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# Metabolomic markers of fatigue: Association between circulating metabolome and fatigue in women with chronic widespread pain

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ABSTRACT

*Background:* Fatigue is a sensation of unbearable tiredness that frequently accompanies chronic widespread musculoskeletal pain (CWP) and inflammatory joint disease. Its mechanisms are poorly understood and there is a lack of effective biomarkers for diagnosis and onset prediction. We studied the circulating metabolome in a population sample characterised for CWP to identify biomarkers showing specificity for fatigue.

*Material and methods:* Untargeted metabolomic profiling was conducted on fasting plasma and serum samples of 1106 females with and without CWP from the TwinsUK cohort. Linear mixed-effects models accounting for covariates were used to determine relationships between fatigue and metabolites. Receiver operating curve (ROC)-analysis was used to determine predictive value of metabolites for fatigue.

*Results:* While no association between fatigue and metabolites was identified in twins without CWP (n = 711), in participants with CWP (n = 395), levels of eicosapentaenoate (EPA) ω-3 fatty acid were significantly reduced in those with fatigue ($\beta = -0.452 \pm 0.116$; $p = 1.2 \times 10^{-4}$). A significant association between fatigue and two other metabolites also emerged when BMI was excluded from the model: 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF), and C-glycosyltryptophan ($p = 1.5 \times 10^{-4}$ and $p = 3.1 \times 10^{-4}$, respectively). ROC analysis has identified a combination of 15 circulating metabolites with good predictive potential for fatigue in CWP (AUC = 75%; 95% CI 69–80%).

*Conclusion:* The results of this agnostic metabolomics screening show that fatigue is metabolically distinct from CWP, and is associated with a decrease in circulating levels of EPA. Our panel of circulating metabolites provides the starting point for a diagnostic test for fatigue in CWP.

## 1. Introduction

Fatigue is a condition of debilitating tiredness, lethargy and lack of energy which manifests as a symptom of many different diseases and, more rarely, on its own (chronic fatigue syndrome, CFS, also known as myalgic encephalomyelitis, ME). The prevalence of fatigue may be as high as 50% in the general population, though in most cases it is transient and diminishes as the causal factor (e.g. viral infection) resolves [1,2]. Fatigue is a characteristic symptom of many chronic rheumatic conditions such as rheumatoid arthritis (RA), system lupus erythematous (SLE), and fibromyalgia. Patients with SLE and RA report persistent fatigue in up to 80–90% cases and there is no clear evidence that it is related to disease activity [3–5]. Fatigue is also common in non-inflammatory conditions such as cancer and neurological disorders.

Fatigue is often associated with chronic pain; in rheumatic diseases both the presence and the intensity of these symptoms are well correlated [3,4,6,7]. In patients with RA and SLE painful symptoms such as arthralgia are important contributing factors to fatigue severity; also, pain has been shown to be the strongest predictor of fatigue in many studies [4,8,9].

Fatigue often occurs in fibromyalgia, a non-inflammatory condition manifesting chronic widespread pain (CWP) accompanied by sleep disturbance [10]. Due to the strong co-morbidity of fibromyalgia and chronic fatigue some researchers debate they are a single syndrome caused by overlapping mechanisms [11]. This is supported by a genetic epidemiology study that showed strong genetic correlation between CWP and fatigue, suggestive of the presence of shared genes and molecular pathways [12]. On the other hand, other studies proposed that co-occurrence between fatigue and CWP is due to their share of

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common psychiatric component (anxiety and depression) [13] which also shares genetic determinants with CWP [12].

The metabolome comprises the sum of small molecule chemicals (amino acids, lipids, fatty acids, sugars, vitamins, etc.) detectable in a sample, usually serum, plasma or urine. It represents the higher end of phenotypic expression of the genome and is, therefore, much closer to the phenotype of interest than, say, protein expression. Metabolomic studies are increasingly successful in identifying mechanisms of complex diseases and may reveal new targets for therapy and provide diagnostic and prognostic tools [14–16].

We have recently demonstrated that individuals with CWP may present with an altered metabolic profile compared to healthy individuals [17]. It is also supported by the findings that the risk of CWP increases with higher body mass index (BMI) [18]. Furthermore, dietary risk factors which affect metabolite levels, including higher consumption of fats but lower consumption of fruit and vegetables, have been found in those with CWP [18].

There are limited metabolome studies in fatigue [19–25] and no studies have examined fatigue in the general population as opposed to a clinical sample. We investigated the circulating metabolome in a large sample of twins taken from the UK population. We were interested to determine whether there is a pattern of circulating metabolome specific for fatigue in people reporting CWP which might provide a diagnostic biomarker for this symptom.

