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FATIGUE, CAFFEINE AND UPPER RESPIRATORY TRACT ILLNESSES

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ABSTRACT

Background: Research has demonstrated that psychosocial factors, such as stress, and health-related behaviors, such as smoking, are associated with an increased risk of upper respiratory tract illness (URTI). A recent review has suggested that these results can be interpreted within a fatigue framework. Caffeine can act as a countermeasure to fatigue which suggests that it may be associated with a reduced incidence of URTIs. **Methods:** These issues were examined here by carrying out a secondary analysis of data from a representative UK sample (N=6418). Fatigue was measured by being tired for no apparent reason. An URTI factor measuring cold/influenza and the symptoms of blocked/runny nose, sore throat and cough was the dependent variable. Caffeine consumption was measured from the number of caffeinated beverages consumed. Established predictors of URTIS (e.g. age and smoking) were also used in the analyses. **Results:** Initial cross-tabulations showed that fatigued individuals and non-caffeine consumers were more likely to be in the high URTI category. Combining fatigue and caffeine showed that the effect of caffeine was to reduce the association between fatigue and URTIs. Logistic regression showed that the effects of fatigue and caffeine remained significant when possible confounders were statistically controlled. Established predictors such as age and smoking showed an association with URTIs, which gives more confidence in the novel findings. **Conclusions:** There are plausible biological mechanisms linking fatigue and susceptibility to URTIs and caffeine and fatigue, which provides a strong theoretical framework for the new interpretation of established findings. The new empirical results presented here provide the first support for this model.

KEYWORDS: Fatigue; Caffeine; Upper respiratory tract illness; Common cold; Influenza; Cough; Sore throat; Blocked nose; Runny nose.

INTRODUCTION

Upper respiratory tract illnesses (URTIs), such as the common cold and influenza, are frequent and common, with adults often having 1-3 such illnesses a year. It has been estimated that these illnesses consume 20 per cent of general practitioner services in the UK and cost over £25 million a year.[1] They are also a major cause of absenteeism from work and education.[1] Research on the association between psychological characteristics and upper respiratory illnesses started over fifty years ago. A critical review of the early research identified poor methodology, including the use of retrospective designs, lack of control for other risk factors for infection, the poor conceptualization of the psychological constructs, no clinical observations, and the failure to control exposure to the virus.[2] These problems have subsequently been addressed by using experimentally induced URTIs, control of many confounders, use of longitudinal designs, and more clearly defined psychological concepts and models.[3] The main findings from this type of study are summarized in the next section.

This research started at the MRC Common Cold Unit, Salisbury, UK. The methods and history of the unit are described in detail elsewhere.[3,4] The volunteers stayed at the unit for ten days, and on the first day, they were given a medical examination and a blood sample taken to measure existing antibody levels. They then went into quarantine for two days to ensure that they had no current illness. Psychosocial questions were completed during this period. They were then given a virus or saline placebo in droplets in the nose. Each day they were assessed by a clinician, and nasal swabs were taken to identify virus shedding. About one-third of the volunteers developed a clinical illness, another third a sub-clinical infection, and the remainder were uninfected (their immune system dealt with the virus very rapidly, and it could not be detected in the subsequent nasal swabs). Another blood sample was returned to the unit three weeks later to assess possible increases in antibodies. A large-scale study[5] found that stress was associated with greater susceptibility to URTIs. These results were largely due to highly stressed individuals being more likely to be infected. Different components of the stress process influenced either infection or the

development of symptoms.[7] Negative life events were associated with a greater likelihood of developing symptoms once infected, whereas perceived stress and negative affect increased the likelihood of becoming infected. These results could not be attributed to health-related behaviors, but both smoking and alcohol consumption influenced infection or illness.[6]

The MRC Common Cold Unit closed in 1990, and after this, the experimental induction of URTIs and the association with psychosocial factors were largely carried out in the USA.[8] An initial study showed that chronic stress was a major risk factor for susceptibility to URTIs.[9] This effect was not due to health-related behaviors or personality, although both were associated with disease outcomes. Another study[10] found that having fewer social ties was associated with a greater risk of having URTIs, whereas more diverse social networks reduced susceptibility to URTIs. Resistance to URTIs was associated with a positive emotional style,[11] and dispositional affect was a moderator of the buffering effect of social support.[12] Low socioeconomic status[13] and parental separation during childhood[14] were other risk factors for URTIs. Shorter sleep duration was a risk factor for URTIs,[15] but other research found that this was only observed in low socioeconomic groups[16] Poor self-rated general health was also identified as a risk factor for URTIs.[17]

