### Rethinking childhood adversity in chronic fatigue syndrome

James E Clark, Sean Davidson, Laura Maclachlan, Megan Lynn, Julia L Newton, Stuart Watson

**Objectives**: Previous studies have consistently shown increased rates of childhood adversity in chronic fatigue syndrome (CFS). However, such aetiopathogenic studies of CFS are potentially confounded by co-morbidity and misdiagnosis particularly with depression. We used a modelling approach with existing data and data generated in our examination of the rates of childhood adversity in a sample of CFS patients who had no lifetime history of depression. **Methods**: The childhood trauma questionnaire (CTQ) was completed by a sample of 52 participants and 19 controls with chronic fatigue syndrome who did not meet criteria for a psychiatric disorder (confirmed using the Structured Clinical Interview for DSM-IV). Subsequently, Mediation Analysis (Baye's Rules) was used to establish the risk childhood adversity poses for CFS with and without depression. Results: In a cohort of CFS patients with depression robustly excluded, CTQ scores were markedly lower than in all previous studies and, in contrast to these previous studies, not increased compared with healthy controls. Post-hoc analysis showed that CTQ scores correlated with the number of depressive symptoms during the lifetime worst period of low mood. The probability of developing CFS given a history of childhood trauma was shown to be 4%, a two-fold increased risk compared to the general population. However, much of this risk is mediated by the concomitant development of major depression. **Discussion**: The data suggests that previous studies showing a relationship between childhood adversity and CFS may be mediated by depression

# Rethinking Childhood Adversity in Chronic Fatigue Syndrome

### 3 Short Title- CTQ in CFS

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#### 15 **ABSTRACT**

#### 16 **Objectives**

17 Previous studies have consistently shown increased rates of childhood adversity in chronic

- 18 fatigue syndrome (CFS). However, such aetiopathogenic studies of CFS are potentially
- 19 confounded by co-morbidity and misdiagnosis particularly with depression. We used a modelling
- 20 approach with existing data and data generated in our examination of the rates of childhood
- 21 adversity in a sample of CFS patients who had no lifetime history of depression.

#### 22 Methods

The childhood trauma questionnaire (CTQ) was completed by a sample of 52 participants and 19
controls with chronic fatigue syndrome who did not meet criteria for a psychiatric disorder
(confirmed using the Structured Clinical Interview for DSM-IV). Subsequently, Mediation
Analysis (Baye's Rules) was used to establish the risk childhood adversity poses for CFS with
and without depression.

#### 28 **Results**

In a cohort of CFS patients with depression robustly excluded, CTQ scores were markedly lower than in all previous studies and, in contrast to these previous studies, not increased compared with healthy controls. Post-hoc analysis showed that CTQ scores correlated with the number of depressive symptoms during the lifetime worst period of low mood. The probability of developing CFS given a history of childhood trauma was shown to be 4%, a two-fold increased risk compared to the general population. However, much of this risk is mediated by the concomitant development of major depression.

### 36 **Discussion**

- 37 The data suggests that previous studies showing a relationship between childhood adversity and
- 38 CFS may be mediated by depression

#### **39 INTRODUCTION**

40 Childhood adversity impacts the development of neuroendocrine and immune systems and is 41 implicated in the vulnerability to, and maintenance of, physical and psychiatric disorders. A 42 number of existing case-control studies have used retrospective questionnaires to assess the 43 prevalence of childhood trauma in chronic fatigue syndrome (CFS) (Kempke et al. 2013). 44 Almost (Taylor & Jason 2001) all have demonstrated a significantly increased prevalence of one 45 or more subtypes of childhood trauma in people with CFS which has led some to hypothesise 46 that early childhood adversity is a risk factor for CFS. Previous work has, however, neglected 47 the potential mediating impact of depressive symptoms on this finding. Our hypothesis is 48 therefore that the increased prevalence of early life adversity is related to the high comorbidity 49 with major depressive disorder found in this patient group rather than being a primary risk factor 50 for CFS itself.

In order to explore the hypothesis that childhood adversity increases the risk of CFS predominantly via its effects on the risk of depression, we determined the prevalence of early adversity in a CFS population who were free of current or lifetime depression and applied this and existing data to a novel mediation analysis using Bayes' rule which allows us to establish the risk that childhood adversity poses for the development of CFS both with and without concomitant depression.

