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High Prevalence of Fatigue in Adults With a 22q11.2 Deletion Syndrome

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The 22q11.2 deletion syndrome (22q11.2DS) is a microdeletion syndrome with high phenotypic variability, including somatic disorders like congenital heart disease and psychiatric disorders such as schizophrenia, anxiety disorders, and mood disorders. Clinical observations suggest that many patients with 22q11.2DS suffer from severe fatigue. However, to the best of our knowledge, no previous study has investigated the potential association between 22q11.2DS and fatigue. Twenty-nine patients (mean age 26.8, 18–38 y) with 22q11.2DS completed the multidimensional fatigue inventory (MFI) measuring severity of fatigue. The results of the study group were compared with published population norms. In addition, cross-sectional associations between fatigue, depression (Beck Depression Inventory—BDI), and a quality of life questionnaire (WHO) in patients with 22q11.2 DS were examined. Subscales and total MFI scores were significantly higher in adults with 22q11.2DS. Approximately 80% of the study group had a total MFI score above the mean of the norms. A significant correlation between depressive symptoms and fatigue was found. Fatigue was also significantly associated with quality of life scores, specifically the general score, psychological health, and environment. This is the first report of high levels of fatigue in adults with the 22q11.2DS. Fatigue is a frequent complaint in this age group and should get the necessary attention given its association with quality of life and depression severity. Taking into account the multisystem nature of the 22q11.2DS, we recommend a systematic clinical examination to exclude underlying somatic or psychiatric causes of fatigue. © 2016 Wiley Periodicals, Inc.

Key words: 22q11.2 deletion syndrome; fatigue; multidimensional fatigue inventory; beck depression inventory; quality of life

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INTRODUCTION

The 22q11.2 deletion syndrome (22q11.2DS) is a genetic syndrome caused by a microdeletion on the long arm of chromosome 22. It is the most frequent microdeletion syndromes with an estimated prevalence of one in 4,000 Live births [Oskarsdottir et al., 2004]. The clinical phenotype is highly variable. Recurring somatic pathology includes a high prevalence of congenital heart disease, velopharyngeal insufficiency, facial dysmorphism, (para)hypothyroidism, thrombocytopenia, anemia, autoimmune disease, immunodeficiency, genitourinary, and gastrointestinal abnormalities [Ryan et al., 1997; Bassett et al., 2005; Tang et al., 2014; McDonald-McGinn et al., 2015]. During childhood and adolescence the average IQ is around 70 [Chow et al., 2006; Butcher et al., 2012]. Other characteristics include learning problems, a mild to moderate intellectual disability, and a high risk of developing severe psychiatric disorders such as ADHD, autism spectrum disorder, anxiety disorders, mood disorders, and schizophrenia spectrum disorders [Schneider et al., 2014].

Studies show a significant psychiatric vulnerability in individuals with a 22q11.2DS from adolescence on. This psychiatric vulnerability includes not only a high prevalence of schizophrenia spectrum disorders, but also anxiety and mood disorders [Schneider et al., 2014]. However, during our psychiatric interviews we were surprised by the high number of (young) adults

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without the presence of any current psychiatric problem that spontaneously complained about fatigue, tiredness, and lack of energy. Most adults and their families were concerned because of the notable impact of these complaints on daily functioning.

To our knowledge no reports on fatigue within this population are found in literature. Butcher et al. [2012] demonstrated that adaptive functioning of adults with a 22q11.2DS is affected and mostly associated to their level of cognitive functioning. In addition, to a lesser extent adaptive functioning was associated to the presence of a schizophrenia spectrum disorder, but not significantly to the presence of mood or anxiety disorders [Butcher et al., 2012]. However, Butcher et al. did not look at the impact of fatigue. Several of the somatic and psychiatric disorders that are highly prevalent in 22q11.2DS are known to be associated with symptoms of fatigue. Moreover, fatigue is associated with several conditions that have an increased prevalence in adults with 22q11.2DS, including congenital heart disease, several autoimmune diseases, infections, hematological disorders, and endocrinological disorders [Ryan et al., 1997; Gennery, 2012]. The latter include anemia, thrombocytopenia, hypothyroidism, and hypoparathyroidism [Cheung et al., 2014; Ryan et al., 1997]. Congenital heart disease has an estimated prevalence of 60% in patients with 22q11.2DS [Bassett et al., 2005]. Most of these cardiac anomalies can be surgically corrected at an early age resulting in a normal adult cardiac function. In a small subgroup of adults with a 22q11.DS a complex and severe cardiopathy induces a deterioration of the cardiac function with a decrease of the ejection fraction causing complaints that include physical fatigue.

Here, we address the following three study questions: (i) What is the level of fatigue in (young) adults with a 22q11.2 DS compared to population norms? (ii) Is there an association between the level of fatigue and prevalent somatic and psychiatric disorders in 22q11.2 DS? (iii) Is there a relation between the level of fatigue and quality of life in 22q11.2 DS?

MATERIALS AND METHODS

Data Collection and Study Participants

Data were collected between January and August 2015. Thirty-four adults with a formal diagnosis of a 22q11.2 microdeletion, based on FISH or microarray, were recruited via the Center for Human Genetics at the University Hospital Leuven, Belgium. Five adults with an IQ below 60 were excluded to insure the reliability of the answers. The final study group included 29 adults (18 women and 11 men) with a 22q11.2DS. All participants were between the ages of 18 and 38 years (Table I). A detailed overview of the age distribution can be found in the supplementary data (Supplemental Fig. S1). Ethical approval for this study was obtained from the Research Medical Ethics Committee UZ KU Leuven (Belgium). All participants provided written informed consent.

