1   **Title: Which factors are associated with quality of life in patients with Graves'**

2   **orbitopathy presenting for orbital decompression surgery?**

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18   **Running Title:** Factors associated with quality of life in GO

25   **Word count:** 2,673

26

27   **ABSTRACT**

28   **Aims:** Graves' orbitopathy (GO) is associated with changes in the appearance of the eyes and visual

29   dysfunction. Patients report feeling socially isolated and unable to continue with day-to-day activities.

30   This study aimed to investigate the demographic, clinical and psychosocial factors associated with

31   quality of life in patients presenting for orbital decompression surgery.

32   **Methods:** One hundred and twenty-three adults with GO due for orbital decompression at Moorfields

33   Eye Hospital London were recruited prospectively. Clinical measures including treatment history,

34   exophthalmos, optic neuropathy and diplopia were taken by an ophthalmologist. Participants

35   completed psychosocial questionnaires, including the Graves' Ophthalmopathy Quality of Life Scale

36   (GO-QOL), the Hospital Anxiety and Depression Scale (HADS) and the Derriford Appearance Scale

37   (DAS24). Hierarchical multiple regression analyses were used to identify predictors of quality of life.

38   **Results:** Higher levels of potential cases of clinical anxiety (37%) and depression (26%) were found

39   in this study sample than in patients with other chronic diseases or facial disfigurements. A total of

40   55% of the variance in GO-QOL *visual function* scores was explained by the regression model and

41   age, asymmetrical GO and depressed mood were significant unique contributors. 75% of the variance

42   in GO-QOL *appearance* scores was explained by the regression model and gender, appearance-

43   related cognitions and depressed mood were significant unique contributors.

44   **Conclusions:** Appearance-related quality of life and mood were particularly affected in this sample.

45   Predominantly psychosocial characteristics were associated with quality of life. It is important when

46   planning surgery for patients that clinicians are aware of factors that could potentially influence

47   outcomes.

2

INTRODUCTION

Graves' orbitopathy (GO) is an autoimmune thyroid disorder that affects the eyes. An estimated 25% to 50% of patients with Graves' disease (GD) develop GO[1].The commonest early symptom of GO is a noticeable change in the appearance of the eyes, including redness of the eyelids, swelling, and disfiguring proptosis[2].

Patients with GO report feeling stared at by others and socially isolated as a consequence of their changed appearance[3] this having a significant impact on mood[4].There is also growing evidence that GO has a detrimental impact on vision-related daily functioning including reading, watching TV, and driving[5,6,7.] People with GO have been found to have a poorer quality of life than patients with other chronic conditions including diabetes, emphysema and heart failure[4,8]. Although it is important to establish the impact GO may have on a patient's well-being, it is equally important to understand what factors explain how some people live within normal levels of mood and experience a better quality of life than others.

There is mixed evidence to support an association between clinical factors and quality of life in GO. For instance, whilst Park et al.[7] found that poorer quality of life was associated with more severe disease, including diplopia and dry eyes, Kulig et al.[9] failed to replicate these findings either before or after treatment for GO. Recent literature about appearance and disfigurement has suggested significant variability amongst individuals with disfiguring conditions – with many adjusting positively to living with a visible difference – and that psychological processes rather than objective measurements can better explain this variability in adjustment[10,11]. In GO, Kahaly et al.[4] found that depressive coping, trivialising the condition and higher levels of emotional distress were associated with poorer physical and mental quality of life. However, other psychosocial variables, identified within a framework for adjustment to disfigurement as proposed by The Appearance Research Collaboration[11], have not been investigated within the GO population. The framework suggests a number of intervening cognitive processes, individual to each patient, might help to explain quality of life in people with a disfiguring condition.

3

74 It was hypothesised that there will be large variation in quality of life between individuals with GO,

75 and that intervening psychosocial processes would better explain this variation than demographic or

76 clinical factors.