#### 57 MATERIALS AND METHODS

In a cross sectional case–control design, 52 participants fulfilling the Fukuda criteria for CFS
(Fukuda et al. 1994) and 19 healthy controls were recruited between 2012 and 2014. Participants
with CFS were recruited from the UK Department of Health Newcastle and North Tyneside CFS
Clinical Service and controls were recruited predominantly through a volunteer database.

62 All participants underwent psychiatric diagnostic assessment using the Structured Clinical

63 Interview for DSM-IV (SCID-I) (First et al. 1997). As part of this, all participants were asked to

64 consider their lifetime worst period of low mood or loss of interest. The number of depressive

65 symptoms coded as threshold or subthreshold during this period was recorded; any participants

66 meeting criteria for current or past major depressive disorder (MDD) or other axis I psychiatric

67 disorder were excluded. The study was approved by the NRES Committee North East -

68 Newcastle & North Tyneside 2. All participants gave written informed consent.

69 Childhood adversity was assessed using the Childhood Trauma Questionnaire (CTQ), a 28 item 70 self-administered questionnaire which provides a retrospective measure of five subtypes of 71 childhood experiences: emotional neglect; emotional abuse; physical neglect; physical abuse; 72 and sexual abuse. Each subtype of abuse is assessed by five items; three additional items assess 73 tendency of respondents to minimise or deny abuse experiences. Participants rate the truth of 74 each statement on a one to five scale from "Never" to "Very often" true when they were growing 75 up. Thus for each subtype, the minimum score is five and the maximum is 25. Cut-off scores 76 based on Bernstein and Fink's CTQ manual were used to group scores into low to moderate, 77 moderate to severe and severe to extreme severity (Bernstein et al. 2003).

- 78 The CFS data was positively skewed and not amenable to transformation hence non-parametric
- 79 statistics were used, specifically the Chi-squared and Mann-Whitney U tests for comparisons of
- 80 categorical and continuous variables respectively. Spearman's rho was used for correlational
- 81 analysis.

#### 82 **RESULTS**

- 83 In the CFS group there were 39 females and 13 males and the mean age was 45.9 years (s.d. =
- 11.8). In the control group there were 12 females and 7 males and the mean age was 45.1 (s.d. =
- 85 16.9). Groups were matched for gender ( $\chi^2 = 0.96$ , df = 1, p = 0.38) and age (U = 491.5, p =
- 86 0.974). CTQ total scores and scores for all sub-scales did not differ between participants in the
- 87 CFS and control groups (table 1).
- 88 Post hoc analysis involving all participants revealed a significant correlation between the
- 89 numbers of depressive symptoms coded as either threshold or subthreshold on the SCID-I with
- 90 CTQ total score and CTQ sub-scale scores for emotional abuse, emotional neglect and physical
- 91 neglect. The analysis also revealed that the number of *threshold* symptoms significantly
- 92 correlated with CTQ total score and CTQ scores for the emotional abuse and emotional neglect
- 93 sub-scales (table 1).

#### 94 MEDIATION ANALYSIS

The mediation analysis makes use of Bayes' rule, which is a simple method for calculating the conditional probability of an event (x) given another event (y). This is termed the *posterior* and is given by:

98 
$$P(x|y)$$

99 The posterior is therefore "the probability that x occurs given y has occurred"; an equivalent way 100 of saying this is "the probability that if y occurs then x occurs". According to Bayes' rule, the 101 posterior is given by the following equation:

102 
$$P(x|y) = \frac{P(y|x)}{P(y)}P(x)$$

103 P(y|x) is the *likelihood* and is "the probability of y given x".

104 P(y) is the "the probability of y" and is termed the *model evidence*.

105 P(x) is "the probability of x" and is the *prior*.

The fundamental tenet of Bayes' rule is its treatment of probability from an epistemic standpoint, where the prior represents an initial belief in the outcome of an event before exposure to some new information. This new information is given by the likelihood over the evidence and can be thought of as the extent to which y is uniquely associated with x, so if y is likely to occur without x, or if y is less likely to occur after x has happened the posterior will be less than the prior. Conversely, if the presence of x increases the probability of y the posterior will be greater. The posterior is therefore an updated belief in a given outcome after exposure to novel information.