Assessments

Participants completed a multidimensional fatigue inventory (MFI-20) and Beck Depression Inventory (BDI) as part of a broader psychiatric assessment [Smets et al., 1995; Beck et al., 1996]. The MFI-20 is a 20 item self-report questionnaire with a Likert scale assessing fatigue in five subdomains, each containing four items. These subdomains consist of general fatigue, physical fatigue, reduced activity, cognitive fatigue, and reduced motivation. The BDI is a 21 item self-report multiple choice questionnaire to assess symptoms that are associated with depression. For the analysis of the BDI an adaptation was made to exclude the items "feeling tired," "sleep disturbances," and "loss of energy." This adapted version was called the BDIc and has already been used in a previous study on fatigue [Kempke et al., 2011]. In our cohort the BDIc had a good internal consistency (Cronbach's $\alpha = 0.83$). All 29 participants completed a MFI-20, but the first 12 participants assessed did not complete a BDI since it was not included in the initial assessment. Cardiac data were only included if a written report from a cardiologist, including an echocardiogram, was present. For thyroid function, anemia, and thrombocytopenia, lab results less than 1 year old or a formal diagnosis were used.

In an effort to measure quality of life (QoL) within adults with a 22q11.2DS, 13 participants completed a validated WHO questionnaire that scored five subdomains of QoL. These subdomains include a general score, physical health, psychological health, social relationships, and environment [Trompenaars et al., 2005]. Based upon the answers a perceived QoL is measured in each of the five subdomains. Data on QoL were collected from a subgroup of patients as part of a study on resilience and QoL in adolescents and adults with a 22q11.2DS running during the same time period. Results are presented in Table III and Figure 2 C–F.

Statistical Analyses

To define severity of fatigue in the sample cohort compared to normal levels, total MFI score, as well as the five subscale scores, were converted into Z-scores based on population norms. Z-scores

TABLE I. Characteristics of the Study Sample and Means of the Questionnaires

	N	Mean	Standard deviation
Age			
Women	18	27.17	4.76
Men	11	26.09	6.19
Total	29	26.76	5.26
MFI general fatigue	29	12.83	3.66
MFI physical fatigue	29	11.55	4.03
MFI reduced activity	29	10.17	3.51
MFI cognitive fatigue	29	10.17	3.69
MFI reduced motivation	29	10.83	3.65
Total MFI score	29	55.55	14.77
BMI	29	27.61	5.79
BDIc	17	6.94	5.90
General score QoL	13	7.31	1.44
Physical health QoL	13	13.89	2.87
Psychological health QoL	13	13.79	3.04
Social relationships QoL	8	16.00	3.19
Environment QoL	13	14.77	3.20

were calculated for every participant using the mean (M^{norm}) and standard deviation (SD^{norm}) of published normative values:

$$\text{Z-score} = (S^{part} - M^{norm})/SD^{norm}$$

with S^{part} = individual score of a participant; M^{norm} = Mean of the population norms; SD^{norm} = Standard deviaton of the population norms.

Normative values for subscales were calculated from an adult general population of 2,037 subjects in Germany [Schwarz et al., 2003]. Values were calculated from a subgroup of 1,500 subjects with an age below 39 years old. As there were no population norms published on the total MFI score for this population, but only on subscales, normative values for total MFI score were based on an adult general population in Colombia [Hinz et al., 2013]. This Colombian cohort is composed of 1,500 subjects that were age 18 years and older at the time of sampling [Hinz et al., 2013].

This method allowed us to use a certain age category (<39 years old) for the subscales and take into account gender for all the scores by using a separate M^{norm} and SD^{norm} for men and women. This approach was chosen because studies have shown that MFI scores are age and sex dependent [Schwarz et al., 2003]. Within our cohort no significant correlation was found between age and MFI scores. There was no significant impact of age on fatigue within this age group of adults between 18 and 38 years old. The means and standard deviations for MFI scores, Z-score, and normative values are presented in Table II. MFI scores and corresponding Z-scores were normally distributed.

To determine if the difference between population norms and sample scores were significant, a two sample T-test for independent samples with unequal variances was performed using the mean and standard deviation of the normative values adhering to the following formula:

$$\text{T-test} = \left(M^{sample} - M^{norm}\right)/\sqrt{\left(V^{norm}/N^{norm} + V^{sample}/N^{sample}\right)}$$

with M^{sample} = Mean of the sample; M^{norm} = Mean of the norms; V^{sample} = Variance of the sample; V^{norm} = Variance of the population norms; N^{sample} = Number of participants in the sample; N^{norm} = Number of participants used in the norm sample.

The approximate degrees of freedom d" was computed based on the Satterthwaite's Method (Table III).

Spearman correlations were performed to look for associations with BDIc results. A simple linear regression was performed (Table III) to investigate the relationship of MFI with BMI, BDIc, and QoL. Preliminary analyses were performed to ensure the assumption of normality and linearity. Statistical analysis was performed using SPSS version 22.0.

