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Co-occurrence and symptomatology of fatigue and depression

Elizabeth C. Corfield[a,*], Nicholas G. Martin[b], Dale R. Nyholt[a]

[a]Faculty of Health, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia
[b]QIMR Berghofer Medical Research Institute, Brisbane, Australia

Abstract

Objective: Fatigue and depression are highly comorbid phenotypes with partially overlapping symptoms. The main aims of the present study are to: (i) identify the risk of current fatigue and depression; (ii) determine if the depression symptoms experienced by individuals who are fatigued (N = 766) and non-fatigued (N = 1849) are different; and (iii) identify if the fatigue symptoms experienced by depressed (N = 275) and non-depressed (N = 2340) individuals are different, in a community-based sample of Australian twins aged over 50 years.
Methods: Fatigue and depression symptom profiles and classifications were generated using the Schedule of Fatigue and Anergia (SOFA); the General Health Questionnaire; and the Delusions-Symptoms-States Inventory, States of Anxiety and Depression questionnaires. The association between co-occurring fatigue and depression was assessed using prevalence ratios. Differences in the preponderance of fatigue and depression symptoms were assessed using logistic regression modeling.
Results: Individuals with either fatigue or depression have an approximately two-fold increased risk for comorbid presentation of both traits, compared to the general population. Logistic regression analysis indicated that fatigued individuals were significantly more likely to report all of the Diagnostic and Statistical Manual of Mental Disorders (DSM) depression symptoms assessed in the study. Similarly, depressed individuals were significantly more likely to report all SOFA fatigue symptoms.
Conclusions: Fatigue and depression are highly correlated traits within the community. Depression symptomatology and prevalence are significantly increased in fatigued individuals. Fatigue and especially the symptoms of insomnia and poor concentration are strong predictors of depression. Notably, the association between fatigue and depression is independent of their overlapping symptomatology. Therefore, presentation with fatigue, and in particular the symptoms of insomnia and poor concentration, should be considered as warning signs of depression in older adults.

1. Introduction

Fatigue is a multidimensional symptom, which is highly prevalent in medical practice, and difficult to quantify [1]. Numerous classifications exist for fatigue, which are based on arbitrary durations and severities, as a result of its continuous nature [2]. Fatigue is associated with numerous physical and psychiatric diagnoses, potentially due to the physical, cognitive, and emotional dimensions the symptoms comprise [3]. Causation of fatigue has been associated with numerous predisposing, precipitating, and perpetuating factors [4]. A common predisposing factor is sex; with females 1.5 times as likely to experience fatigue as males [5]. Additionally, increased age has been associated with fatigue, in both males and females [6]. Comparison of fatigue symptoms based on sex has found that females report a higher prevalence of tiring easily and needing rest [7]. However, knowledge of the biological mechanisms underlying fatigue, which could account for the differences between the sexes, is limited. Reduced health outcomes and quality of life are associated with fatigue, which is commonly linked to psychiatric disorders, particularly major depressive disorder (MDD) [8,9].

MDD is classified according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), which requires the presence of at least one major depressive episode [10]. The criterion for a major depressive episode requires a two-week period where at least five of nine symptoms are exhibited and either depressed mood or

* Corresponding author at: Institute of Health and Biomedical Innovation, Queensland University of Technology, GPO Box 2434, Brisbane, QLD, 4001, Australia. Tel.: +61 7 3180875.
E-mail addresses: elizabeth.corfield@hdr.qut.edu.au (E.C. Corfield), Nick.Martin@qimrberghofer.edu.au (N.G. Martin), d.nyholt@qut.edu.au (D.R. Nyholt).

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anhedonia (an inability to feel pleasure in normally pleasurable activities) is reported. The symptoms of a major depressive episode are: (1) depressed mood, (2) anhedonia, (3) a change in weight or appetite, (4) insomnia (difficulty sleeping) or hypersomnia (excessive sleeping), (5) psychomotor (i.e., thought and physical movement) agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or excessive guilt, (8) inability to concentrate or make decisions, and (9) thoughts about death, suicidal thoughts, suicidal plans, or suicidal attempts [10]. Minor depressive disorder (MiDD) is also classified using the criterion for a major depressive episode [10,11]. However, only two to four symptoms occurring over a two-week period are required for diagnosis, of which at least depressed mood or anhedonia must be exhibited. Differences in the prevalence of depression occur over the lifespan, with the prevalence increasing from puberty before declining after the age of approximately 60 years [12,13]. The preponderance of depression in females has been frequently investigated with numerous risk factors attributed to the increased prevalence observed compared to males [14].

Investigation of differences in depression symptom prevalence (assessed using the Composite International Diagnostic Interview [CIDI]) of individuals with depression in Sri Lanka based on sex, revealed that males report more hypersomnia and fewer thoughts about death than females [15]. Furthermore, in the Netherlands, males reported increased levels of anhedonia and psychomotor symptoms, while females reported higher levels of mid-nocturnal insomnia, increases in weight, and somatic complaints (the depression symptoms were assessed by the 30 item Inventory of Depressive Symptomatology) [16]. Depression symptom profiles have been investigated in individuals with seasonal affective disorder, and differential symptoms have been identified among patients with unipolar, bipolar I, and bipolar II depression [17]. Finally, individuals with depression were able to be distinguished from those with Alzheimer's disease based on items from three depression scales using regression modeling [18].

