Original Article

Factors associated with generic health-related quality of life (HRQOL) in patients with chronic obstructive pulmonary disease (COPD): a cross-sectional study

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Background: Health-related quality of life (HRQOL) is impaired in chronic obstructive pulmonary disease (COPD) patients, but determining factors for HRQOL are still not unequivocal. This study measures HRQOL among patients with COPD and aims to determine factors associated with HRQOL.

Methods: Data for cross-sectional analyses were obtained from the baseline of a cohort study. The study population includes adult COPD patients (disease duration ≥3 months), recruited from primary and secondary care settings in Germany, without acute psychiatric/neurologic disease (exception: affective/anxiety disorders). HRQOL was assessed using the Short-Form 12 (SF-12) Health Survey Questionnaire, comprising a physical and mental component. Independent variables encompass socio-demographic, disease-specific, treatment-related and psychological factors. Multivariable linear regression analyses were conducted.

Results: In total, 206 COPD patients (60.7% male; mean age: 65.3 years) took part in the study. In multivariable analysis, the physical component score showed a significant negative association with the COPD Assessment Test (CAT) (P<0.001) and a higher total number of prescribed medications (P=0.001). A higher forced expiratory volume in 1 second (FEV1) value in percent predicted was significantly related to the physical component score in a positive manner (P=0.006). The mental component score was significantly associated with elevated patient-reported symptoms of anxiety (P=0.002) or depression (P<0.001), measured by the hospital anxiety and depression scale (HADS) in a negative way. Like for the physical component score (P<0.001), a worse CAT score was significantly associated with a lower mental component score (P=0.033).

Conclusions: Focusing on patient reported outcomes and screening for depression and anxiety with potential successive treatment might be promising approaches to improve HRQOL in patients with COPD.

Keywords: Chronic obstructive pulmonary disease (COPD); determinants; health-related quality of life (HRQOL); Short-Form 12 (SF-12)

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease with life-time prevalences ranging from 1.2% (Malta) to 13.2% (Germany) in Europe (1,2). Globally, COPD is the third leading cause of death (3). COPD is usually a progressive disease which is characterized by an airflow limitation that is not fully reversible. Common symptoms are chronic cough, sputum production and dyspnea (4). Due to the ongoing demographic change and the higher prevalence with increasing age (2), the number of COPD patients is estimated to rise by 47% by the year 2050 in Germany compared to numbers of 2007 (5). Since COPD has a major negative impact on the quality of life (QOL) and work productivity of COPD patients, it also poses a high burden on the economy in Germany (6).

In order to fully display the whole burden of disease, many studies emphasize the importance of measuring QOL (7-10). Particularly health-related quality of life (HRQOL) is more and more investigated, meaning the part of QOL in general that is determined by health. In order to quantify the impact of the disease on patients, studies use both generic and disease-specific instruments (11). Generic instruments, such as the Short-Form 12 (SF-12) questionnaire (12) used in this study, measure overall HRQOL and provide an advantage compared to disease-specific questionnaires, as they allow comparisons with other diseases or the general population.

Compared to healthy persons, previous studies showed a significantly lower physical and mental HRQOL in patients with COPD (13,14). Therefore, one aim in the German guidelines for diagnosis and therapy of COPD is the improvement of both health status and QOL (15).

Knowledge about determining factors of HRQOL is a mandatory prerequisite to improve it. Previous studies considered factors such as age, sex and co-morbidity (14,16) and revealed conflicting results (7). For instance, one study performed in the Netherlands found a higher age as a negative predicting factor for the health status of COPD patients (8) while another study from the USA found that younger patients had worse health status (17). Clear findings regarding influencing factors in previous studies exist for dyspnea, which seems to be the most important determinant of HRQOL in COPD patients (7,13). Based on strong evidence arising out of a systematic review, reduced HRQOL in COPD patients is negatively associated with depression and anxiety (18). So far, most studies have focused either on mild severity of disease using population based (13,19) or primary care based samples (8,20) or on severe cases only using data from secondary care settings (17,21).