RESULTS

Internal Consistency of the MFI Subscales

Statistical analysis was performed to assess the internal consistency of the MFI scores within a group of adults with 22q11.2DS. Cronbach's α was calculated for total MFI score (20 items) as well as for each subscale of four items. Results showed it to be a reliable questionnaire for adults with 22q11.2 DS and an IQ

TABLE II. Internal Consistency of the MFI Subscales: Crohnbach's α and Pearson Correlations

	MFI general fatigue	MFI physical fatigue	MFI reduced activity	MFI reduced motivation	MFI cognitive fatigue	Total MFI score
Cronbach's α	0.816	0.741	0.758	0.783	0.723	0.911
Pearson correlation (2-tailed *P*-value) N = 29						
MFI general fatigue	1	0.799*** (0.000)	0.691*** (0.000)	0.489** (0.007)	0.662*** (0.000)	0.915*** (0.000)
MFI physical fatigue		1	0.592*** (0.001)	0.336 (0.075)	0.568*** (0.001)	0.835*** (0.000)
MFI reduced acitivity			1	0.535** (0.003)	0.469* (0.010)	0.819*** (0.000)
MFI reduced motivation				1	0.294 (0.122)	0.662*** (0.000)
MFI cognitive fatigue					1	0.751*** (0.000)

Pearson correlation (two-tailed): $^{***}\alpha < 0.001$; $^{**}\alpha < 0.01$; $^{*}\alpha < 0.05$.

above 60. Total MFI score and five subscales had a good internal consistency with a Cronbach's α above 0.7 (Table II). Pearson correlation found a high correlation for the general fatigue subscale with all four other subscales. Highest correlation between subscales could be found between general fatigue subscale and the physical fatigue subscale of the MFI ($\rho = 0.799$). Correlations between other subscales were moderate to low.

Severity of Fatigue in Adults With 22q11.2DS

The histogram (Fig. 1A) and mean calculated Z-scores of total MFI score (Table III) suggest an increase in mean total MFI score in adults with 22q11.2DS. Looking at 95% confidence intervals, and based on the two sample t-test with unequal variances, the mean total fatigue score in adults with 22q11.2DS is significantly higher than the mean of the normative values ($\alpha < 0.005$). A two sample t-test of men and women separately comparing the mean of the population norms with the mean of the adults with 22q11.2DS identified a significantly higher mean in women with 22q11.2DS, but only a trend in men (Table III).

Based on the two sample t-tests, as well as the 95% confidence intervals, the subscale score on all five subscales are significantly higher than the population norms (Table III). The largest increase compared to the general population was found in the subscales general fatigue and physical fatigue. For these subscales the difference was comparable in both men and women. For the subscale general fatigue the histogram showed that almost all adults with 22q11.2DS scored above the mean of the population norms (Fig. 1B). The general fatigue score in 22q11.2DS was almost twice as high as the norms, even when looking at men and women separately. The increase in the mean physical fatigue score in 22q11.2DS was also significant in both women and men (Table III). The histogram showed that more than 90% scored above the mean of the population norms (Fig. 1D).

For the reduced activity and cognitive fatigue subscales of the MFI and for the total MFI score, a more pronounced effect was observed in women. Figure 1C shows that 86% of the participants had a cognitive fatigue score above the mean of the normative values. The difference with the population norms is larger in women (mean Z-score = 1.67) than in men (mean Z-score = 0.76). About 83% of the adults with 22q11.2DS had a reduced activity score above the mean of the normative values (Fig. 1E). Comparable to what was seen in the subscale cognitive fatigue, the increase in the reduced activity subscale was more pronounced in women with 22q11.2DS.

For the reduced motivation subscale of the MFI the mean increase is higher in men than in women (Table III). About 83% of the group had a reduced motivation score above the mean of the population norm (Fig. 1F). 95% confidence intervals and two sample t-tests found the increase to be significant in both men and women.