Identification of differential symptoms between disorders facilitates increased accuracy of diagnosis, thereby enabling utilization of the most effective treatment options. Medically unexplained symptoms are associated with depressive disorders in 50–75% of patients [19]. Furthermore, fatigue or loss of energy is the second most frequently reported criterion of the DSM classification, experienced by 87.2% of MDD patients [20]. The co-occurrence of fatigue and depression is likely due, in part, to their overlapping symptomatology. Therefore, identification of symptoms which enable differential diagnosis would assist physicians in distinguishing between fatigue and depression, thereby facilitating symptom-guided management [21].

Depression has a polythetic definition — whereby categorical diagnosis occurs based on an arbitrarily defined threshold of symptoms being reached from a specified criteria list, of which not all are required; therefore, the DSM classification is highly heterogeneous, enabling a diagnosis of MDD in patients with entirely different symptom profiles [22]. The minimum requirement of 5 symptoms, of which at least one is depressed mood or anhedonia, enables 227 potential symptom profiles and allows the diagnosis of MDD in a subgroup of individuals who are non-fatigued [23].

Fatigue and depression are highly comorbid, with fatigued individuals reporting higher levels of depression than the general population [24,25]. Individuals with medically unexplained fatigue are approximately 11 times (OR = 10.9) more likely to have a lifetime diagnosis of depression than non-fatigued individuals, within the community [26]. Furthermore, the prevalence of co-occurring fatigue and psychological distress within primary care is approximately 23% [27]. The high prevalence of comorbid fatigue and depression and idiopathic fatigue cases often results in fatigue being perceived as a purely psychological symptom. However, a subgroup of fatigued individuals exists which are not depressed [27–29]. Although, longitudinally (over a thirteen year period), individuals with remitted (relative risk [RR] = 4.5), incident (RR = 53.2), and recurrent (RR = 28.4) medically unexplained fatigue have significantly increased risk of new onset depression compared to individuals who have never been fatigued (RR = 1.0) [26]. Therefore, understanding the relationship between fatigue and depression is vital to facilitating diagnosis and enhanced treatment outcomes.

Initially, the present study will investigate the risk of co-occurring fatigue and depression. Logistic regression modeling will then be utilized to determine if the proportion of specific depression symptoms differs between individuals who are fatigued and non-fatigued. Furthermore, the full symptom model will be investigated to identify the distinguishing depression symptoms between fatigued and non-fatigued individuals. The same approach will be utilized to assess if differential fatigue symptoms are experienced by depressed and non-depressed individuals. Finally, these analyses will identify the specific symptoms most strongly associated with comorbid fatigue and depression.

2. Method

2.1. Sample and questionnaires

Data from the over 50s (aged) study conducted by the Genetic Epidemiology group within QIMR Berghofer Medical Research Institute (QIMRB) was used in this study. Informed written consent was obtained from each participant and the study was approved by the Health Research Ethics Committee (HREC) of QIMRB. The study was conducted from 1993 to 1996, with 2281 twin pairs from the Australian Twin Registry aged over 50 years asked to complete a mailed Health and Lifestyle Questionnaire [30,31]. The survey contained numerous self-report questionnaires, of which the Schedule of Fatigue and Anergia (SOFA), the twelve-item General Health Questionnaire

(GHQ), and the fourteen-item Delusions-Symptoms-States Inventory, States of Anxiety and Depression (DSSI/sAD), were used throughout this study [32–34].

The SOFA was originally designed to identify chronic fatigue syndrome cases. Therefore, physical (i.e., muscular pain or tiredness), neurocognitive (i.e., memory and concentration problems), and neurovegetative (i.e., sleep problems) fatigue symptoms are assessed by the questionnaire. Consequently, the fatigued state identified by the SOFA is distinct from the fatigue experienced within a major depressive episode. Ten questions are contained in the SOFA; however, a shorter eight-item version was included in the survey due to two questions being replicated within the GHQ. The SOFA questions contained within the survey had a binary yes/no response set, which was scored as 1–0. Throughout the GHQ there are two response sets: (1) "not at all", "no more than usual", "rather more than usual", and "much more than usual"; and (2) "more so than usual", "same as usual", "less than usual", and "much less than usual". Standard scoring of 0–0–1–1 was used for both response sets of the GHQ. Responses to the DSSI/sAD questionnaire were dichotomized, with the scores 0–0–1–1 representing the answers "not at all", "a little", "a lot", and "unbearably", respectively.

Responses to the eight SOFA items and the two overlapping GHQ questions (Table 1) were summed to give an overall score out of ten which was used to assess fatigue. Individuals with three or more positive self-report responses were classified as fatigued.

MDD and MiDD were classified using the nine criteria of a major depressive episode, as defined by the DSM (version IV) criteria [10]. A combination of questions from the GHQ and DSSI/sAD were used to assess depression (Table 2), through the assignment of specific questions to the appropriate criterion of the major depressive episode criteria. If a question did not assess any of the criteria of a major depressive episode it was not used in the analysis. When multiple questions assessed a criterion at least one positive response indicated that the individual exhibited a symptom from the specific criterion. Each criterion was assessed by assigning one to the criterion if a symptom was exhibited by the individual and zero if none of the symptoms for the criterion were met. The survey did not contain any assessment of change in weight or appetite; therefore, the third criterion of a major depressive episode ("a change in weight or appetite") was not assessed. The scores of the eight criteria assessed were summed if the individual scored positively on criteria (1) or (2), otherwise the individual was

Table 1
Questionnaire items used to assess fatigue.