MATERIALS & METHODS

Participants

79 Patients were recruited from Moorfields Eye Hospital, London. Eligible patients aged 18 years or over

80 with a consultant-led diagnosis of GO, and having been listed for orbital decompression surgery, were

81 invited to participate in the study by a researcher (SW). Patients were excluded if they were

82 considered by the consultant ophthalmologist to have inadequate comprehension of written and

83 spoken English, or were suffering from psychiatric or co-morbid health conditions that rendered them

84 too ill or distressed to take part.

Study design

86 A prospective cross-sectional design was used.

Measures

88 <u>Demographics</u>

89 Self-reported age, gender, marital status and ethnicity were collected.

90 <u>Clinical measures</u>

91 The clinical measures assessed when patients were listed for surgery included ophthalmic disease

92 duration, thyroid function, treatment history, laterality of GO and planned surgery, smoking status,

93 upper and lower margin-reflex distance (MRD1 and MRD2; mm), and the presence of corneal

94 superficial punctate keratopathy (SPK), diplopia and/or signs of hydraulic orbital disease. Disease

95 activity was measured using the Clinical Activity Scale (CAS;[12]) , a 10-item measure covering four of

96 the five classic signs of inflammation (pain, redness, swelling, and impaired ocular function). Visual

97 acuity was measured for each eye using a Snellen Chart. This was converted to the log of the minimal

98 angle of resolution (LogMAR), ranging between -0.20 and 2.1, with a score of 2.2 assigned to patients

4

99 with vision of counting fingers or worse. Optic neuropathy was identified using Ishihara colour

100 testing and, the presence of a relative afferent pupillary defect (RAPD). Proptosis was measured

101 using an Oculus exophthalmometer (in mm) and the degree of asymmetry gauged from the difference

102 between each eye (in mm).

103 <u>Psychosocial measures</u>

104 Self-report questionnaires were completed by participants at the time they were listed for surgery. The

105 questionnaires chosen for this study were based on a proposed framework of adjustment to GO

106 developed by the research team (Figure 1) adapted from The Appearance Research Collaboration's

107 framework[11]. Existing validated measures were used where possible, and brief versions of

108 questionnaires were adopted to reduce participant burden.

109 <u>Primary outcome measure</u>

110 Quality of life was measured using the Australian version of Graves' Ophthalmopathy Quality of Life

111 Questionnaire (GO-QOL)[7]. The GO-QOL is made up of two subscales: "vision-related" and

112 "appearance-related" quality of life[5]. The GO-QOL has been found to be a valid and reliable disease-

113 specific measure of quality of life with high internal consistency (α=0.86 for the visual function scale

114 and α=0.82 for the appearance scale)[13]. Subscale scores were calculated following the questionnaire

115 guidelines[13] and higher scores on each subscale indicate better health-related quality of life.

116 ***Socio-cognitive factors***

117 *The Brief Fear of Negative Evaluation scale (BFNE)*[14] was used to measure anxiety about others'

118 opinions. This 12-item brief version correlates highly with the original scale (α = 0.96) and higher

119 scores indicate a greater fear of negative evaluation from others.

120 *The Iowa-Netherlands Comparison Orientation Measure (INCOM)*[15] measures how well respondents

121 feel they are doing in life when comparing him or herself to others. This 11-item scale has been

122 demonstrated to have good internal consistency (α = 0.83) and higher scores indicate a greater

123 tendency to make social comparisons.

124 *The Multidimensional Scale of Perceived Social Support (MSPSS)*[16] measures subjective levels of

125 social support from family, friends and significant others. The overall scale has demonstrated good

126   internal consistency (α=0.88) and test-retest reliability (r=0.85). Higher scores on each 4-item

127   subscale indicate greater perceived social support.

128   *Patient expectations of treatment*

129   *Expectations of GO Surgery*: In the absence of a GO-specific measure of a patients' expectations of

130   treatment, an existing questionnaire – the Expectations of Strabismus Surgery Questionnaire (ESSQ)[17]

131   – was adapted with the items being reviewed for relevance to GO. The 23-item questionnaire

132   assessed patients' expectations in relation to three domains: "appearance concerns", "visual

133   functioning", and "intimacy and social relationships". Participants were instructed to rate how they

134   expected surgery to change these aspects of their lives, for instance "my vision" on a Likert scale

135   from 1 ('Made considerably worse') to 5 ('Considerably improve'). Higher scores indicate a greater

136   expectation for these areas to improve after surgery.