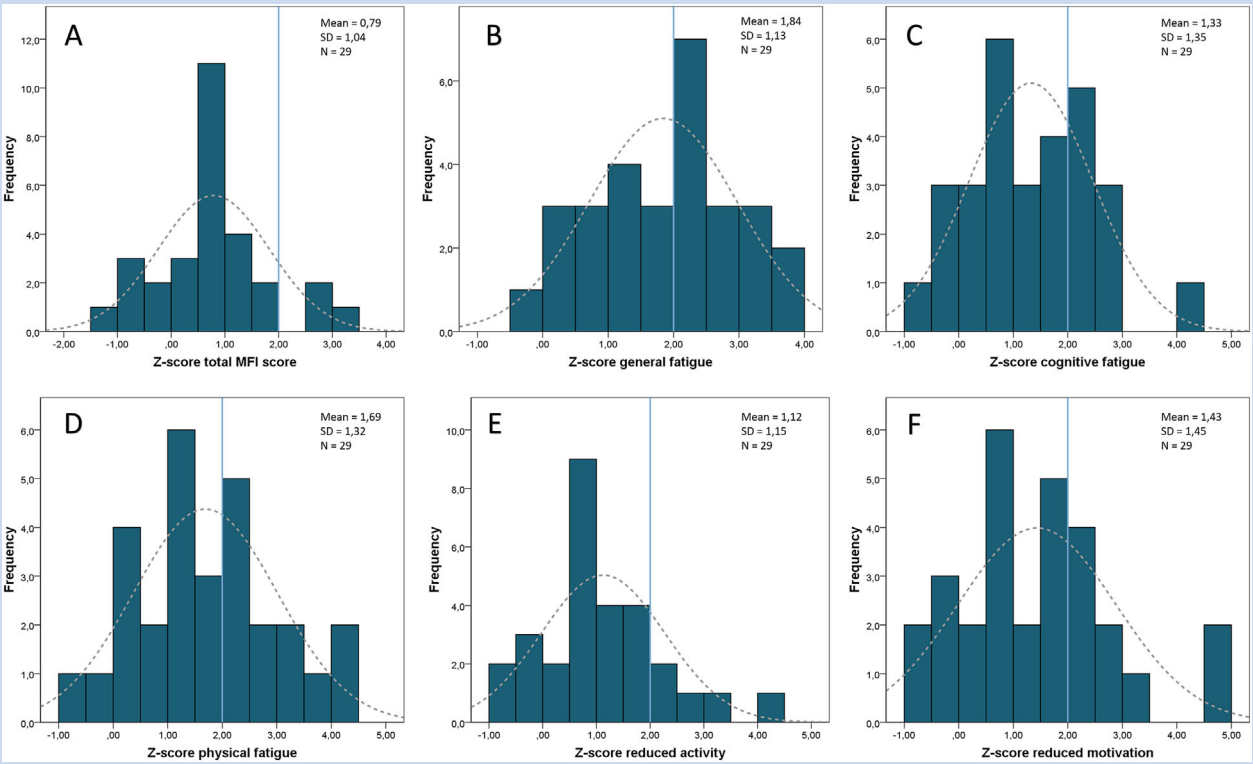

FIG. 1. (A–F) Histograms showing the Z-scores for MFI subscales. The blue line represents the 95% border in the norm group which means that in the general population 95% of the people will have a score that is lower than the score represented by this line. [Color figure can be viewed at wileyonlinelibrary.com].

TABLE III. Descriptive Statistics, Z-score and two Sample T-test

	MFI general fatigue	MFI physical fatigue	MFI reduced activity	MFI reduced motivation	MFI cognitive fatigue	Total MFI score
Mean of the adults with 22q11.2DS						
Women	13.6 (4.1)	12.3 (4.6)	10.9 (3.7)	9.9 (3.9)	12.3 (3.5)	59.1 (16.1)
Men	11.6 (2.4)	10.3 (2.5)	8.9 (3.0)	10.6 (3.5)	8.5 (2.5)	49.7 (10.4)
Total	12.8 (3.7)	11.6 (4.0)	10.2 (3.5)	10.2 (3.7)	10.8 (3.7)	55.6 (14.8)
95% CI for the mean of adults with 22q11.2DS						
Women	11.6–15.7	10.0–14.6	9.1–12.8	8.0–11.9	10.5–14.0	51.1–67.1
Men	9.9–13.2	8.6–11.9	6.9–10.9	8.2–12.9	6.8–10.1	42.7–56.7
Mean norm population (SD)						
Women[a]	7.7 (3.2)	6.8 (3)	7.1 (3)	6.7 (2.7)	7.1 (3.1)	45.1 (14)[b]
Men[a]	6.6 (2.7)	6.1 (2.9)	6.4 (2.9)	6.2 (2.4)	6.4 (2.7)	43.4 (14.1)[b]
Mean Z-score (SD)						
Women[a]	1.85 (1.28)	1.84 (1.54)	1.28 (1.22)	1.20 (1.45)	1.67 (1.13)	1.0 (1.15)
Men[a]	1.83 (0.90)	1.44 (0.86)	0.87 (1.03)	1.81 (1.44)	0.76 (0.93)	0.45 (0.74)
Total	1.84 (1.13)[d]	1.69 (1.32)[d]	1.12 (1.15)[d]	1.43 (1.45)[d]	1.33 (1.13)[d]	0.79 (1.04)[d]
T-test[c] (df")[f]						
Women	6.03*** (17)	5.03*** (17)	4.4*** (18)	3.48** (17)	6.15*** (18)	3.62** (18)
Men	6.61*** (10)	5.41*** (11)	2.74* (10)	4.14** (10)	2.66* (10)	1.95 (11)
Total[e]	8.60*** (29)	6.80*** (29)	5.18*** (29)	5.26*** (29)	6.19*** (29)	4.03*** (30)

T-distribution two sided significance levels (two-tailed): $^{***}\alpha < 0.001$; $^{**}\alpha < 0.01$; $^{*}\alpha < 0.05$.
[a]Population from Germany, age <39 years old, men and women respectively n = 282 and n = 396.
[b]Population from Columbia, all ages, n = 1500 (724 men; 776 women).
[c]Significance level: $\alpha = 0.05$; there is a significant difference between the sample mean and the mean of thenorms if the Z-test > 1.96 or < (−1.96).
[d]Mean Total Z-scores were calculated directly from the individual Z-scores.
[e]T-test for Total scores were calculated using Mean = 0 en SD = 1 with n = 678 (definition of a standardized normal distribution).
[f]df" approximate degrees of freedom was calculated based on Satterthwaite's method for every subgroup and subscale separately.