An underlying assumption of most of the above studies was that the psychological factors influenced the immune system, which increased the risk of infection. Research found that shorter CD8CD28-T-cell telomere length was related to a greater risk of getting an URTI.[18] Other studies provided support for the view that interleukin-6 might be the mechanism linking psychological factors and risk of infection.[19,20] Another study demonstrated an association between cortisol production and URTI infection.[21] This led to the "glucocorticoid receptor resistance-inflammation-disease" model.[22] In this model, chronic stressors interfere with hormones that suppress pro-inflammatory cytokines. The immune system then over responds, which leads to an increase in the symptoms of the URTI.

A recent article[23] has suggested that the different results linking psychosocial factors to URTIs can be put in a fatigue framework. The first part of this review showed that fatigue was positively correlated with negative life events, perceived stress, and loneliness. It was negatively correlated with social support and hedonic tone. Short sleep and poor health are also associated with fatigue, as is childhood stress.[24] The underlying mechanisms linking psychosocial factors to URTIs are also associated with fatigue (cortisol,[25] IL-6,[26]; and telomere length.[27]) Furthermore, two studies[28,29] have shown that those with chronic fatigue syndrome (CFS) are more sensitive to illness and infection by URTIs. The first aim of the present study was to examine whether analysis of a large-scale epidemiological study could provide evidence of an association between fatigue and URTIs that was independent of other predictors.

There are large individual differences in reported fatigue, and one relevant factor is the consumption of caffeine. Studies of the acute effects of caffeine demonstrate that it reduces fatigue.[30 -36] For example, caffeine may reduce the impairments observed in those working at night, sleep deprivation, prolonged work, circadian dips in alertness, prolonged work and minor illness [37,38]. There are plausible biological mechanisms for caffeine reducing fatigue, with the major one being the effect of caffeine on adenosine.[39] The literature on the effects of regular patterns of consumption of caffeine is less extensive but does provide support for the view that caffeine may reduce fatigue. There is some evidence that regular caffeine consumption may reduce susceptibility to URTIs,[40] and the second aim of the present study was to examine this association and determine whether a beneficial effect of caffeine consumption reflected removal of the negative effect of fatigue.

MATERIALS AND METHODS

The present study involved a secondary analysis of data from the Bristol Stress and Health at Work study.[41] There were three main reasons why this was an appropriate database. First, it was the only one that could be accessed with variables relevant to the present hypotheses. Secondly, the sample was shown to be representative of the specific area where sampling occurred, and in many cases, representative of the UK population. Finally, data collection occurred in 1998, which was a similar time to many of the studies of psychosocial factors and susceptibility to URTIs. Participants were selected at random from the electoral register and completed a postal survey following informed consent. The study was approved by the local regional ethics committee.

Sampling procedure

Seventeen thousand project packs consisting of a covering letter, the questionnaire, and a Freepost envelope to return the questionnaires were sent to a random sample selected from the Bristol electoral register. These were posted using regular mail. Reminder letters and questionnaires were sent by regular mail four weeks later. Telephone reminders followed after a further month, and a final letter and questionnaire were sent by recorded delivery after another four weeks. Over 14,000 were delivered to the correct person, and the completion response rate was 49%. Comparison with census data[38] showed that the sample was generally representative of the population of that area. The only group that was under-represented were young single adults in rented accommodation. This group are more likely to change address which plausibly explains why the use of the sampling frame based on an electoral register may miss them.

Participants

Seven thousand sixty-nine questionnaires were returned. Four hundred seventy-six only completed the informed consent but no questions. 6593 completed at least one of the relevant questions, and 6148 (97.3%) completed all of them and were used in the analyses. Their demographic and lifestyle characteristics can be summarized as follows:

- 60.4% were working
- 54.4% were female
- 65.8% were married/cohabiting; 18.7% were single; 15.4% were divorced/separated or widowed
- Mean age = 48.5 years (s.d. = 17.5, range = 18-88 years)
- Highest education level: 27.1% no ordinary level secondary qualifications; 22.9% ordinary level GCSE; 8.1% advanced level GCSE; 18% city and guilds or national diploma; 6.6% BA or BSc; 17.3% higher degree or professional qualification.
- 25.8% smokers

Measures of fatigue, upper respiratory tract illness and caffeine consumption.

