosky DS, Stewart J, Marsh J. Psychologic functioning among mothers of children with insulin-dependent diabetes mellitus: a longitudinal study. *J Consult Clin Psychol*. 1990;58:189–195
- Rangel L, Garralda ME, Jeffs J, Rose G. Family health and characteristics in chronic fatigue syndrome, juvenile rheumatoid arthritis, and emotional disorders of childhood. *J Am Acad Child Adolesc Psychiatry*. 2005;44:150–158
- Fisher L, Chalder T. Childhood experiences of illness and parenting in adults with chronic fatigue syndrome. *J Psychosom Res*. 2003;54:439–443
- Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *BMJ*. 2005;330:14

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

1

AQA—AUTHOR: Please provide the highest academic degree(s) earned for each author.

AQB—AUTHOR: Note that all statistical values were deleted from the abstract per journal style. Also, per journal style, all abstracts must be less than 300 words and fit completely onto the first page of the article (note also that no abbreviations can be used). If your abstract extends onto the second page, please edit as necessary so that it fits entirely on the first page (if necessary, include or e-mail an electronic text file with the new abstract).

AQC—AUTHOR: Please verify that the correct units are shown in each row of the tables or edit where necessary.