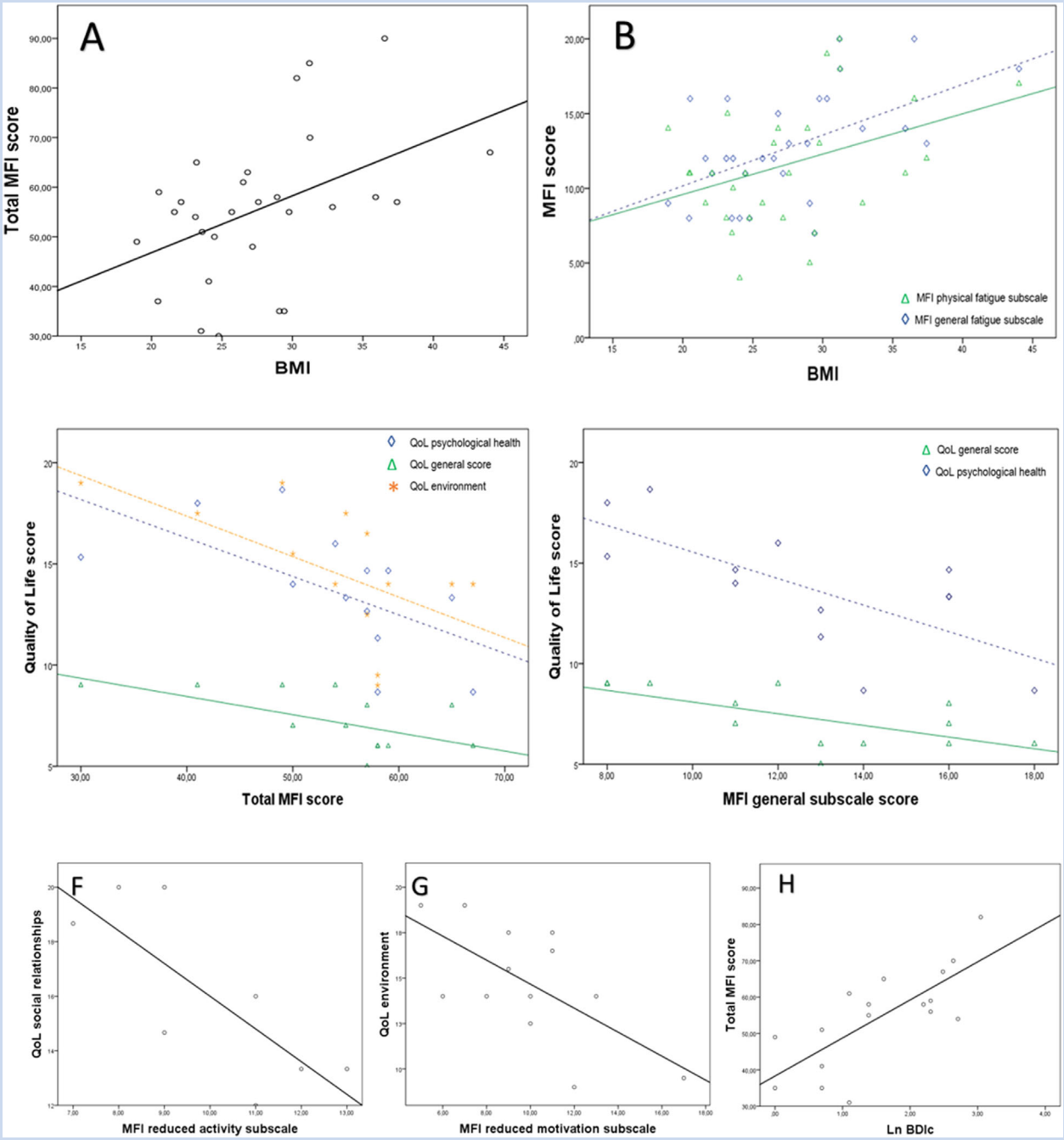

FIG. 2. (A–G) Linear regression models predicting MFI scores. (A) Total MFI score based upon BMI (N = 29); (B) physical (Δ) and general fatigue score (◇) based upon BMI (N = 29) with, respectively $R^2 = 0.147$ and $R^2 = 0.295$; (C) Quality of life scores based upon total MFI score; (D) Quality of life scores predicted based upon MFI general fatigue scores; (E) Quality of life scores predicted based upon MFI reduced activity subscale scores; (F) Quality of life scores predicted based upon MFI reduced motivation subscale score; (G) Total MFI scores predicted based upon the Ln of BDIc scores. [Color figure can be viewed at wileyonlinelibrary.com].

When using the Z-scores to define the extent of the increase compared to the general population, the reduced motivation subscale is the only subscale showing a larger increase in men than women with 22q11.2DS. Total MFI score and other subscales have an increase that is as large or larger in women with 22q11.2DS.

Somatic Factors Associated With 22q11.2DS Involved in the Development of Fatigue

Data included recent and extensive cardiac histories for 26 out of 29 (90%) participants. Only two subjects had a significant deterioration

TABLE IV. Spearman Correlation and Linear Regression Between MFI, BMI, BDIc, and WHO Quality of Life Questionnaires