Abbreviated fatigue symptom	Questionnaire and question number	Question[a]
Muscle pain at rest	SOFA 10	I get muscle pain even at rest
Post-exertional muscle pain	SOFA 6	I get muscle pain after physical activity
Post-exertional muscle fatigue	SOFA 3	My muscles feel tired after physical activity
Post-exertional fatigue	SOFA 1	I feel tired for a long time after physical activity
Hypersomnia	SOFA 5	I need to sleep for long periods
Insomnia	GHQ 2	Lost much sleep over worry
Poor concentration	GHQ 1	Been able to concentrate on what you're doing
Speech problems	SOFA 8	I have problems with my speech
Poor memory	SOFA 9	My memory is poor
Headaches	SOFA 4	I get headaches

SOFA: Schedule of Fatigue and Anergia; GHQ: General Health Questionnaire.

[a] Participants were asked to respond with relation to their health, in general, over the past few weeks.

Table 2
Questionnaire items used to assess the criteria of a major depressive episode.

DSM Major depressive episode criteria	Questionnaire and question number	Question[a]
Depressed mood	GHQ 9	Been feeling unhappy and depressed
	DSSI/sAD 5	Recently, I have been depressed without knowing why
Anhedonia	GHQ 7	Been able to enjoy your normal day-to-day activities
	DSSI/sAD 12	Recently, I have lost interest in just about everything
Insomnia	DSSI/sAD 2	Recently, I have been so miserable that I have had difficulty with my sleep
	DSSI/sAD 11	Recently, worrying has kept me awake at night
Psychomotor agitation	DSSI/sAD 4	Recently, I have been so 'worked up' that I couldn't sit still
Loss of energy	DSSI/sAD 8	Recently, I have been so low in spirits that I have sat for ages doing absolutely nothing
Feeling worthless	GHQ 3	Felt that you are playing a useful part in things
	GHQ 6	Felt that you couldn't overcome your difficulties
	GHQ 11	Been thinking of yourself as a worthless person
	DSSI/sAD 10	Recently, The future has seemed hopeless
Inability to concentrate	GHQ 4	Felt capable of making decisions about things
	DSSI/sAD 13	Recently, I have been so anxious that I couldn't make up my mind about the simplest thing
Suicidal thoughts	DSSI/sAD 6	Recently, I have gone to bed not caring if I never woke up
	DSSI/sAD 14	Recently, I have been so depressed that I have thought of doing away with myself

DSM: Diagnostic and Statistical Manual of Mental Disorders; GHQ: General Health Questionnaire; DSSI/sAD: Delusions-Symptoms-States Inventory, States of Anxiety and Depression.

[a] Participants were asked to respond with relation to their health, in general, over the past few weeks.

assigned a score of zero. Individuals were designated MDD, MiDD, or non-depressed, if they had a self-report score of five or more, two to four, or less than two, respectively.

2.2. Statistical analyses

2.2.1. Prevalence ratios

The association between fatigue and depression was investigated using contingency tables to assess the prevalence of co-occurrence within the cohort. The likelihood of a fatigued individual having comorbid depression compared to non-fatigued individuals and the total cohort was assessed using the prevalence ratio (PR) measure of association and its 95% confidence interval (CI). The PR has the same interpretation as the relative risk (RR) with respect to its null value of 1 and values greater or less than 1. The PR is the ratio of the prevalence rate in one group divided by the prevalence rate in a second group. For example, the prevalence of depression in fatigued individuals was divided by the prevalence of depression in non-fatigued individuals. Similarly, the prevalence of fatigue in depressed individuals was divided by the prevalence of fatigue in non-depressed individuals. To assist interpretation of the numerous PR estimates, we also calculated PRs for specific groups relative to the total sample, by dividing the prevalence in the specific group by the prevalence in total sample.

The fatigued individuals likelihood of experiencing depression was re-calculated in the subgroup of individuals without (screening negative for) overlapping DSM depression symptoms (i.e., insomnia, poor concentration, and hypersomnia) to remove the effect of overlapping symptoms. Likewise, the likelihood of depressed individuals experiencing fatigue was re-calculated in the subgroup of individuals without (screening negative for) fatigue symptoms (i.e., insomnia, inability to concentrate, and loss of energy).

2.2.2. Multiple test correction

The matrix spectral decomposition (matSpD) web-based tool (http://neurogenetics.qimrberghofer.edu.au/matSpD/) estimates the effective number of independent variables from a pairwise correlation matrix [35–38]. Briefly, to retain an experiment-wide type I error rate of 5%, the significance thresholds for analyzing the full set of fatigue and depression symptom measures were calculated by dividing the nominal significance threshold of p-value 0.05, by the effective number of independent measures estimated by matSpD analysis of the pairwise correlation matrix calculated using R [39] for the fatigue and depression symptom measures.

2.2.3. Logistic regression modeling

Demographic differences in age and sex, with respect to fatigue and depression classification, were initially assessed by logistic regression in R [39].