Fatigue and URTIs were measured as part of a symptom checklist covering the last 14 days. These questions had a Yes/No response. The measure of fatigue was "Feeling tired for no reason". This was used to try and avoid fatigue-related to URTIs or other known risk factors for fatigue. The questions related to URTIs were the presence in the last 14 days of:

- A cold or influenza
- A runny or blocked nose
- A cough
- A sore throat

Total daily caffeine consumption was calculated from the consumption of different types of coffee and tea. The levels of caffeine in the different beverages were based on the values described in the literature.[30]

Data analysis

The two main predictor variables were feeling tired and caffeine consumption. Caffeine consumption was dichotomized to distinguish non-consumers from consumers. Demographic variables and smoking status were used as covariates in the analyses. The dependent variable was the URTI score. The URTI variables loaded on a single factor accounting for 57.4% of the variance. The factor score was saved and then dichotomized into low and high URTI groups. Statistical analysis was carried out using IBM SPSS v27. Initial cross-tabulations between fatigue and URTIs and caffeine and URTIs were carried out. These were followed by logistic regressions controlling for possible confounders. Finally, the fatigue and caffeine variables were combined to test the hypothesis that caffeine would have its main effect by reducing the effect of fatigue.

RESULTS

Descriptive statistics

Table 1: Shows the descriptive statistics for the fatigue and URTI measures.

Symptom	Per cent reporting that symptom
Tired for no apparent reason in the last 14 days	36.1%
Cold/flu in the last 14 days	26.4%
Blocked/runny nose in the last 14 days	32.0%
Cough in the last 14 days	41.9%
Sore throat in the last 14 days	24.6%

The mean caffeine consumption was 272mg/day (range 0-2040mg). There were 566 non-consumers.

Cross-tabulations

Table 2 shows the cross-tabulation between URTIs and being tired. Those who reported being tired were more likely to be in the high URTI category (chi-square = 38.5 $p < 0.001$).

Table 2: Cross-tabulation of URTIs and being tired for no reason.

	Not tired	Tired
Low URTI	56.1%	48.1%
High URTI	43.9%	51.9%

Table 3 shows a similar cross-tabulation for URTIs and caffeine consumption. Non-consumers of caffeine were more likely to be in the high URTI category (chi-square = 15.7 $p < 0.001$).

Table 3: Cross-tabulation of URTIs and caffeine consumption.

	Non-consumer of caffeine	Consumer
Low URTI	41.5%	50.2%
High URTI	58.5%	49.8%

An analysis of the data from only the caffeine consumers showed no differences in the consumption levels of the low URTI (mean = 296.3 mg s.e. 2.8) and high URTI group (mean = 294.4 mg s.e. = 2.9). This shows that the crucial distinction is between consumers and non-consumers of caffeine.

The final cross-tabulation (Table 4) looked at the combination of being tired with caffeine and URTIs. This showed that the tired non-consumers of caffeine were most likely to be in the high URTI category (chi-square = 53.9 $p < 0.001$).

Table 4: Cross-tabulation of URTIs, being Tired and Caffeine consumption.

	Non-consumer, not tired	Non-consumer, tired	Consumer, not tired	Consumer, tired
Low URTI	53.9%	34.6%	56.2%	49.0%
High URTI	46.1%	65.4%	43.8%	51.0%

Logistic regressions

The next set of analyses used logistic regressions to examine whether the associations between fatigue, caffeine and URTIs remained significant when possible confounders (demographics, lifestyle) were included in the model. As well as fatigue and caffeine, it was predicted that being younger, working and being a smoker would be associated with a higher URTI score. The first logistic regression (Table 5) shows that all of the predictor variables had a significant effect. The likelihood of having an URTI increased with greater fatigue, being a smoker, being younger, being at work and being a non-consumer of caffeine.

Table 5: Logistic regression showing predictors of URTIs.

	B	S.E	Wald	df	Sig	Exp(B)	95% CI	
Smoker	.364	.061	34.998	1	.000	1.439	1.275	1.623
Caffeine consumer	-.283	.108	6.872	1	.009	.753	.609	.931
Older	-.012	.002	44.462	1	.000	.988	.985	.992
Not working	-.176	.062	8.075	1	.004	.839	.743	.947
Tired	.643	.056	134.121	1	.000	1.902	1.706	2.121
Constant	.870	.147	34.872	1	.000	2.386		

The second logistic regression (Table 6) combined the fatigue and caffeine variables, with the no caffeine not tired group being set as the reference category. The no caffeine and tired group were significantly more likely to have an URTI than the reference group, whereas the other groups were not. This shows that being tired increased the risk of an URTI in the non-consumers of caffeine, but that this effect of fatigue was reduced by caffeine consumption.

