
Correlation of psychological and physical symptoms with chronically elevated cytokine levels associated with a common immune dysregulation

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Background: Chronically elevated levels of proinflammatory cytokines are associated with inflammatory diseases and psychological symptoms of depression and tiredness.

Objective: To test the prediction that, in a healthy population without medically diagnosed diseases, psychological symptoms (depression and tiredness) associated with proinflammatory cytokines correlate with physical symptoms associated with inflammatory disease.

Methods: A total of 1,143 women between 45 and 65 years old completed a health complaint checklist containing 11 target symptoms (5 related to allergy, 4 to gastrointestinal symptoms, and 2 to pain), 7 control symptoms or health complaints, and 2 psychological symptoms (depression and tiredness). They also completed a menopausal quality-of-life questionnaire; to compensate for response bias, we removed variance attributable to quality of life.

Results: The partial correlations show that tiredness (but not depression) correlated with 9 of the 11 target symptoms ($P < .001$) but with 0 of the 7 control symptoms or complaints. Symptoms of both the specific and the systemic components of inflammatory disease are correlated in a healthy population.

Conclusion: Immune dysregulation may explain the existence and covariation of psychological and physical symptoms in the healthy population, including people with medically unexplained symptoms.

Ann Allergy Asthma Immunol. 2007;99:348–351.

INTRODUCTION

Asthma, eczema, and rhinitis are allergic diseases that merge imperceptibly with normality: allergic symptoms are found in the healthy population. Similarly, the symptoms of inflammatory bowel disease, irritable bowel syndrome, and esophageal reflux merge with normality, as do the symptoms of osteoarthritis. It is thought that diseases of immune dysregulation have, in addition to the disease-specific component, a systemic component comprising circulating proinflammatory cytokines, and this systemic component has been recorded for allergic diseases,^{1–5} gastrointestinal diseases,^{6–9} osteoarthritis,^{10,11} and rheumatoid arthritis.¹² It is, therefore, possible that this systemic proinflammatory component of increased cytokines is responsible for subclinical symptoms in a healthy population.

Systemic proinflammatory cytokines are associated with psychological symptoms (eg, tiredness is associated with tumor necrosis factor α ¹³ and with interleukin 6 [IL-6] in patients with cancer,¹⁴ and tumor necrosis factor α and IL-6

are associated with major depression¹⁵ and humor or laughter¹⁶). Elevated IL-6 is also associated with reduced positive affect.¹⁷ The exact form of the relationship and mechanisms linking cytokines (individually and in combination) and particular symptoms have yet to be elucidated. If subclinical physical symptoms (ie, symptoms in a healthy population) are also associated with increased levels of proinflammatory cytokines, then they should correlate with tiredness, depression, or both. The purpose of this study was to investigate, in a community sample, the relation between allergic, gastrointestinal, and arthritic symptoms on the one hand and tiredness and depression on the other hand.

Symptoms are measured through self-report, and all self-report measurements are subject to a variety of response biases. Thus, a correlation between physical and psychological symptoms may not be because of true variance shared by these symptoms but because of common variance created by a shared response bias. For example, some people are more likely to recognize and report symptoms because of neuroticism or social desirability; all forms of health reporting correlate with neuroticism.¹⁸ To compensate for response bias shared by physical and psychological scales, we measured quality of life (QOL). The QOL evaluation correlates highly with neuroticism and is subject to the same set of response biases as symptom evaluation. Therefore, partial correlations between the physical and psychological symptoms after controlling for QOL will provide an estimate of the true associ-

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Authors have nothing to disclose.

Mr Whalley was supported by an Economic and Social Research Council studentship award.

Received for publication March 19, 2007.

Received in revised form June 15, 2007.

Accepted for publication June 19, 2007.

ation between physical and psychological symptoms, by excluding the common variance created by response bias. In addition, as a validating check, we measured health complaints and symptoms that are not associated with a chronic inflammatory disease. Such complaints are unlikely to be linked to chronically elevated levels of proinflammatory cytokines (in contrast to short-term elevation) and so they should not correlate with trait depression or tiredness after controlling for QOL.

METHODS

Participant Recruitment

A random sample of 3,000 women between 45 and 65 years old (500 each from 6 Health Authority patient lists in England and Wales) were sent anonymous postal questionnaires with free postal envelopes for return. The 6 Health Authorities were chosen so that women from rural and urban populations and from a variety of socioeconomic and ethnic backgrounds would be represented in the sample.