	MFI general fatigue	MFI physical fatigue	MFI reduced activity	MFI reduced motivation	MFI cognitive fatigue	Total MFI score
BMI (N = 29)						
β	0.543	0.383	0.339	0.198	0.326	0.449
F	11.30	4.64	3.51	1.10	3.21	6.83
P-value	0.002**	0.040*	0.072	0.304	0.084	0.014*
BDIc (N = 17)						
Correlation coefficient[a]	**0.752****	**0.521***	**0.562***	0.329	**0.603***	**0.744****
β						1.7
F						18.8
P-value						0.001
Quality of life general score (N = 13)						
Correlation coefficient[a]	**−0.671***	−0.389	−0.453	−0.087	−0.178	**−0.692****
β	−0.29					−0.09
F	8.32					6.20
P-value	0.015					0.03
Quality of life psychological heatlh (N = 13)						
Correlation coefficient[a]	**−0.720****	−0.527	−0.480	−0.159	−0.055	**−0.733****
β	−0.66					−0.33[b]
F	10.88					11.53[b]
P-value	0.007					0.007[b]
Quality of life social relationships (N = 8)						
Correlation coefficient[a]	−0.296	0.013	**−0.738***	−0.494	0.442	−0.374
β			−1.2			
F			9.29			
P-value			0.023			
Quality of life environment score (N = 13)						
Correlation coefficient[a]	**−0.570***	−0.220	−0.479	**−0.562***	−0.185	**−0.712****
β	−0.49			−0.66		−0.2
F				8.10		6.26
P-value	0.085			0.016		0.03

[a]Correlation coefficient and *P*-value for the Spearman correlation.
[b]N = 12, linear regression model with one individual removed based on Cook's value.
*P-value < 0.05; **P-value < 0.01.

of the cardiac function with an ejection fraction below 60%. Recent measurements of thyroid function (<1 year) were present for 13 participants, of which three were being treated for hypothyroidism. Recent blood control showed a stable thyroid function in two of these three participants. Adults with 22q11.2DS also have a higher risk of developing anemia and thrombocytopenia, mostly caused by an autoimmune reaction. Data included recent measurements of these blood cell types in 15 of the participants with four having a mild form of anemia and eight having a mild form of thrombocytopenia.

Since adults with 22q11.2DS are known to have a higher risk of developing obesity, a linear regression was performed to examine the relation between MFI subscales and BMI. A significant association was found between BMI and subscales general fatigue, physical fatigue, and total MFI score (Table IV). A higher BMI was associated with higher levels of general and physical fatigue and a higher total MFI score (Fig. 2A and B).

The Association Between Depression and the Development of Fatigue in 22q11.2DS

Seven out of 17 participants demonstrated significant depressive symptoms determined by the BDI. Five participants showed mild symptoms, one had moderate depressive symptoms, and one reported severe depressive symptoms. An adapted BDI (BDIc) was used to look at the association between depressive symptoms and MFI scores. Spearman correlation between BDIc and MFI scores showed a significant and strong correlation with the subscale general fatigue and total MFI score. A moderate correlation was found between BDIc and the subscales cognitive fatigue, physical fatigue, and reduced activity (Table IV). Surprisingly, no significant correlation was found between BDIc score and the reduced motivation subscale of the MFI. A linear regression equation that predicted total MFI score based upon the Ln of the BDIc score ($F(1,27) = 18.8$, $P = 0.001$) showed an R^2 of 0.56 (Fig. 2G).

Impact on Quality of Life

A Spearman correlation found a significant negative correlation between total MFI score and the general QoL score, psychological health score, and environment score (Table IV). A simple linear regression was performed for each of these correlations (Fig. 2C and Table IV). The regression equation for psychological health ($F(1,12) = 6.34$, $P = 0.03$) showed an R^2 of 0.37 (Fig. 2C). Based on Cook's distance we identified one outlier that had an important impact on the regression equation. When excluding this outlier our regression equation for psychological health predicted from total MFI score ($F(1,11) = 11.53$, $P = 0.007$) increased to an R^2 of 0.54. These results identify a significant relation between total MFI score and QoL. Higher scores on the MFI, indicating a higher level of fatigue, were associated with a lower psychological health, lower perceived quality of the environment ($R^2 = 0.36$), and a lower general score for QoL ($R^2 = 0.36$).

When focusing on the MFI subscales a significant negative Spearman correlation and a negative linear regression equation was found between the general fatigue subscale and the general QoL score as well as the psychological health score (Table IV). Simple linear regression (Fig. 2D) predicted a decrease of general QoL score ($R^2 = 0.43$) and psychological health score ($R^2 = 0.50$) when the MFI general fatigue subscale score is increased.

Furthermore, we found two other significant negative Spearman correlations. First, we found a significant negative correlation between the MFI reduced activity subscale and the perceived quality of social relationships. Secondly, we found a significant negative correlation between the MFI reduced motivation subscale and the perceived quality of the environment (Table IV). A simple linear regression predicted a lower quality of social relationships in the case of higher reduced activity subscale scores (R^2 of 0.61). A similar relation was found with a higher MFI reduced motivation score predicting lower perceived quality of the environment (R^2 of 0.42).

DISCUSSION

This exploratory study is the first in objectifying the frequent complaint of fatigue in (young) adults with 22q11.2DS. The presence of higher levels of fatigue was confirmed based on MFI scores. The symptoms of fatigue include both physical and mental aspects. In addition, the level of fatigue has a major impact on daily activity and motivation. Although subscale scores of the MFI are not as high as typically seen in adults with chronic fatigue syndro me (CFS), about 10–20% of the adults with 22q11.2 DS show subscale scores as high or higher than mean MFI subscale scores in adults with CFS [Lin et al., 2009].