137   *Appearance-specific cognitions*

138   *The Derriford Appearance Scale (DAS24)*[18] measures the impact of appearance-related distress

139   including social anxiety and avoidance. This measure has demonstrated high internal consistency (α

140   = .92) and good test-retest reliability (r=0.82) and higher scores represent greater levels of

141   appearance-related distress and social avoidance.

142   *The Valence and Salience of Appearance scales (CARVAL & CARSAL)*[19] measure how an individual

143   evaluates his or her own physical appearance (CARVAL) and the extent to which physical appearance

144   is important to the individual (CARSAL). Higher scores on each brief measure indicate a more

145   negative self-evaluation of appearance and that greater value is placed on appearance, respectively.

146   Both questionnaires have demonstrated high internal consistency (Pearson's r correlations between

147   0.72 and 0.84).

148   *Perceived Visibility of GO*: Patients were asked to rate how visible they felt their proptosis was to

149   other people on a 7-point Likert scale from 1 ('Not at all visible') to 7 ('Extremely visible').

150   *Mood*

151 *The Hospital Anxiety & Depression scale (HADS)*[20] has been designed to screen for depression and

152 anxiety in patients with health problems. Higher total subscale scores on this valid and reliable

153 measure indicate greater levels of anxious or depressed mood. Cut-off scores were also applied to

154 identify non-cases (0 to 7), doubtful cases (8 to 10), and cases of possible clinical anxiety or

155 depression (scores of 11 and over).

156 **Statistical analysis**

157 Using G*Power (version 3.1.7), it was estimated that between 64 and 97 patients would be needed to

158 achieve a power of 90% with effect sizes of 0.45 and 0.9 for the GO-QOL appearance and GO-QOL

159 visual function subscales, respectively[13].

160 All other statistical analyses were performed using IBM SPSS 21. Levels of missing data, analysed

161 using Little's Missing Completely at Random (MCAR) test were shown to be MCAR ($\chi^2 = 7127$, $df =$

162 8177, $p = 1.000$), with 11.9% of the data missing at item level. Multiple imputation was undertaken

163 and 10 imputed datasets were generated. Scale scores for the psychosocial variables were re-

164 calculated and the analysis was conducted on all 10 datasets and the results pooled.

165 Univariate linear regressions were performed to explore the relationship between each of the

166 independent variables and the GO-QOL subscale scores (dependent variables). Hierarchical multiple

167 regressions were conducted using only the variables found to be significantly associated with each

168 GO-QOL subscale. The hierarchy used to enter the predictors into the regression was based on the

169 framework outlined in Figure 1. Cohen's f^2 was used to calculate effect sizes for each of these

170 regressions[21]. The variables were also examined for multicollinearity, linearity and homoscedasticity.

171 Multicollinearity was identified using VIF scores provided in SPSS after each regression analysis,

172 with scores above 10 indicating multicollinearity[22]. Histograms and normal probability plots were

173 assessed for linearity and homoscedasticity.

174 **Statement of ethics**

7

175 Ethical approval was obtained from the North London Research Ethics Committee (Reference

176 11/H0724/6). We certify that all applicable institutional and governmental regulations concerning the

177 ethical use of human volunteers were followed during this research

178 **RESULTS**

179 Of 192 patients identified as eligible for the study, 135 (70%) agreed to take part, and 123 of the 135

180 enrolled (91%) returned their questionnaire. Two participants' data was removed from analysis

181 because of high proportions of missing data (>50%).

182 The descriptive characteristics of the study population are shown in Table 1.

183 Summary statistics for the psychosocial variables are shown in Table 2. Possible cases of clinical

184 depression were detected in 26% of patients and 37% had possible clinical levels of anxiety; 25 (21%)

185 participants experienced both. The large standard deviations (SDs) for both GO-QOL subscales

186 indicate great variability in adjustment from patient to patient.