Questionnaire Measures

The questionnaire pack was designed to measure the health of women during the menopausal transition. The pack contained a questionnaire to measure minor health complaints.^{19,20} This questionnaire, in addition to psychological symptoms, covers 19 physical symptoms or health complaints. We divided the physical symptoms into 4 categories: (1) allergic symptoms (wheeze, sneeze, blocked nose, itchy eyes, and itchy skin), (2) gastrointestinal symptoms (constipation, watery diarrhea, explosive diarrhea, and heartburn), (3) pain symptoms (back pain and painful joints), and (4) other physical health complaints or symptoms that are not associated with chronic inflammatory disease (thrush, cystitis, colds or flu, sore throat, mouth ulcers, cold sores, and fungal infections of the scalp or groin). Two psychological symptoms were evaluated (tiredness for no reason and depression). (The "Results" section contains the exact wording of these items.) Thus, there were 11 target symptoms that are associated with inflammatory disease and may, therefore, correlate with depression and tiredness and 7 control symptoms or complaints that are not associated with inflammatory disease and should not correlate after controlling for common response bias. For each item, participants replied on a 5-point frequency scale of occurrences (0 indicates 0; 1, 1; 2, 2 or 3; 3, 4–6; and 4, ≥ 7), except for the items on itchy skin, sneeze, blocked nose, back pain, painful joints, and depression, which were responded to on 3-point severity scales (0 indicates no; 1, a little; and 2, yes). Finally, the pack contained a 48-item disease-specific menopausal QOL scale,²¹ which includes items relating to sleep, energy, feelings, love life, home life and everyday activities, social life, and work activities. Respondents reply to each item on a 5-point scale, and the total scale has an α coefficient of .82. Respondents were also asked to write (free form) whether they had any medically diagnosed diseases, and we identified those who reported any diagnosed disease.

Statistical Analysis

We examined the correlations between symptoms and QOL by Kendall τ_b correlations. We used nonparametric partial correlations²² to test the correlations between symptoms after removing the effect of QOL. We analyzed whether those who had reported any medically diagnosed disease were more depressed or tired than those without disease using the Mann-Whitney test. All analyses are based on the maximum of people completing the relevant parts of the questionnaire. Significance was set at $P < .001$ (2-tailed) because of multiple testing.

RESULTS

A total of 1,143 women (38.1%) returned the questionnaires, of whom 621 (20.7%) included a completed menopausal QOL questionnaire (many patients returned the health checklist without completing the longer QOL scale). The mean age was 50 years 10 months (SD, 6 years 8 months). Based on the free-form responses, 132 women (11.5%) reported 1 or more diagnosed illnesses, of whom 37 (3.2%) had asthma, 14 (1.2%) had an allergic disease, 17 (1.5%) had irritable bowel syndrome, and 31 (2.7%) had arthritis. In response to the question, "Do you get depressed easily?" 589 women (51.5%) responded no; 330 (28.9%) reported a little, and 198 (17.3%) reported yes. The number of people experiencing "tiredness for no reason in the last month" was never in 432 (37.8%), once in 78 (6.8%), 2 or 3 times in 221 (19.3%), 4 to 6 times in 98 (8.6%), and 7 or more times in 220 (19.2%). People who reported a medically diagnosed disease were more tired ($z = 3.5$, $P < .001$) but were not more depressed ($z = -0.73$, $P = .47$) than those who did not report a disease.

The following analyses have excluded all those who reported a diagnosed disease. Table 1 provides the frequency and percentage of those reporting any level of each symptom or health complaint. Table 1 also provides the raw correlations of all physical symptoms with depression and tiredness, the correlation between depression and tiredness, and the same correlations after removing variance associated with QOL. After removing common variance attributable to response bias, 8 of the 11 target symptoms were significantly correlated with tiredness and 0 with depression. By contrast, 0 of the 7 control symptoms or complaints was significantly correlated with tiredness or depression.

DISCUSSION

Allergic and gastrointestinal diseases and arthritis are characterized by chronically increased systemic proinflammatory cytokines. We found that, in a healthy population, 8 of 11 symptoms associated with these diseases were correlated with tiredness after removing common variance attributable to response bias. Thus, our data show that, in people without disease, psychological markers of systemic proinflammatory cytokines correlate with symptoms associated with inflammatory diseases (ie, those diseases known to be characterized by increased proinflammatory cytokines). The partial corre-

Table 1. Bivariate and Partial Nonparametric Correlations of Symptoms With Depression and Tiredness, Controlling for QOL^a