Table 6: Logistic regression showing the effects of different fatigue/caffeine combinations on URTIs.

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Tired Caffeine			32.962	3	.000			
No caff Tired	.669	.210	10.134	1	.001	1.953	1.293	2.949
Caff Not Tired	-.113	.130	.746	1	.388	.893	.692	1.154
Caff Tired	.110	.134	.677	1	.411	1.116	.859	1.451
Smoker	.266	.059	20.115	1	.000	1.304	1.161	1.465
Not working	-.161	.060	7.108	1	.008	.851	.756	.958
Older	-.012	.002	45.050	1	.000	.988	.985	.992
Constant	.632	.117	29.057	1	.000	1.881		

DISCUSSION

The results of the present study support the view that fatigue is a risk factor for URTIs.[23] The link between fatigue and infection has a long history, with anecdotal reports being published in 1911.[42] For example, during plague or cholera, those with physical or mental exhaustion were more susceptible to infection. Animal studies with rats also showed that the risk of anthrax was increased by overexertion.[43] Research with other infecting agents and animal species confirmed these results.[44] Underlying mechanisms were also identified and described in terms of the immunological concepts of the time. Leukopenia, a decrease in leukocytes, was more prevalent in fatigued animals. Polynucleosis, an increase in neutrophils, was less persistent and intense in fatigued animals. The subsequent mononucleosis, the increase in

monocytes and lymphocytes, was less intense when animals were fatigued. Fatigued animals also produced less agglutin, antibodies that lead to aggregation of antigens. More recent mechanisms linking fatigue to URTIs were described in the introduction, with neuroendocrine changes, cytokine changes and different telomere lengths being suggested.[24-27]

The present study also showed that established predictors of URTIs, namely age and smoking, had significant effects. This gives greater confidence to the finding that fatigue is also a significant risk factor. One limitation of the study was that it was cross-sectional, and it is possible that reverse causality may have occurred, with URTIs leading to fatigue. Ideally, longitudinal studies should be carried out to examine whether fatigue at time one is associated with URTIs at a later time. The measure of fatigue used here was "Tired for no apparent reason", which suggests that fatigue attributed to an URTI would not have been put in this category.

The second novel area examined here was the association between consumption of caffeine and URTIs. Caffeine consumers were less likely to be in the high URTI category than non-consumers. The literature shows that caffeine reduces fatigue, and the second set of analyses examine whether the reduced number of URTIs in the caffeine consumers reflected an effect on fatigue. These analyses showed that caffeine consumption had its greatest effect on those reporting high fatigue and had a much smaller impact in non-fatigued individuals. The biological mechanisms underlying the alerting effects of caffeine are well established,[33] and studies of acute ingestion[30-36] demonstrate that caffeine reduces both endogenous fatigue (e.g., circadian troughs; sleep deprivation) and fatigue due to exogenous factors (e.g., prolonged work). Again, longitudinal research, preferably with an intervention manipulating caffeine, would provide stronger support for this view.

CONCLUSIONS

The link between psychosocial factors such as stress, health-related behaviors and susceptibility to URTIs is well established. A recent review suggested that these findings could be interpreted in terms of an association between fatigue and URTIs. The results from the present study supported this view, with feeling tired for no apparent reason being significantly associated with high scores on the URTI factor (measuring the presence of colds/flu and the symptoms of a blocked or runny nose, sore throat and cough). It is well established that caffeine can reduce fatigue, and the results showed that the association between fatigue and URTIs was stronger in non-caffeine consumers. The results also demonstrated significant effects of established predictors, which gives one more confidence in the novel results. There are plausible biological mechanisms linking fatigue and susceptibility to URTIs and caffeine and fatigue, which provides a strong theoretical framework for the new interpretation of established findings.[23] The new empirical results presented here provide the first support for this model.

Institutional review board statement

"The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Bristol Local Regional Ethics Committee (Approval number: HPRU – 1996- 001)."

Informed consent statement

"Informed consent was obtained from all volunteers involved in the study."

Data availability statement

Data related to the analyses described here are available from the author.

Conflicts of interest

"The author declares no conflict of interest."

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