Binomial logistic regression modeling was used to compare the depression symptoms between the fatigued and the non-fatigued groups [39]. The depression symptoms were assessed individually (univariable analysis) and as part of the full model (multivariable analysis) containing all eight symptoms. The Akaike information criterion (AIC) was used to assess the parsimony of the depression symptom model compared to the null model, with lower AIC indicating a better fit [40,41]. To account for relatedness, an exchangeable conditional covariance matrix was used (i.e., we allowed for correlated residuals between members of the same family) and tests were based on the robust (sandwich-corrected) standard errors, using the rms package in R [39]. Analysis of deviance containing the chi-squared test was used to assess statistical differences between the logistic regression of the fatigued and non-fatigued groups. The eight depression symptoms were compared between the fatigued and non-fatigued groups using a two-tailed p-value and odds ratio (OR) with their 95% CI. The approach was replicated to compare the ten fatigue symptoms between depressed and non-depressed individuals. Additionally, ordinal logistic regression, using rms, was utilized to compare the use of a broad, two-category depression classification (non-depressed, MiDD/MDD) to an ordered three-category depression classification (non-depressed, MiDD, MDD).

To obtain subgroup specific odds ratios, multinomial logistic regression modeling was used to compare the fatigue symptoms between the MDD, MiDD, and non-depressed groups. Relatedness was not accounted for due to its negligible effect on the binomial logistic regression results. The fatigue symptoms were assessed individually and as part of the full model. Multinomial regression modeling conducted throughout the study followed the protocol defined by Morris et al. (2010), using the mlogit package within R [39,42]. Parsimony of the model was assessed using the AIC and statistical differences between the MDD, MiDD, and non-depressed groups were identified using analysis of deviance containing the chi-squared test. The fatigue symptoms were compared between the depression groupings using a two-tailed p-value and OR with their 95% CI.

Fatigue and depression symptoms which were significantly different were identified using the thresholds obtained from matSpD.

3. Results

3.1. Study population

The over 50s (aged) study consisted of 4562 participants. However, 1947 individuals returned incomplete responses to SOFA, GHQ, and/or DSSI/sAD questionnaire items utilized to assess depression and fatigue in the present study and were therefore excluded. The remaining 2615 individuals with complete responses comprised the study cohort which was used in all analyses (Table 3). Supplementary Table 1 lists the number of individuals reporting each specific symptom. The study cohort (including 496 complete monozygotic twin pairs, 440 complete dizygotic twin pairs, 5 complete twin pairs of unknown zygosity, and 733 unpaired twin singles), had a mean age of 60.5 years (range = 50–92), which was not significantly different from the non-responders. As

Table 3
Prevalence ratios of fatigue and depression.

	Counts (%)			PR (95% CI) of fatigue		PR (95% CI) of depression	
	Non-fatigued	Fatigued	Total	Non-depressed[a]	Total[b]	Non-fatigued[c]	Total[d]
All symptoms							
Non-depressed	1750 (66.9)	590 (22.6)	2340 (89.5)	NA	0.86 (0.79–0.94)	NA	0.51 (0.41–0.64)
Depressed	99 (3.8)	176 (6.7)	275 (10.5)	2.54 (2.27–2.84)	2.18 (1.96–2.43)	4.29 (3.40–5.41)	2.18 (1.84–2.59)
Total	1849 (70.7)	766 (29.3)	2615 (100.0)				
Non-overlapping symptoms							
Non-depressed	1531 (83.4)	253 (13.8)	1784 (97.2)	NA	0.96 (0.82–1.13)	NA	0.78 (0.51–1.20)
Depressed	34 (1.9)	17 (0.9)	51 (2.8)	2.35 (1.57–3.52)	2.27 (1.51–3.39)	2.90 (1.64–5.11)	2.27 (1.33–3.86)
Total	1565 (85.3)	270 (14.7)	1835 (100.0)				

All symptoms: all individuals; Non-overlapping symptoms: individuals without the fatigue and depression overlapping symptoms; PR: prevalence ratio; CI: confidence interval; NA: not applicable.

[a] Prevalence ratio of fatigue in depressed compared to non-depressed individuals.
[b] Prevalence ratio of fatigue in depressed individuals compared to the total cohort.
[c] Prevalence ratio of depression in fatigued compared to non-fatigued individuals.
[d] Prevalence ratio of depression in fatigued individuals compared to the total cohort.

typically found, significantly higher response rates ($p < 2 \times 10^{-16}$) were observed for females (71.9%) compared to males (58.7%).

Depressed individuals had a two-fold (PR = 2.18, 95% CI = 1.96–2.43) increase in risk of fatigue, compared to the total population sample. Stratification of depressed individuals revealed that the increased risk of fatigue was slightly (although not significantly) higher in MDD cases (PR = 2.32, 95% CI = 1.90–2.83) compared to individuals with MiDD (PR = 2.15, 95% CI = 1.92–2.42). Meanwhile, non-depressed individuals had a reduced risk of fatigue (PR = 0.86, 95% CI = 0.79–0.94). Significantly, depressed individuals risk of fatigue was significantly increased, independent of insomnia, concentration problems, and hypersomnia (PR = 2.27, 95% CI = 1.51–3.39). Similarly, fatigued individuals had a two-fold (PR = 2.18, 95% CI = 1.84–2.59) increased risk of depression, compared to the total population sample. Furthermore, stratification of fatigued individuals risk of depression revealed fatigued individuals had a slightly (although not significantly) higher risk of MDD (PR = 2.32, 95% CI = 1.51–3.56) than MiDD (PR = 2.15, 95% CI = 1.77–2.62). Meanwhile, non-fatigued individuals had a reduced risk of depression (PR = 0.51, 95% CI = 0.41–0.64). Notably, fatigued individuals risk of depression was significantly increased, independent of insomnia, concentration problems and loss of energy (PR = 2.27, 95% CI = 1.33–3.86).