The objective of this study is to identify factors associated with generic HRQOL in patients with COPD recruited from both primary and secondary care settings in Germany.

Methods

Study design and study population

The design of this study has been previously described in Böhmer *et al.* 2016 (22). In short the current study is based on data collected for a prospective patient cohort study investigating the influence of beliefs about medicines on adherence in patients with asthma or COPD. For the study presented here only patients with COPD are investigated. In order to cover a broad range of disease severity, patients were recruited from primary care and specialist practices as well as from in- and outpatients from hospital settings. The study sites are located in the region of Regensburg in the German federal state of Bavaria. The recruitment period for the baseline survey was from June 2013 until December 2014. Only patients who met the following inclusion criteria were enrolled in the study: COPD as main diagnosis ascertained by a physician, age ≥18 years; disease duration ≥3 months; no acute psychiatric/neurological disease (exception: depression or affective disorders) and sufficient knowledge of the German language. After a short introductory explanation all patients gave informed consent on-site before filling in the questionnaire. Data was collected both by using validated instruments and information from the patients' medical records. Based on previous studies we determined a priori that we would investigate variables belonging to the domains patient characteristics, disease characteristics, treatment-related factors and psychological characteristics, as we aimed to take a broad perspective on variables likely influencing HRQOL.

Definition of variables

HRQOL: dependent variable

As a short version of the Short-Form (SF) 36 questionnaire (23), the SF-12 questionnaire contains 12 items in two scales: a physical (PCS-12) and mental health component scale (MCS-12) (12). The SF-12 explains the majority of the variance (80–85%) of the

SF-36. The scores for the two scales were calculated as described by Ware *et al.* (12). Response categories differ from binary to six response options (like "always" to "never"). A range of 0 (worst conceivable QOL) to 100 (best conceivable QOL) is possible. For analysis, two summary scores were computed (12). The mean value of the German norm sample, which was used for standardization of scale scores in this study, is 50 in both the mental and physical component.

Patient characteristics

Sociodemographic data (age, gender and migration background), as well as information on estimated travelling time to the treating physician (in minutes) and the living situation (whether participants lived alone or not) were collected. Furthermore, the patients' current smoking status was queried.

Level of education was divided into two groups for this analysis: low education level (no school degree or school leaving diploma after 9 school years) and high education level (school diploma after 10 school years or university entrance diploma).

Characteristics of disease

COPD symptoms and functional status were measured using the COPD Assessment Test (CAT) (24,25). The CAT score has an overall range of 0–40 and comprises eight questions with five response categories each (0= no impairment). The overall CAT score can be derived as a sum of each single item score. A score of <10 indicates a low impact, a score between 10 and 20 a medium impact and a score of more than 20 indicates a high impact level (26). For this analysis, CAT was calculated as continuous variable. Higher scores indicate more symptoms and functional impairment.

In addition, the duration of disease (in years) was obtained by asking for year of first diagnosis. Furthermore, we assessed the exacerbation history in the previous 12 months as an important reflection of disease control and as a potential predictor of the course of disease (27). The latest forced expiratory volume in 1 second (FEV1) value in percent predicted (obtained from the medical record) was also taken into account. A classification of severity of airflow limitation in COPD patients is given from the "Global Initiative for chronic obstructive lung disease" (GOLD) (4) and is based on post bronchodilator FEV1 values. Patients are classified as mild COPD (GOLD1) if their FEV1 is ≥80% predicted. A moderate COPD (GOLD2) includes FEV1 values between 50% and 80% predicted. If the patients' FEV1 is between 30% and 50% predicted they are categorized as severe COPD or GOLD3. Very severe COPD (GOLD4) is present if FEV1 is less than 30% predicted. For analysis, only FEV1 in % predicted is taken into account, as GOLD status comprises the pulmonary function parameter and is therefore redundant.

Treatment of disease

The presence of severe side effects and the number of medical consultations due to COPD during the last year were enquired in the questionnaire. Patients were also asked whether they had ever taken part in a rehabilitation measure owing to COPD. Valid information on the patient´s current medication was obtained from the medical record. For analysis the total number of prescribed drugs was taken into account.