Type of symptom	No. (%) of 621 patients reporting symptoms ^b	Raw correlations (τ)		Partial correlations (τ_{xyz})	
		Depression	Tiredness	Depression	Tiredness
Target symptoms					
Patches of dry itchy skin	171 (27.5)	0.10	0.08	0.06	0.04
Wheeze in the past year	177 (28.5)	0.10	0.14 ^c	0.04	0.08
Sneeze a lot even without having a cold	287 (46.2)	0.04	0.25 ^c	0.001	0.23 ^c
Itchy eyes in the past month	301 (48.5)	0.18 ^c	0.27 ^c	0.11	0.21 ^c
A blocked nose, even without a cold	254 (40.9)	0.10	0.26 ^c	0.05	0.23 ^c
Constipation in the past month	228 (36.7)	0.16 ^c	0.16 ^c	0.12	0.11
Watery diarrhea in the past month	265 (42.7)	0.13 ^c	0.23 ^c	0.08	0.18 ^c
Explosive diarrhea in the past month	264 (42.5)	0.17 ^c	0.22 ^c	0.13	0.18 ^c
Heartburn in the past month	131 (21.1)	0.10	0.22 ^c	0.05	0.18 ^c
Back pain	479 (77.1)	0.18 ^c	0.29 ^c	0.10	0.22 ^c
Painful joints	462 (74.4)	0.14 ^c	0.36 ^c	0.06	0.31 ^c
Control symptoms or health complaints					
Colds or flu in the past year	488 (78.6)	0.10	0.14 ^c	0.06	0.10
Sore throats in the past year	413 (66.5)	0.12	0.21 ^c	0.06	0.16
Thrush in the past year	200 (32.2)	0.09	0.10	0.04	0.06
Athlete's foot in the past year	176 (28.3)	-0.04	-0.01	-0.05	-0.02
Cystitis in the past year	165 (26.6)	0.07	0.08	0.05	0.06
Cold sores in the past year	222 (35.7)	0.02	0.06	-0.001	0.05
Mouth ulcers in the past year	208 (33.5)	0.04	0.13 ^c	0.002	0.09
Fungal infections of the groin or scalp in the past year	233 (37.5)	0.16 ^c	0.03	0.15	0.004

Abbreviation: QOL, quality of life.

^a For correlations with depression, the number varies between 508 and 614; for tiredness, the number varies between 506 and 584. The raw correlation of tiredness with depression is as follows: $\tau_{579} = 0.29$; the partial correlation, controlling for QOL, is as follows: $\tau_{xyz579} = 0.18$ ($P < .001$ for both).

^b Nonzero scores and percentages are drawn from the group completing the QOL assessment.

^c $P < .001$.

lations are in the order of 0.2, suggesting that, after excluding response bias, approximately 4% of variance is shared between tiredness and the physical symptom. Low correlations are expected because tiredness has multiple causes.⁶

We measured the reported symptom of depression, not psychiatrically diagnosed depression. Although some of the raw correlations between the target symptoms and depression were significant, none were significant after removing the effect of QOL. People with disease were more tired but not more depressed than people without disease. The failure of depressive symptoms to be related to physical symptoms may be either because depression is less directly related to increased cytokines than tiredness or because of a scaling effect (eg, the severity measure of depression is less reliable than the frequency measure of tiredness). As a validation check of our methods, we examined the correlations between 7 health complaints or symptoms that are not linked to chronically increased cytokines. None were significantly correlated with tiredness.

A major limitation of our study was that we used single-item measures of tiredness and depression and for the physical symptoms. Single items tend to be less reliable than multi-item questionnaires, so the true common variance may be greater than the 4% recorded herein. Future research

should use an established fatigue questionnaire. Measures of immune variables would also contribute to a better understanding of the underlying mechanisms.

The term *medically unexplained symptoms (MUSs)* is used for patients who report troubling symptoms but have no identifiable pathophysiological features. Our data suggest that there may be physiological reasons why patients with MUSs often report both tiredness and physical symptoms associated with inflammatory disease. The cause of MUSs may not be “all in the mind”²³ but because of a physiological dysregulation of proinflammatory cytokines. Rather than suggesting that psychological states cause physical disease,²⁴ it may be that both are the result of the same immune dysregulation. Further research is needed to establish whether our finding of correlations between psychological and physical symptoms in the healthy population is mediated by immune dysregulation, as we originally hypothesized.

ACKNOWLEDGMENTS

We thank Julie Griffin, PhD, for helping to collect the data; Ian Dennis, PhD, for his helpful statistical advice; and the 2 referees for their helpful comments.

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