Interestingly, the risk of depression (PR = 4.29, 95% CI = 3.40–5.41) in fatigued compared to non-fatigued individuals is approximately two-fold greater than the risk of fatigue (PR = 2.54, 95% CI = 2.27–2.84) in depressed compared to non-depressed individuals.

3.2. Fatigued individuals report a higher proportion of depression symptoms

The matSpD analysis indicated moderate intercorrelation between the eight depression symptom measures, and estimated them to be equivalent to six effectively independent measures. Therefore, to keep type I error rate at 5%, the significance threshold used for univariable analysis of the eight depression symptoms was adjusted for six independent tests (i.e., Bonferroni adjusted experiment-wide significant threshold, $p = 0.05/6 = 8.3 \times 10^{-3}$).

Analysis of age and sex revealed no significant differences between fatigued and non-fatigued individuals. Therefore, the age and sex variables were not included as covariates in the logistic regression analysis of fatigue symptoms.

Notably, all eight depression symptoms were significantly different (univariable $p < 8.3 \times 10^{-3}$) between fatigued and non-fatigued individuals (Table 4). Furthermore, the full logistic regression model (AIC = 2960.5) comparing fatigued versus non-fatigued individuals, was more parsimonious than the null model (AIC = 3164.8). Therefore, the results provided (in Table 4) are for the more parsimonious model. Comparison of the fatigued and non-fatigued groups (Table 4) revealed an overall significant difference in depression symptoms ($\chi^2 = 220.32$, $p < 2.2 \times 10^{-16}$). In particular, the proportion of fatigued cases reporting anhedonia, insomnia, and feeling worthless, was significantly higher than non-fatigued individuals.

3.3. Depressed individuals report higher proportions of fatigue symptoms

The matSpD analysis of the ten fatigue symptom measures revealed minimal intercorrelation being equivalent to nine effectively independent measures. Therefore, to keep type I error rate at 5%, the significance threshold used for analyses involving all the fatigue symptoms was 5.6×10^{-3} ($p = 0.05/9$).

Demographic analysis of the difference in age and sex revealed no significant differences between depressed and non-depressed individuals. Therefore, the age and sex variables were not included as covariates in the logistic regression analysis of fatigue symptoms.

Table 4
Logistic regression, unadjusted and adjusted for, relatedness, comparing the depression symptoms exhibited by fatigued individuals ($N = 766$) to non-fatigued ($N = 1849$) individuals.

Depression symptoms[a]	Univariable				Multivariable[b]			
	Unadjusted for relatedness		Adjusted for relatedness		Unadjusted for relatedness		Adjusted for relatedness	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Depressed mood	3.88 (2.96–4.97)	$<2.2 \times 10^{-16}$	3.83 (2.96–4.98)	$<2.2 \times 10^{-16}$	1.42 (1.02–1.99)	0.04	1.42 (1.01–2.00)	0.04
Anhedonia	3.89 (3.04–4.98)	$<2.2 \times 10^{-16}$	3.89 (3.05–4.97)	$<2.2 \times 10^{-16}$	1.97 (1.46–2.65)	7.67×10^{-6}	1.97 (1.46–2.66)	1.02×10^{-5}
Insomnia	6.60 (4.36–9.98)	$<2.2 \times 10^{-16}$	6.60 (4.33–10.05)	$<2.2 \times 10^{-16}$	2.14 (1.29–3.53)	3.10×10^{-3}	2.14 (1.23–3.73)	0.01
Psychomotor agitation	9.69 (4.96–18.93)	2.92×10^{-11}	9.69 (5.02–18.71)	1.30×10^{-11}	2.75 (1.26–6.00)	0.01	2.75 (1.23–6.16)	0.01
Loss of energy	4.47 (2.36–8.45)	4.11×10^{-6}	4.47 (2.37–8.44)	3.95×10^{-6}	0.72 (0.32–1.60)	0.42	0.72 (0.29–1.75)	0.47
Feeling worthless	4.25 (3.32–5.46)	$<2.2 \times 10^{-16}$	4.25 (3.33–5.43)	$<2.2 \times 10^{-16}$	2.12 (1.56–2.87)	1.22×10^{-6}	2.12 (1.56–2.79)	1.24×10^{-6}
Inability to concentrate	4.31 (3.00–6.20)	2.78×10^{-15}	4.31 (3.02–6.16)	8.88×10^{-16}	1.75 (1.14–2.68)	0.01	1.75 (1.10–2.79)	0.02
Suicidal thoughts	6.02 (3.06–11.87)	2.10×10^{-7}	6.02 (3.08–11.77)	1.48×10^{-7}	0.85 (0.38–1.93)	0.70	0.85 (0.35–2.05)	0.72

OR: odds ratio; CI: confidence interval.
[a] Defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM).
[b] Multivariable model includes all 8 depression symptoms.