187 Ten of the original 36 variables were significantly associated with the GO-QOL *visual function*

188 subscale using univariate analyses: age ($F_{1,119} = 16.6$, $p < 0.001$, $f^2 = 0.14$), optic neuropathy ($F_{1,119} =$

189 15.8, $p < 0.001$, $f^2 = 0.15$), LogMAR ($F_{1,119} = 15.6$, $p < 0.001$, $f^2 = 0.12$), previous immunosuppression

190 ($F_{1,119} = 11.1$, $p = 0.001$, $f^2 = 0.09$), asymmetrical GO ($F_{1,119} = 6.12$, $p = 0.015$, $f^2 = 0.05$), hydraulic

191 orbit ($F_{1,119} = 9.22$, $p = 0.003$, $f^2 = 0.06$), diplopia ($F_{1,119} = 7.77$, $p = 0.006$, $f^2 = 0.07$), CAS ($F_{1,119} =$

192 6.22, $p = 0.014$, $f^2 = 0.05$), appearance-related social anxiety and avoidance ($F_{1,119} = 3.95$, $p = 0.049$,

193 $f^2 = 0.06$), anxiety ($F_{1,119} = 12.9$, $p < 0.001$, $f^2 = 0.11$), and depression ($F_{1,119} = 41.6$, $p < 0.001$, $f^2 =$

194 0.36).

195 After entry of these variables into the model in the order shown in Figure 1, 55% of the observed

196 sample variation in GO-QOL visual function score was accounted for ($R^2=0.55$, $F_{1,119} = 9.89$, $p <$

197 0.001, $f^2 = 0.8$). Beta-coefficients indicated that age, asymmetrical GO and depression made

198 significant unique contributions to the model, above other factors (Table 3).

199   Univariate analyses indicated that 13/36 variables were significantly associated with GO-QOL

200   *appearance*: age ($F_{1,119}$ = 5.42, p = 0.022, f^2 = 0.05), gender ($F_{1,119}$ = 8.13, p = 0.005, f^2 = 0.07),

201   previous surgery ($F_{1,119}$ = 5.55, p = 0.020, f^2 = 0.06), family support ($F_{1,119}$ = 5.12, p = 0.025, f^2 =

202   0.04), friends support ($F_{1,119}$ = 7.39, p = 0.008, f^2 = 0.06), fear of negative evaluation ($F_{1,119}$ = 58.8, $p <$

203   0.001, f^2 = 0.52), social comparison ($F_{1,119}$= 12.2, p = 0.001, f^2 = 0.11), appearance-related social

204   anxiety and avoidance ($F_{1,119}$ = 60.0, $p <$ 0.001, f^2 = 0.59), salience of appearance ($F_{1,119}$ = 64.6, $p <$

205   0.001, f^2 = 0.51), valence of appearance ($F_{1,119}$ = 98.9, $p <$ 0.001, f^2 = 0.76), perceived visibility ($F_{1,119}$

206   = 27.5, $p <$ 0.001, f^2 = 0.24), anxiety ($F_{1,119}$ = 42.2, $p <$ 0.001, f^2 = 0.39), and depression ($F_{1,119}$= 70.5,

207     $p <$ 0.001, f^2 = 0.57).

208   After entry of the variables using the same model as before, 75% of the observed sample variation in

209   GO-QOL appearance scores was accounted for (R^2=0.75, $F_{13,107}$ = 20.7, $p <$ 0.001, f^2 = 2.3). Beta-

210   coefficients indicated that gender, appearance-related social anxiety and social avoidance, salience of

211   appearance, valence of appearance, perceived visibility of GO, and depression all made significant

212   contributions to the model (Table 4).

213   **DISCUSSION**

214   This study investigated the factors that may be associated with quality of life in patients with GO

215   presenting for orbital decompression surgery. It was found that being older, having asymmetrical

216   proptosis and having higher levels of depressed mood were associated with poorer vision-related

217   quality of life. Likewise, a greater value being placed on appearance, a more negative evaluation of

218   appearance, greater perceived visibility of GO, and having higher levels of depressed mood were all

219   associated with poorer appearance-related quality of life.