## 2. Material and methods

### 2.1. Sample

Participants were a sample of MZ and DZ twins enlisted in the TwinsUK registry [26]. This is a bioresource which has been collected and maintained by the Department of Twin Research and Genetic Epidemiology at King's College London over the last 25 years. Ethical approval is available from the St Thomas' Hospital Research Ethics Committee and, at each visit, the participating twins provided fully informed consent for their biological specimens, clinical and demographic information to be used in molecular epidemiology studies. Many of the data including metabolome are available to internal and external researchers subject to approval by the Twin Research Executive Committee (http://www.twinsuk.ac.uk/data-access/submission-procedure/). Complete confidentiality was assured and the twins were unaware of any specific hypotheses.

An original sample for the current study comprised 4898 twins with known status of CWP established as described elsewhere [17]. The status of fatigue was assessed using three self-administered health questionnaires collected in 2000, 2002 and 2008 (Supplementary Table 1). Even though the definitions of fatigue using different time points (2000 vs 2002 and 2008) were not the same; the prevalence of fatigue using definitions from questionnaires of 2000 and 2008 were similar: 25.2% and 22.6%, respectively, and did not differ statistically ($p = 0.494$). Only two persons from 2002 were included in the final sample, both having no fatigue. Therefore, we analysed all the sample together to increase the sample size and statistical power. Collection of concomitant socio-demographic information and physical examination was carried out during twin visits or via self-administered questionnaires. Each twin completed the questionnaires without reference to co-twin and were unaware of the precise research hypothesis addressed in the study. Twins reporting inflammatory disease such as RA, SLE and inflammatory bowel disease were excluded from the study.

### 2.2. Metabolome

Non-targeted metabolite detection and quantification of 280 structurally named biochemicals was conducted by the metabolomics provider Metabolon, Inc. (Durham, USA) on fasting plasma or serum samples from the participants, as described previously [27]. Day median normalization followed by inverse transformation of ranks to normality was applied to the metabolites levels. Metabolite traits with > 20% missing were excluded and missing values were imputed to the day minimum. This produced 209 metabolites for the study. We used both plasma and serum samples as they are highly correlated and depend on the same genes [28]. However, we initially investigated possible differences between the metabolomic profiles derived from fasting serum and fasting plasma collected from the same twin volunteers. We have found that the results on plasma and serum were in keeping with one another and elected, therefore, to increase the sample size and hence the power by using both sample types. Moreover, we adjusted for the specimen type in statistical analysis (see Statistical analysis section). Throughout we refer to this plasma and serum metabolome as the “circulating metabolome”.

### 2.3. C-reactive protein

C-reactive protein (CRP) levels from serum of twin volunteers were established as described elsewhere [29]. The raw values of CRP were normalized by inverse transformation of ranks prior to statistical analysis.

### 2.4. Statistical analysis

The statistical analysis was carried in three steps. First, risk factors for fatigue were sought using univariate and multivariable mixed-effects regression including CWP, BMI and age, adjusting for family structure and zygosity. Then, we assessed associations between fatigue and metabolite levels using analysis of covariance (ANCOVA) by fitting linear mixed-effects models with metabolites as dependant variables and fatigue an independent factor, also adjusting for age, BMI, biological specimen type (plasma or serum) and processing batch, family structure and zygosity. Mediation analysis stratifying for presence/absence of CWP was carried out to determine if BMI was a mediator of the effects of fatigue on the levels of metabolites. Statistical significance threshold was set at $p < 0.0005$ corresponding to 100 independent tests with Bonferroni correction. The number of independent tests was estimated using the correlation structure of the observed metabolites in the TwinsUK dataset [30]. Finally, we assessed predictive capacity of the circulating metabolome for fatigue using ROC-analysis. Association between CRP levels and fatigue was assessed using ANCOVA in the same way as for the metabolites. Adjustment was made for age, BMI, family structure and zygosity. All analyses were performed in R using basic functions and packages “lme4” [31], “mediation” [32] and “PredictABEL” [33].

## 3. Results

### 3.1. The prevalence and risk factors for fatigue

A total sample of 4898 twins from the TwinsUK dataset has been assessed for fatigue using postal questionnaires. Complete covariate data were available for 2055 female individuals, which have been analysed further. In this sample, the prevalence of fatigue was 22.3% (Table 1) with much higher frequency in individuals with CWP as compared to those without CWP (38.6 vs 15.2%, $p = 2.2 \times 10^{-16}$).

Both in the CWP group and in non-CWP group, fatigue was associated with the increased BMI: $28.7 \pm 6.4$ vs $26.7 \pm 4.9\ kgm^{-2}$ ($p = 3.9 \times 10^{-5}$) in individuals with CWP and $26.2 \pm 5.2$ vs $25.4 \pm 4.8\ kgm^{-2}$ ($p = 0.030$) in those without CWP, respectively. Also, females with fatigue were younger that those without it, though it was only marginally statistically significant in the non-CWP group: $57.7 \pm 11.1$ vs $60.8 \pm 10.2$ years ($p = 5 \times 10^{-4}$) with CWP and $50.4 \pm 15.5$ vs $52.5 \pm 14.8$ years ($p = 0.060$) in those without CWP.

CWP was significantly associated with fatigue independent of BMI and age (Table 2) as it remained highly statistically significant with

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