Interestingly, all ten fatigue symptoms were significantly different (univariable $p < 5.6 \times 10^{-3}$) between depressed and non-depressed individuals (Table 5). Furthermore, the full symptom model (AIC = 1342.0) comparison of the fatigue symptoms endorsed by depressed versus non-depressed individuals was more parsimonious than the null model of no differences between the groups (AIC = 1760.7). The comparison revealed an overall significant difference in the depression symptoms ($\chi^2 = 438.77$, $p < 2 \times 10^{-16}$) experienced by depressed and non-depressed individuals (Table 5). In particular, the proportion of depression cases reporting insomnia, poor concentration, and headaches, was significantly higher than non-depressed individuals. Results were comparable between the binomial and ordinal logistic regression modeling (Table 6).

The analyses comparing MDD ($N = 50$), MiDD ($N = 225$), and non-depressed ($N = 2340$) individuals exhibited comparable trends to the results of the 'complete' depressed cohort. All ten fatigue symptoms were significantly different between MiDD and non-depressed individuals (Table 6). Similarly, all the fatigue symptoms except post-exertional muscle pain are significantly different between MDD and non-depressed individuals.

The full fatigue symptom model (AIC = 1585.3) was more parsimonious than the null model (AIC = 2023.5), comparing MDD, MiDD, and non-depressed individuals. Comparison of the MDD and MiDD groups (Table 6) to the non-depressed group revealed an overall significant difference in fatigue symptoms ($\chi^2 = 478.28$, $p < 2.2 \times 10^{-16}$). In particular, the proportion of MiDD cases reporting post-exertional fatigue,

Table 5
Logistic regression, both unadjusted and adjusted for relatedness, of fatigue symptoms exhibited by depressed ($N = 275$) and non-depressed ($N = 2340$) individuals.

Fatigue symptoms[a]	Univariable				Multivariable[b]			
	Unadjusted for relatedness		Adjusted for relatedness		Unadjusted for relatedness		Adjusted for relatedness	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Binomial logistic regression								
Muscle pain at rest	2.79 (2.04–3.80)	8.40×10^{-11}	2.79 (2.05–3.79)	7.70×10^{-11}	1.35 (0.88–2.07)	0.17	1.35 (0.84–2.18)	0.22
Post-exertional muscle pain	2.32 (1.80–2.99)	9.91×10^{-11}	2.32 (1.79–3.00)	1.54×10^{-10}	1.11 (0.77–1.60)	0.57	1.11 (0.76–1.63)	0.59
Post-exertional muscle fatigue	2.48 (1.93–3.19)	1.78×10^{-12}	2.48 (1.92–3.21)	5.50×10^{-12}	1.05 (0.71–1.54)	0.81	1.05 (0.70–1.56)	0.82
Post-exertional fatigue	3.46 (2.66–4.49)	$<2.2 \times 10^{-16}$	3.46 (2.65–4.51)	$<2.2 \times 10^{-16}$	1.77 (1.20–2.60)	3.70×10^{-3}	1.77 (1.17–2.67)	0.01
Hypersomnia	2.31 (1.74–3.07)	6.24×10^{-9}	2.31 (1.73–3.09)	1.83×10^{-8}	1.05 (0.72–1.53)	0.79	1.05 (0.71–1.56)	0.80
Insomnia	11.68 (8.67–15.74)	$<2.2 \times 10^{-16}$	11.68 (8.62–15.83)	$<2.2 \times 10^{-16}$	8.08 (5.78–11.29)	$<2.2 \times 10^{-16}$	8.08 (5.68–11.50)	$<2.2 \times 10^{-16}$
Poor concentration	12.12 (8.95–16.41)	$<2.2 \times 10^{-16}$	12.12 (9.04–16.25)	$<2.2 \times 10^{-16}$	6.92 (4.85–9.87)	$<2.2 \times 10^{-16}$	6.92 (4.79–9.99)	$<2.2 \times 10^{-16}$
Speech problems	2.01 (1.48–2.72)	7.08×10^{-6}	2.01 (1.48–2.73)	8.15×10^{-6}	1.01 (0.67–1.52)	0.97	1.01 (0.67–1.51)	0.97
Poor memory	2.38 (1.79–3.16)	2.66×10^{-9}	2.38 (1.78–3.18)	4.57×10^{-9}	1.09 (0.74–1.62)	0.66	1.09 (0.72–1.66)	0.68
Headaches	2.78 (2.14–3.63)	3.73×10^{-14}	2.78 (2.13–3.564)	1.01×10^{-13}	1.76 (1.28–2.44)	5.92×10^{-4}	1.76 (1.24–2.50)	1.41×10^{-3}

OR: odds ratio; CI: confidence interval.
[a] Assessed by the Schedule of Fatigue and Anergia (SOFA).
[b] Multivariable model includes all 10 fatigue symptoms.

Table 6
Logistic regression of fatigue symptoms exhibited by individuals with major depressive disorder ($N = 50$), minor depressive disorder ($N = 225$), and are non-depressed ($N = 2340$).