220   Participants in this study experienced levels of anxiety and depression greater than the general

221   population[23] and those living with other visibly disfiguring conditions[24]. GO-QOL visual-function

222   scores were comparable to normative values established in a previous GO sample[13], but GO-QOL

223   appearance scores were considerably lower. These results suggest that, for many, the changed

224 appearance caused by GO has a greater impact and is more debilitating than previously reported in the

225 literature.

226 Appearance-related quality of life was significantly associated with gender. For women the eyes

227 might be regarded as central in perceived attractiveness, and changes in ocular appearance could have

228 a detrimental influence on self-confidence and willingness to appear in photographs. Recent studies

229 have suggested that women with visible differences, including strabismus, may experience higher

230 levels of appearance-related distress than men[25,26], which in turn could impact on their quality of life

231 in this domain. Furthermore age was found to be associated with vision-related quality of life, which

232 might reflect the greater disease severity often found in older age.

233 Appearance-related cognitions were particularly important in predicting appearance-related quality of

234 life. Increased social anxiety was associated with both poorer vision-related and appearance-related

235 quality of life in this study, analogous to strabismus[27]. Increased importance of appearance-related

236 information, as well as having a poorer evaluation of one's own appearance, were also associated with

237 quality of life in this sample. Terwee et al.[28] found in a study investigating perceptions of the severity

238 of GO in different groups of observers and patients themselves that clinicians tended to under-rate,

239 and patients over-rate, the severity of GO: This emphasises the importance of eliciting a patient's

240 perspective during pre-surgical assessment to improve the chance of generating realistic patient

241 expectations about what surgery can achieve.

242 A limitation of the study is the cross sectional design, which does not enable causal direction to be

243 established and longitudinal studies that follow patients over time are needed. If patients in this study

244 were not euthyroid, present hyper- or hypothyroidism could have impacted on their quality of life.

245 However, recent research found no difference in the quality of life of people with thyroid dysfunction

246 compared to people with normal thyroid levels[29] and it is possible that this may not have biased the

247 results of this study. It is also possible that quality of life may predict mood in GO. However, mood

248 has been found to be a strong predictor of quality of life in strabismus[24], supporting the current

249 findings. Furthermore, by exploring other factors that might explain variance in quality of life in this

250   population, rather than examining quality of life and mood in isolation, this study has expanded on

251   previous studies and has provided a new insight into the experiences of patients with GO.

252   In conclusion, there was significant variation in quality of life in this sample suggesting that some

253   people adjust successfully to living with GO, but for others the impact is extreme. Contrary to

254   conventional medical perspectives, this variation was predominantly accounted for by intervening

255   cognitive processes, rather than objective measures. There was however evidence that older age and

256   asymmetrical disease were associated with poorer vision-related quality of life. The high proportion

257   of patients with potentially diagnosable clinical depression and anxiety should be of concern to

258   clinicians and highlights the need for additional psychosocial support.

263   **COMPETING INTERESTS**

264   The authors have no competing interests.

265

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TABLES

Table Error! Main Document Only.**. Demographic and clinical characteristics of the study sample**

Variable	n (%)	Range	Mean±SD
Age (years)		22 - 79	47.1 ± 12.3
Gender			
Male	33 (27)		
Female	88 (73)		
Ethnicity			
Asian	11 (9.1)		
White British/Irish/Other	95 (78)		
Black African/Caribbean/Other	15 (12)		
Relationship Status			
Married/Living with partner	73 (60)		
Single/Other	48 (40)		
Disease duration (months)		4 - 336	62.01 ± 42
Laterality of GO			