113	Bayes' rule is therefore a powerful tool for reasoning about the probabilities of given outcomes							
114	in particular demographic groups. As such, it allows us to calculate the three probabilities							
115	mentioned above in turn, thereby constructing a novel mediation analysis to explore the risk that							
116	childhood adversity poses for the development of CFS, both with and without concomitant							
117	MDD.							
118	In order to construct our mediation analysis we considered the following probabilities:							
119	1. That an individual currently has, or has had, a diagnosis of MDD given they have a							
120	threshold or higher score on measures of early life adversity (ELA)							
121	2. That an individual is diagnosed with CFS given they have a lifetime history of MDD							
122	3. That an individual has a diagnosis of CFS given no lifetime history of MDD given a							
123	threshold or higher score on measures of ELA							

124 We calculate **probability 1** using Bayes' rule as follows:

125 
$$P(MDD \mid ELA) = \frac{P(ELA \mid MDD)}{P(ELA)} P(MDD)$$

This is the probability that an individual has received a diagnosis of MDD at some point throughout the lifetime if they have suffered adversity during childhood. The prior is simply the lifetime prevalence of depression, for which 16% is a reasonable estimate (Kessler et al. 2003). The evidence in this case is the probability of having experienced early life adversity in childhood, which a large study of 1007 representative healthy individuals has placed at 35% (Scher et al. 2004). The likelihood is the probability of an individual with depression having suffered adversity in childhood, which generally varies widely across studies, though a recent

- 133 study has placed this at 75% according to cut-off scores on the childhood trauma questionnaire
- 134 (CTQ) (Bernet & Stein 1999). We therefore calculate the posterior:

135 
$$P(MDD \mid ELA) = \frac{0.75}{0.35} 0.16 = 0.34$$

136 This shows that we expect, using the available evidence, that 35% of individuals who meet

137 threshold criteria for childhood adversity have a diagnosis of MDD, a roughly twofold increase

138 on baseline prevalence.

139 **Probability 2** is given by:

140 
$$P(CFS \mid MDD) = \frac{P(MDD \mid CFS)}{P(MDD)} P(CFS)$$

141 This is the probability of an individual having a lifetime diagnosis of CFS given they have

142 received a diagnosis of MDD. The prior is the lifetime prevalence of CFS which is estimated at

143 2% (Newton et al. 2007). The evidence, as mentioned above, we will take as 16%. The

144 likelihood in this case is the probability of having depression given a diagnosis of CFS which has

145 been placed at 67% (Taerk et al. 1988). We therefore calculate:

146 
$$P(CFS \mid MDD) = \frac{0.67}{0.16} 0.02 = 0.08$$

147 Current evidence, examined using Bayes' Rule therefore shows that there is an 8% chance that if148 an individual has a lifetime history of MDD they will also have CFS.

149 **Probability 3** is the probability that an individual receives a diagnosis of CFS, given no history

150 of MDD, given they have experienced ELA. In formal notation this is given by:

151 
$$P(CFS|(-MDD|ELA))$$

- 152 According to (Milne 1997) this is equal to the probability that the individual has CFS given no
- 153 history of MDD and a history of adversity such that:

154 
$$P(CFS|(-MDD|ELA)) = P(CFS|(-MDD,ELA))$$

155 This simplifies calculation of probability 3 somewhat:

156 
$$P(CFS \mid -MDD, ELA) = \frac{P(-MDD, ELA \mid CFS)}{P(-MDD, ELA)} P(CFS)$$

157 The evidence here, i.e. P(-MDD, ELA) is the probability that someone in the general population 158 will not have depression and will have life adversity). This can be calculated as the probability

159 that someone who has experienced ELA will not also have depression multiplied by the

160 probability that someone in the general population will have ELA.

161 
$$P(-MDD,ELA) = P(-MDD|ELA)P(ELA)$$

We have already shown that 35% of individuals who have experienced ELA will develop MDD and can therefore say that 65% will not develop MDD. Therefore P(-MDD/ELA)=0.65. We have already stated that P(ELA) is 0.35. Therefore:

165 
$$P(-MDD,ELA) = 0.65 * 0.35 = 0.23$$

166 We have already stated that the prior in this case (P(CFS)) is 2%.

167 Estimates for the likelihood (P(-MDD,ELA | CFS)) are sparse, given most studies have not

168 routinely screened for history of depression. For this value we use data our study which showed,

- 169 in a sample of patients with no history of depression, prevalence of ELA was 17% (see table 1)
- 170 across all trauma domains. Substituting these values into Bayes' rule we obtain:

171 
$$P(CFS \mid -MDD,ELA) = \frac{P(-MDD,ELA \mid CFS)}{P(-MDD,ELA)}P(CFS)$$

172 
$$P(CFS \mid -MDD, ELA) = \frac{0.17}{0.23} 0.02$$

173 
$$P(CFS \mid (-MDD \mid ELA)) = 0.015$$

This shows that if an individual experiences ELA, but does not develop MDD there is a 1.5%risk that they will develop CFS.