Fatigue symptom[a]	Univariable		Multivariable[b]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
MiDD versus non-depressed				
Muscle pain at rest	2.77 (1.98–3.88)	2.75×10^{-9}	1.33 (0.85–2.06)	0.21
Post-exertional muscle pain	2.42 (1.83–3.20)	4.62×10^{-10}	1.22 (0.84–1.79)	0.30
Post-exertional muscle fatigue	2.38 (1.80–3.13)	7.75×10^{-10}	0.99 (0.66–1.48)	0.95
Post-exertional fatigue	3.35 (2.52–4.45)	$<2.2 \times 10^{-16}$	1.80 (1.21–2.70)	3.98×10^{-3}
Hypersomnia	2.15 (1.58–2.94)	1.46×10^{-6}	1.00 (0.68–1.48)	0.98
Insomnia	8.50 (6.12–11.81)	$<2.2 \times 10^{-16}$	6.08 (4.23–8.73)	$<2.2 \times 10^{-16}$
Poor concentration	10.03 (7.22–13.93)	$<2.2 \times 10^{-16}$	6.13 (4.21–8.92)	$<2.2 \times 10^{-16}$
Speech problems	1.89 (1.35–2.65)	2.03×10^{-4}	0.96 (0.62–1.48)	0.86
Poor memory	2.35 (1.72–3.20)	8.16×10^{-8}	1.15 (0.76–1.73)	0.51
Headaches	2.89 (2.17–3.86)	4.44×10^{-13}	1.87 (1.34–2.61)	2.31×10^{-4}
MDD versus non-depressed				
Muscle pain at rest	2.84 (1.46–5.51)	2.01×10^{-3}	1.53 (0.62–3.75)	0.36
Post-exertional muscle pain	1.91 (1.08–3.39)	0.03	0.63 (0.29–1.40)	0.26
Post-exertional muscle fatigue	3.00 (1.70–5.28)	1.40×10^{-4}	1.51 (0.68–3.37)	0.31
Post-exertional fatigue	3.97 (2.26–5.27)	1.78×10^{-6}	1.61 (0.71, 3.65)	0.26
Hypersomnia	3.11 (2.73, 7.00)	1.54×10^{-4}	1.47 (0.67, 3.20)	0.34
Insomnia	48.38 (25.10, 93.26)	$<2.2 \times 10^{-16}$	33.64 (16.80, 67.34)	$<2.2 \times 10^{-16}$
Poor concentration	27.27 (15.05, 49.41)	$<2.2 \times 10^{-16}$	12.98 (6.54, 25.77)	2.41×10^{-14}
Speech problems	2.58 (1.37, 4.83)	3.20×10^{-3}	1.33 (0.59, 2.98)	0.49
Poor memory	2.53 (1.37, 4.68)	3.13×10^{-3}	0.983 (0.36, 1.90)	0.66
Headaches	2.32 (1.28, 4.21)	0.01	1.20 (0.58, 2.48)	0.61
Ordinal logistic regression				
Muscle pain at rest	2.77 (2.04–3.77)	8.62×10^{-11}	1.30 (0.86–1.98)	0.22
Post-exertional muscle pain	2.30 (1.79–2.97)	1.35×10^{-10}	0.99 (0.69–1.42)	0.97
Post-exertional muscle fatigue	2.49 (1.93–3.20)	1.44×10^{-12}	1.17 (0.81–1.69)	0.41
Post-exertional fatigue	3.46 (2.66–4.49)	$<2.2 \times 10^{-16}$	1.66 (1.14–2.41)	0.01
Hypersomnia	2.33 (1.76–3.09)	4.25×10^{-9}	1.09 (0.76–1.56)	0.64
Insomnia	12.79 (9.49–17.23)	$<2.2 \times 10^{-16}$	8.72 (6.31–12.05)	$<2.2 \times 10^{-16}$
Poor concentration	12.57 (9.32–16.95)	$<2.2 \times 10^{-16}$	7.10 (5.03–10.01)	$<2.2 \times 10^{-16}$
Speech problems	2.02 (1.49–2.74)	5.61×10^{-6}	1.04 (0.70–1.55)	0.84
Poor memory	2.38 (1.79–3.16)	2.56×10^{-9}	1.00 (0.68–1.48)	0.99
Headaches	2.76 (2.12–3.59)	5.55×10^{-14}	1.62 (1.18–2.22)	2.68×10^{-3}

MiDD versus non-depressed: results from multinomial logistic regression analysis for MiDD subgroup compared to non-depressed group; MDD versus non-depressed: results from multinomial logistic regression analysis for MDD subgroup compared to non-depressed group; Ordinal logistic regression: results from ordinal logistic regression analysis of the three (MDD, MiDD and non-depressed) subgroups; OR: odds ratio; CI: confidence interval.

[a] Assessed by the Schedule of Fatigue and Anergia (SOFA).

[b] Multivariable ("full") model includes all 10 fatigue symptoms.

insomnia, poor concentration, and headaches was significantly higher than non-depressed individuals. Similarly, the proportion of MDD cases reporting insomnia and poor concentration was higher than non-depressed individuals.

4. Discussion

The results demonstrate that individuals presenting with either fatigue or depression have a two-fold increase in risk for a co-occurring presentation of both traits. The risk of depression in fatigued individuals compared to non-fatigued individuals, is two-fold greater than the risk of fatigue in depressed individuals compared to non-depressed individuals, indicating that fatigue could be used as a predictor to facilitate early detection of depression. This is particularly interesting considering that fatigue severity has been identified as a good predictor of MDD within cancer patients [43]. Although fatigue severity is subjective, the use of specific fatigue symptoms might facilitate more accurate prediction of depression.