Similar to the general population, women with 22q11.2DS have higher scores on the MFI than men. The one exception in this study were men with 22q11.2DS scoring higher on the reduced motivation subscale of the MFI. A possible explanation for this exception could be found in characteristics that are more prevalent in men with 22q11.2DS than women. For example, a high prevalence of ADHD in boys with 22q11.2DS has been described as a failure to give close attention to detail, failure to follow instructions, and a reluctance to engage in tasks that require sustained mental effort [Antshel et al., 2007; Schneider et al., 2014]. The fatigue might increase the existing difficulties with sustained mental effort. As obstacles seem to increase over time, men with 22q11.2DS (already experiencing more difficulties with sustaining their attention than women with 22q11.2DS) might be more affected by the fatigue in performing complex cognitive tasks. Therefore, they might experience less motivation to overcome those obstacles.

An important question was to what extent somatic disorders play a role in the development of fatigue in adults with 22q11.2DS. Since only a limited amount of data with a low prevalence was available for the study group, no extensive analysis could be performed. To answer this question in future studies a standardized somatic evaluation in every study participant, including (para) thyroid function and blood cell counts, should be performed at the same time point as the fatigue measurement. A significant positive relation was found for BMI with the physical fatigue subscale as well as the general fatigue subscale. Obesity and higher levels of fatigue seem to be associated. The direction of this association can have an important impact on treatment. If being obese causes fatigue, a combination of dietary interventions together with physical

rehabilitation might not only reduce the health risks that accompany being obese, but also reduce the fatigue in adults with 22q11.2DS. On the other hand, if the fatigue is causing the obesity, etiology and treatment of fatigue could become an important part of handling the weight problems in adults with 22q11.2DS.

Although only a subgroup of participants (7/17) reported relevant depressive symptoms, the high correlations between BDIc and MFI scores do suggest a relation between fatigue and depression in adults with 22q11.2DS. Based on our findings, assumptions about the nature and direction of this relation cannot yet be made. Results suggest that either depressive symptoms play a role in the development of fatigue within this population or that the presence of fatigue makes adults with 22q11.2DS more vulnerable to develop a depression.

Although the four items on the reduced motivation subscale (having plans; feeling like doing all sorts of nice things; dreading having to do things; not feeling like doing anything) intuitively seem to be the closest related to depressive symptoms, this subscale is surprisingly not significantly correlated with the BDIc. The reason for this might be a lack of power, but it is also possible that the reduced motivation subscale is identifying another cognitive/emotional process that seems to be impaired in association with the fatigue. These results emphasize that besides mood and anxiety disorders other cognitive and emotional factors can play a role in fatigue. Also, reduced motivation in this population should not be too easily interpreted as a symptom of depression.

Taking into account the known psychiatric vulnerability in adults with 22q11.2DS, the results of this preliminary study do imply that it is important to determine if the fatigue is contributing to the psychiatric vulnerability or rather caused by it. Recent research investigating fatigue and psychiatric disorders such as major depressive disorder is focusing on the role of endocrinological as well as immunological factors in their development. Several psychiatric disorders including depression and schizophrenia have been associated with changes in the stress system and a pro-inflammatory state of the immune system [Gibney and Drexhage, 2013; Gold et al., 2015]. Also, a variety of abnormalities of the immune system have already been found in patients with CFS [Lorusso et al., 2009]. In addition, not only thyroid disorders, but also pituitary and adrenal disorders are associated with fatigue [Kaltsas et al., 2010]. A different approach focusing on the combination of physical measurements and psychological symptoms could contribute to understanding the development of fatigue and the interaction with the psychiatric vulnerability in adults with 22q11.2DS. In addition it could help understand the role of endocrine and immune systems in the development of fatigue.

Fatigue has an important association with QoL, even in this relatively small sample size. The impact of fatigue seems to be higher on psychological and environmental factors, but not on physical quality of life. Another important observation is the relation between reduced activity and lower quality of social relationships. As adults with 22q11.2DS already have difficulties with socialization and developing social skills, fatigue causing reduced activity might aggravate the impact of this deficit. Although not measured in this study, several participants reported that the fatigue severely impacts their level of daily functioning with an increased amount of sleep, problems concentrating at the end of a workday, and the need to limit the amount of activities in a day. The impact on QoL does seem to support this and is in accordance with the questions and concerns reported by patients and their families.

Limitations

This study was performed with a small sample size and did not include a healthy age-matched control population. Confirming these results in a larger group of adults with 22q11.2DS is warranted. The question regarding the role of somatic pathology in fatigue in 22q11.2 DS could not be answered because the prevalence of cardiac, hematological, and endocrinological pathology was too low in the available data. Medication and quality of sleep, both factors known to cause fatigue, were not included in our report. QoL data were only available in a subgroup of our patients so data should be interpreted with caution.

CONCLUSION

In summary, our results show a high prevalence of fatigue in (young) adults with 22q11.2DS and an association of fatigue with BMI, depressive symptoms, and quality of life. These results confirm the clinical observations and support the reported impact of this fatigue on daily life functioning. The evaluation of fatigue should be an important part of the multidisciplinary follow-up in adults with 22q11.2DS already from the age of 18 years on. Clinicians need to be aware of this symptom. They should perform a good clinical examination combined with the necessary investigations (weight, blood cell counts, immune function, (para) thyroid function, and cardiac function) to diagnose and treat known somatic causes for which 22q11.2DS adults have a higher risk. Furthermore it is important to pay attention to the presence of psychiatric diseases such as a major depressive disorders. Further research into the role of specific causes of fatigue in 22q11.2DS is necessary to help develop preventive strategies. Investigating the role of several somatic and psychiatric disorders that have a high prevalence within this population might help elucidate the etiology of the fatigue.