176 Having calculated all three probabilities we can construct the following path diagram (Figure 1). 177 Considered as a whole this diagram shows that the total probability (through both paths) of 178 having CFS given a history of early life adversity =(0.34\*0.08)+0.015=4% - a twofold increased 179 risk compared to the general population (Note that this is slightly lower than Heim *et al.* due to 180 generally higher prevalence of CFS estimated in their study). However, the majority of this risk 181 (3%) is mediated through a path including concomitant MDD. It is therefore of little surprise that 182 conclusions regarding the aetiopathogenic role of early life adversity vary according to the 183 proportion of patients with MDD. Indeed, a quick calculation shows that prevalence of adversity 184 in patients who have not been screened is expected to be very high (66%); interestingly this is 185 almost exactly in line with two large and well-designed studies (Heim et al, 2009; Heim et al, 186 2006). Our results show that by removing the increased risk mediated by depression this figure 187 drops to 17%

#### 188 **DISCUSSION**

The case controls study revealed that reported history of childhood trauma did not differ between people with CFS and matched controls, this finding, together with the Bayesian analysis support our hypothesis that childhood adversity increases the risk of CFS predominantly via its previously demonstrated effects on the risk of depression.

193 The inferential method used is a novel way of decomposing the risk conferred by early life 194 adversity into direct and mediated effects. The use of Bayes' rule requires no assumptions about 195 data, simple calculations and subsequent interpretation is relatively simple; the validity of the 196 inferences is therefore robust. We acknowledge that soundness of the values used could be 197 disputed, though all figures were either taken from published sources or represent widely 198 accepted and quoted prevalence rates- indeed in some cases our estimates may be conservative. 199 This simple but effective analysis demonstrates that a sizeable proportion of the risk posed by 200 early life adversity for developing CFS is not direct.

201 The elevated CTQ scores seen in previous CFS studies have been reported as confirmatory 202 evidence that early adversity is an important risk factor for CFS, an interpretation which has 203 become clinical lore and which influences perception of the aetiology of CFS and arguably 204 increases stigmatisation. Data in this current study however suggests that a degree of caution is 205 needed when considering this interpretation. Consideration needs to be given to the hypothesis 206 that childhood adversity does not increase vulnerability to CFS and that the high rates of 207 adversity seen in previous studies of CFS (Heim et al. 2009; Heim et al. 2006; Kempke et al. 208 2013; Taylor & Jason 2001) are mediated by concomitant depression. It is noteworthy that CFS 209 shares many symptoms with depression and the two are frequently co-diagnosed (Fuller-

210 Thomson & Nimigon 2008; Heim et al. 2009; Heim et al. 2006). Despite this, the current study 211 appears to be the only examination of childhood trauma in CFS which rigorously excluded 212 people with MDD and other psychiatric disorders. This may explain the contrast with existing 213 literature; a view which is supported by the post hoc analysis in the case-control study which 214 demonstrated that in all participants CTQ total score and CTQ scores for emotional abuse, 215 emotional neglect and physical neglect subtypes correlated with the number of depressive 216 symptoms during lifetime worst period of low mood or loss of interest in patients who did not fulfil criteria for depression (table 1). This result is in keeping with two previous population 217 218 based studies of people with CFS which reported a positive correlation between measures of 219 childhood adversity and measures of current depressive symptoms (Heim et al. 2009; Heim et al. 220 2006).

Future studies investigating the impact of childhood adversity in CFS should acknowledge the substantial effect of MDD and depressive symptoms on this relationship, either by careful screening of participants or through simultaneous rating of depression. We suggest that, given the important role of depression in CFS, a re-evaluation of the hypothesised aetiological role of adversity is required. This entails formal investigation preferably involving direct comparison of patients with and without comorbid MDD.