Significantly, fatigued individuals reported more depression symptoms than non-fatigued individuals. These results are consistent with previous findings showing that fatigued individuals have higher depression levels [24,25]. However, a proportion of the fatigued individuals will not have comorbid depression; although pure fatigue appears to be a dynamic state with numerous cases exhibiting symptoms of psychological distress [27,28]. That said, the analysis comparing non-depressed individuals with depressed cases revealed significant differences for all ten fatigue symptoms. Therefore, although fatigue and depression symptoms were reported in

individuals who were non-depressed and non-fatigued, respectively, the increased number of symptoms exhibited by fatigued and depressed cases suggests an underlying association.

Heritable associations have been identified between fatigue and depression [44] in a twin sample that partially overlaps the present one. The heritability of fatigue and depression are both estimated to have unique genetic and environmental factors but no contribution of common environmental factors. Multivariate twin modeling estimated a common additive genetic component explained 36.0%, 23.3%, 25.0%, and 20.3% of the variance in psychological distress, anxiety, depression, and fatigue, respectively. Moreover, a second common additive genetic component explained 11.0%, 9.0%, and 5.1% of the variance in anxiety, depression, and fatigue, respectively. Additionally, a third additive genetic component (independent of psychological distress, anxiety, and depression) was found to explain a further 20.3% of variance in fatigue. Furthermore, depression and fatigue were both estimated to have independent unique environmental factors which explained 28% and 54.3% of their variance, respectively [44]. Therefore, the observed comorbidity between fatigue and depression may be explained, in part, by shared underlying genetically determined disease mechanisms.

Insomnia was assessed as both a fatigue and depression symptom. Therefore, the identification of insomnia as a distinguishing symptom between fatigued and non-fatigued individuals is unsurprising. Although poor concentration was also assessed as a symptom of both fatigue and depression, it is not a distinguishing symptom between fatigued and non-fatigued individuals. However, concentration problems may not have reached significance in the full symptom model due to differences in the wording of the fatigue and depression questions for its assessment potentially resulting in different responses by individuals. Therefore, insomnia is a key indicator of co-occurring fatigue and depression. Considering depression diagnosis is particularly difficult within older adults, insomnia and to a lesser extent poor concentration, should be considered as warning signs of depression. Indeed, Deckx and colleges have previously shown fatigue to be an indicator of depression in older cancer patients [43]; whereas, our results demonstrate the broader applicability of fatigue, and in particular insomnia, as an indicator of depression within older adults in the community. Evidence for overlapping molecular mechanisms between fatigue, depression, and insomnia has been provided by heritability estimates within females [45]. Common and symptom-specific additive genetic and unique environmental factors were identified which explain the variance of insomnia, fatigue, and depression. Therefore, overlapping genetic factors could explain the high levels of insomnia in fatigued and depressed individuals and potentially account for a proportion of the high comorbidity of fatigue and depression.

The present study is the first to investigate both fatigue and depression symptoms experienced by depressed and fatigued individuals, respectively. A possible limitation of our study lies in the relatively small number of individuals with MDD and inability to assess the third DSM criterion of a major depressive episode — change in weight or appetite. Although re-running the analysis removing the small proportion (6.4%) of non-depressed individuals who report either depressed mood or anhedonia (and could therefore be depression cases if they reported a change in weight or appetite) did not change the study findings (data not shown). Also, the large number of individuals who did not complete the questions used throughout this study could potentially be due to a reduced likelihood of depressed individuals completing the survey. Although the increased age of the present cohort has possibly contributed to the lower levels of depression observed, we note that comparable prevalence estimates have been reported for individuals over 65 years old in the United States. The Centers for Disease Control and Prevention (2010) reported the prevalence of a current diagnosis of MDD and MiDD in adults at 4.1% and 5.1%, respectively, compared to 2.1% and 4.8%, respectively, in individuals over 65 years old [13]. Furthermore, symptomatic differences have been identified between younger and older adults with depression [46]. Therefore, investigating fatigue and depression in older adults is clinically significant; particularly considering the increased prevalence of fatigue in this age group — although the age of participants increased the likelihood of medically explainable fatigue within the cohort, thereby potentially reducing the specificity of the study. However, fatigue and depression were assessed independently using validated self-report questionnaires; allowing the utilization of consistent assessment measures throughout the complete study cohort, enabling comparable classifications between individuals. Furthermore, utilizing a current depression status was advantageous because it enabled investigation of self-reported co-occurring fatigue and depression. Finally, the use of a community study cohort removed potential confounding with medical healthcare-seeking behavior.

In summary, increased preponderance of depression and fatigue symptoms in fatigued and depressed cases, respectively, indicates that an underlying association exists between the two entities. Furthermore, the polythetic definition of depression and the spectrum of fatigue symptoms imply that the underlying genetics of both entities are heterogeneous. Therefore, utilization of distinguishing symptoms could facilitate the selection of more homogeneous subgroups, potentially enabling identification of risk loci associated with varying phenotype presentations. Future analyses should investigate the comorbidity of fatigue and depression by characterizing the type of relationship which exists between the two entities and their underlying genetics.

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