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REFERENCES

Antshel KM, Faraone SV, Fremont W, Monuteaux MC, Kates WR, Doyle A, Mick E, Biederman J. 2007. Comparing ADHD in velocardiofacial syndrome to idiopathic ADHD: A preliminary study. J Atten Disord 11:64–73.

Bassett AS, Chow EWC, Husted J, Weksberg R, Caluseriu O, Webb GD, Gatzoulis MA. 2005. Clinical features of 78 adults with 22q11 deletion syndrome. Am J Med Genet Part A 138A:307–313.

Beck AT, Steer RA, Ball R, Ranieri W. 1996. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. J Pers Assess 67:588–597.

Butcher NJ, Chow EWC, Costain G, Karas D, Ho A, Bassett AS. 2012. Functional outcomes of adults with 22q11.2 deletion syndrome. Genet Med 14:836–843.

Cheung ENM, George SR, Costain GA, Andrade DM, Chow EWC, Silversides CK, Bassett AS. 2014. Prevalence of hypocalcaemia and its associated features in 22q11·2 deletion syndrome. Clin Endocrinol (Oxf) 81:190–196.

Chow EWC, Watson M, Young DA, Bassett AS. 2006. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. Schizophr Res 87:270–278.

Gennery AR. 2012. Immunological aspects of 22q11.2 deletion syndrome. Cell Mol Life Sci 69:17–27.

Gibney SM, Drexhage HA. 2013. Evidence for a dysregulated immune system in the etiology of psychiatric disorders. J Neuroimmune Pharmacol 8:900–920.

Gold PW, Machado-Vieira R, Pavlatou MG. 2015. Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress. Neural Plast 2015:581976.

Hinz A, Barboza CF, Barradas S, Körner A, Beierlein V, Singer S. 2013. Fatigue in the general population of Colombia—normative values for the multidimensional fatigue inventory MFI-20. Onkologie 36: 403–407.

Kaltsas G, Vgontzas A, Chrousos G. 2010. Fatigue, endocrinopathies, and metabolic disorders. PMR 2:393–398.

Kempke S, Van Houdenhove B, Luyten P, Goossens L, Bekaert P, Van Wambeke P. 2011. Unraveling the role of perfectionism in chronic fatigue syndrome: Is there a distinction between adaptive and maladaptive perfectionism? Psychiatry Res 186:373–377.

Lin J-MS, Brimmer DJ, Maloney EM, Nyarko E, Belue R, Reeves WC. 2009. Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. Popul Health Metr 7:18.

Lorusso L, Mikhaylova SV, Capelli E, Ferrari D, Ngonga GK, Ricevuti G. 2009. Immunological aspects of chronic fatigue syndrome. Autoimmun Rev 8:287–291.

McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JAS, Zackai EH, Emanuel BS, Vermeesch JR, Morrow BE, Scambler PJ, Bassett AS. 2015. 22q11.2 deletion syndrome. Nat Rev Dis Prim 1:15071.

Oskarsdottir S, Vujic M, Fasth A. 2004. Incidence and prevalence of the 22q11 deletion syndrome: A population-based study in Western Sweden. Arch Dis Child 89:148–151.

Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, Seidel H, Schuffenhauer S, Oechsler H, Belohradsky B, Prieur M, Aurias A, Raymond FL, Clayton-Smith J, Hatchwell E, McKeown C, Beemer FA, Dallapiccola B, Novelli G, Hurst JA, Ignatius J, Green AJ, Winter RM, Brueton L, Brøndum-Nielsen K, Scambler PJ. 1997. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: A European collaborative study. J Med Genet 34:798–804.

Schneider M, Debbané M, Bassett AS, Chow EWC, Fung WLA, van den Bree M, Owen M, Murphy KC, Niarchou M, Kates WR, Antshel KM, Fremont W, McDonald-McGinn DM, Gur RE, Zackai EH, Vorstman J, Duijff SN, Klaassen PWJ, Swillen A, Gothelf D, Green T, Weizman A, Van Amelsvoort T, Evers L, Boot E, Shashi V, Hooper SR, Bearden CE, Jalbrzikowski M, Armando M, Vicari S, Murphy DG, Ousley O, Campbell LE, Simon TJ, Eliez S. 2014. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: Results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Am J Psychiatry 171: 627–639.

Schwarz R, Krauss O, Hinz A. 2003. Fatigue in the general population. Onkologie 26:140–144.

Smets EMA, Garssen B, Bonke B, De Haes JCJM. 1995. The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 39:315–325.

Tang SX, Yi JJ, Moore TM, Calkins ME, Kohler CG, Whinna DA, Souders MC, Zackai EH, McDonald-McGinn DM, Emanuel BS, Bilker WB, Gur RC, Gur RE. 2014. Subthreshold psychotic symptoms in 22q11.2 deletion syndrome. J Am Acad Child Adolesc Psychiatry 53:e2.

Trompenaars FJ, Masthoff ED, Van Heck GL, Hodiamont PP, De Vries J. 2005. Content validity, construct validity, and reliability of the WHO-QOL-Bref in a population of Dutch adult psychiatric outpatients. Qual Life Res 14:151–160.

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