Psychological influences

To measure symptoms of anxiety and depression the German version of the hospital anxiety and depression scale (HADS) was used (28). The total of 14 items was divided into two subscales (anxiety and depression scale) with 7 items each. Scores are constructed by summation, whereby both scores were classified into three categories: inconspicuous findings (≤7), marginally noticeable findings (8-10) and noticeable findings (≥11) (29). In Germany, the mean scores of the general population are 4.7 for women and 4.6 for men (HADS-D) and 5.0 and 4.4 (HADS-A), respectively (30).

Statistical analysis

First, we performed a descriptive analysis. Continuous variables are reported as means (with minimum and maximum) and categorical variables as proportions. In a second step, we performed a univariate analysis in which all potential determinants were entered separately in linear regression models, with the physical and mental component summary scores (PCS-12/MCS-12) of the SF-12 as dependent variables, respectively. Finally, all variables with a significant association in the univariate analysis were used as predictive variables in the multivariable model. For regression analysis, the level of significance was defined based on the confidence interval with an alpha error less than 0.05. In case of missing data, the respective variables of these patients were not included in the analysis. All analyses were performed by using SPSS 22 (SPSS Inc., Chicago, USA).

Results

Characteristics of the study population

Data from 206 patients with COPD were analyzed. Of the seven study sites, three were practice and four were hospital settings. On average, COPD patients were 65 years old (SD =8.85) and approximately two thirds of them were of male sex. In total, 20.2% stated current smoking. On average, the diagnosis of COPD was made eight years (SD =7.92) before enrolment into the study. When categorizing the disease in four stages of disease severity, only a minority (4.7%) was grouped in the mildest stage GOLD 1. The largest group with 66 patients was GOLD 4 (34.7%), closely followed by GOLD 3 (32.1%) and GOLD 2 (28.4%). The number of exacerbations during the last year ranged from zero to 12, while about one third of the patients had more than two exacerbations (65 patients, 34.3%). An even greater range was found in the number of doctor visits during the last year. The number ranged from zero to 52 (one a week), while nearly one fifth visited the doctor 10 times or more last year due to COPD problems. About one third of COPD patients were in an outpatient treatment at time of enrolment. Concerning the patients' total number of prescribed medications, the variation was between one and 17 different medications, while the median number was 7. Just less than half of the patients had an inconspicuous score in the HADS-A score. The same goes for the depression score of the HADS, indicating that more than half of the patients reported symptoms of depression. The mean value of the physical and mental component scale was 31.8 and 38.0, respectively. Characteristics of the study population are displayed in *Table 1*.

Univariate analysis

In total, 194 patients could be included in univariate regression analysis. As shown in *Table 2*, mainly disease-related, treatment-related and psychological factors were univariately associated with both component scales of the SF-12. Regarding socio-demographic factors, only female gender and migration background play a nearly significant or significant role in MCS-12 or PCS-12, respectively. Furthermore, the CAT score, the number of exacerbations during the last year, the total number of prescribed medications and reporting symptoms of depression or anxiety show a significant negative association with both scale scores of the SF-12. The FEV1 value in percent predicted was positively associated with both scores, PCS-12 and MCS-12. Having taken part in a rehabilitation measure was associated with a significantly lower PCS score. The same is true for ever having experienced serious side effects due to medications taken for COPD treatment (*Table 2*).

Multivariable analysis

The multivariable model was built of variables which showed significant associations with HRQOL in univariate analysis. Looking at the final model, PCS-12 score showed a significant negative association with the CAT score. Furthermore, a higher total number of medications prescribed was significantly associated with PCS-12 score in a negative way. A higher FEV1 value in percent predicted was significantly related to PCS-12 score in a positive manner. These variables explained 57% of the variance in the PCS-12 variable in the final multivariable model.