Bilateral	101 (83)			
Unilateral	20 (17)			
Laterality of planned surgery				
Bilateral	79 (65)			
Unilateral	42 (35)			
Treatment history				
Previous immunosuppressants	58 (48)			
Previous radiotherapy	18 (15)			
Previous eyelid or orbital surgery	14 (12)			
Thyroid function				
Stable	106 (88)			
Unstable	15 (12)			
Visual acuity (LogMAR conversion)†		0 - 2	0.1 ± 0.4	
Superficial punctate keratopathy	39 (32)			
Hydraulic orbital signs	25 (21)			
Optic neuropathy	15 (12)			
Diplopia	62 (51)			
Marginal reflex distance 1 (mm)†		1.5 - 13	5.9 ± 2.1	
Marginal reflex distance 2 (mm)†		4 - 11	6.7 ± 1.4	
Exophthalmometry (mm)†		15 - 33	23.7 ± 2.7	
Asymmetry (mm)		0 - 8	1.8 ± 1.8	
Clinical Activity Score		0 - 9	1.12 ± 1.9	
Smokers	38 (31)			

† *A worst eye analysis was conducted on these variables, based on amount of proptosis*

Table Error! Main Document Only.**. Scores for the psychosocial measures at baseline for the study sample**

Variable	Min	Max	Max Possible	Mean	SD
GO-QOL Appearance Score	0	93.8	100	36.3	24.1
GOQOL Visual function Score	2.8	100	100	64.0	26.7
BFNE	14	60	60	38	9.2
INCOM	16	54	55	36	7.2
MSPSS Family	4	20	20	15.3	4.5
MSPSS Friends	4	20	20	15.2	4.2
MSPSS Significant other	4	20	20	15.6	5.2
CARSAL	5	30	30	25.2	4.7
CARVAL	11	48	48	38.7	8.4
DAS24	22	83	96	51.3	13
Men (n = 33)	22	83	96	50.7	15
Women (n = 88)	22	83	96	51.6	12
Visibility	1	7	7	5.7	1.5
HADS Depression	1	21	21	9.2	4.9

		0	19	21	7.6	4.7
HADS Anxiety						

Table Error! Main Document Only.. **The final step of a hierarchical multiple regression model, with GO-QOL visual function score as the dependent variable**

	B	SE B	t	p
(Constant)	**119.49**	**13.78**	**8.67**	**0.000****
Age	**-0.50**	**0.19**	**-2.63**	**0.009***
LogMAR	-11.28	6.45	-1.75	0.080
CAS	-1.92	1.31	-1.46	0.144
Asymmetry	**-2.25**	**1.13**	**-2.00**	**0.046***
Optic neuropathy	-4.09	9.54	-0.43	0.669
Hydraulic orbit	2.55	6.47	0.39	0.694
Previous immunomodulation	-6.79	4.90	-1.38	0.168
Diplopia	-4.39	4.29	-1.02	0.307
DAS24	0.05	0.21	0.23	0.815
HADS Anxiety	-0.69	0.58	-1.20	0.231
HADS Depression	**-2.41**	**0.59**	**-4.10**	**0.000****

* $p < 0.05$, ** $p < 0.001$

Table Error! Main Document Only.. **The final step of a hierarchical multiple regression model, with GO-QOL appearance-related score as the dependent variable**

	B	SE B	t	p
(Constant)	**132.09**	**13.84**	**9.55**	**0.000****
Age	0.11	0.11	0.94	0.346
Gender	**6.56**	**3.02**	**2.17**	**0.03***
Previous surgery	-5.04	5.08	-0.99	0.325
BFNE	-0.23	0.22	-1.03	0.302
INCOM	0.01	0.23	0.06	0.950
MSPSS Family	-0.29	0.34	-0.87	0.382
MSPSS Friends	0.56	0.37	1.53	0.127
DAS24	**-0.39**	**0.13**	**-2.93**	**0.004***
CARSAL	**-1.23**	**0.33**	**-3.69**	**0.000****
CARVAL	**-0.58**	**0.21**	**-2.76**	**0.006***
Perceived visibility	**-2.75**	**0.96**	**-2.86**	**0.004***
HADS Anxiety	-0.05	0.39	-0.14	0.891
HADS Depression	**-1.12**	**0.43**	**-2.60**	**0.009***

* $p < 0.05$, ** $p < 0.001$