Alternatively, the negative result in our case-control study may be a type II error, the risk of this is increased by the relatively small sample size particularly the small number of healthy controls (n=19). It is noteworthy however that the rates of adversity in this current study were in keeping with rates of adversity in comparators recruited in our centre for other clinical studies (Watson et al. 2014). Our *post hoc* analysis must also be interpreted with caution because the clustering of CTQ and SCID-I results around low scores could potentially have created a false correlation.

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233 The SCID-I is a diagnostic tool; if participant's responses are not coded as *threshold* or 234 subthreshold when asked about low mood or loss of interest, they are not asked about the other 235 seven depressive symptoms on the SCID-I. Thus not all of our participants were asked about 236 every symptom. The confounding effect of MDD on studies of childhood trauma may be 237 mediated both by the aetiological role that early adversity plays in the pathogenesis of depression 238 (Bateson et al. 2004; Wiersma et al. 2009) and also by the potential for MDD to engender 239 negative recall bias of past trauma and hence inflate CTQ scores (Lewinsohn & Rosenbaum 240 1987).

241 Further analysis of existing CFS studies which have recorded, but not excluded, co-morbid MDD 242 (Heim et al. 2009; Heim et al. 2006), ideally using meta-analytic tools to utilise data from the 243 available trials, would be of interest, however, a larger study which compares reported childhood 244 adversity between CFS patients with and without MDD and with a healthy comparator group 245 may be required in order to address the question of whether, as has been previously assumed, 246 childhood adversity is a significant risk factor for CFS. This question affects our understanding of the aetiology of CFS and also has implications for the interpretation of pathophysiological 247 248 studies in CFS which may be equally confounded by inclusion of participants with co-morbid 249 MDD.

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### 299 Acknowledgements

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- 302 Table 1. CTQ scores of participants with CFS compared with controls, correlation between CTQ and SCID-I scores and the
- 303 prevalence of childhood trauma in people with CFS in this and previous studies.<sup>a</sup>

CTQ trauma	Mean CTQ scores		Mann-	SCID-I number of	SCID-I number of	Prevalence of childhood trauma	
subtype			Whitney	subthreshold and	threshold	by sub-scale <sup>b</sup>	
			Comparison	threshold symptoms	symptoms only		
	CFS	Control	р	r (p)	r (p)	This study	Previous
	N = 52	S					studies <sup>(Heim et al.</sup>
		N = 19					2009; Heim et al. 2006;
							Johnson et al. 2010)
Emotional abuse	7.0	6.8	0.59	0.32 (0.007)	0.32 (0.007)	5.8%	24.7 to 42.0%
Physical abuse	5.3	5.4	0.96)	-0.06 (0.64)	-0.098 (0.32)	0.0%	24.7 to 33.0%
Sexual abuse	5.5	5.1	0.91	-0.08 (0.51)	-0.03 (0.78)	3.8%	28.0 to 33.0%
Emotional neglect	7.8	7.3	0.64	0.36 (0.003)	0.29 (0.01)	7.7%	25.5 to 60.0%
Physical neglect	5.7	5.3	0.96	0.31 (0.008)	0.24 (0.048)	3.8%	14.0 to 24.5%
Total CTQ score	31.2	29.8	0.80	0.38 (0.001)	0.32 (0.006)	17.3% <sup>c</sup>	

- 305 a Table showing the mean CTQ scores of CFS and control groups with a comparison using the Mann-Whitney U test; the Spearman's
- 306 rho correlational analysis between CTQ scores and number of depressive symptoms recorded as *subthreshold* or *threshold* and
- 307 threshold only on the SCID-I in all participants; and the proportion of participants with CFS meeting the moderate to severe CTQ cut-
- 308 off scores for each sub-scale in this and previous studies.
- <sup>b</sup> In line with previous studies, participants were considered to have a particular type of childhood trauma if they met the moderate to
- 310 severe CTQ cut-off score for that sub-scale; cut-offs are from Bernstein and Fink's CTQ manual (Bernstein et al. 2003). The figure
- 311 17.3%<sup>c</sup> is the percentage of CFS patients who meet moderate to severe or severe to extreme cut-offs for any sub-scale.
- 312 CTQ: Childhood Trauma Questionnaire.
- 313 SCID-I: Structured Clinical Interview for DSM-IV Research Version.
- 314 U: Mann Whitney U.
- 315 r: Spearman's rho correlation coefficient.
- 316 \*This figure is the percentage of CFS patients who meet criteria f

#### Figure 1. Path diagram