Like with PCS-12, having a higher CAT score was associated with a significantly lower MCS-12 score. In contrast to PCS-12, MCS-12 score was significantly associated with elevated patient-reported symptoms of anxiety or depression in a negative way. More precisely, even reporting marginally noticeable symptoms of anxiety as well as reporting noticeable symptoms of anxiety or depression were associated with a reduced mental HRQOL. In total, 54% of the variance in the MCS-12 variable was explained by the just named variables (*Table 3*).

Sensitivity analyses were performed in order to investigate whether association patterns would differ between patients recruited from primary *vs.* secondary care. CAT score and FEV1 (in percent predicted) emerged as the strongest predictive factors in both subsamples and were, significantly related to PCS-12 score in both groups. For MCS-12 score, a noticeable HADS-D remained the factor most strongly associated in both groups (data not shown).

Discussion

Principal findings

This cross-sectional study, investigating determinants of generic HRQOL in COPD patients, indicates a lower PCS-12 score and MCS-12 score in COPD patients compared to the German norm population (31). Regarding significant determinants, the CAT score was the only factor associated with both the physical and mental component of the SF-12. Lung function and total number of medications, both of which reflect disease severity, were related to worse physical

Table 1 Characteristics of the study population (N=206)

Characteristic	N	Mean value/absolute number	[Minimum; maximum] & SD or %
Socio-demographic & lifestyle factors			
Age	206	65.30	[41; 93]; 8.85
Male gender	206	125	60.7%
Education level	195		
Low		145	74.4%
High		50	25.6%
Living alone	202	45	22.3%
Having migration background	202	10	5%
Estimated travelling time to practitioner (minutes)	198	30.1	[5; 120]; 18.05
Current smokers	198	40	20.2%
Disease-specific factors			
FEV1 in % predicted	143	46.89	[4.03; 109.4]; 21.44
GOLD 1	190	9	4.7%
GOLD 2	190	54	28.4%
GOLD 3	190	61	32.1%
GOLD 4	190	66	34.7%
CAT	192	23.26	[5; 39]; 7.20
Number of exacerbations	189	2.06	[0; 12]; 2.10
Duration of disease	190	8.44	[0; 54]; 7.92
Treatment related factors			
Total number of medications	206	6.9	[1; 17]; 3.97
Serious side effects	198	48	24.2%
Number of doctor visits (1 year)	194	6.30	[0; 52]; 6.41
Inpatient treatment	206	143	69.4%
Rehabilitation	200	95	47.5%
Psychological factors			
HADS-A	200		
Inconspicuous		93	46.5%
Marginally noticeable		51	25.5%
Noticeable		56	28.0%
HADS-D	194		
Inconspicuous		89	45.9%
Marginally noticeable		38	19.6%
Noticeable		67	34.5%
Health-related quality of life			
SF-12: mental component scale	194	37.99	[9.81; 69.66]; 14.3
SF-12: physical component scale	194	31.78	[11.91; 57.76]; 9.71

SD, standard deviation; CAT, COPD assessment test; FEV1, forced expiratory volume in 1 second; HADS-A, hospital anxiety and depression scale—anxiety scale; HADS-D, HADS—depression scale; SF-12, Short-Form 12; MCS-12, mental component of the SF-12; PCS-12, physical component of the SF-12.

Table 2 Associations between PCS-12/MCS-12 and potential determinants in COPD patients: results of univariate linear regression analysis

Determinants	PCS-12			MCS-12		
	B	β	P	B	β	P
Disease-specific-factors						
CAT	–0.76	–0.58	<0.001	–0.96	–0.49	<0.001
FEV1 % predicted	0.27	0.56	<0.001	0.20	0.30	<0.001
Number of exacerbations	–1.84	–0.40	<0.001	–2.75	–0.40	<0.001
Disease duration (years)	–0.03	–0.03	0.740	–0.10	–0.05	0.467
Socio-demographic factors						
Age (years)	0.05	0.05	0.487	0.02	0.01	0.844
Female gender	–0.73	–0.04	0.611	–3.86	–0.13	0.068
Having Migration background[a]	7.63	0.17	0.019	–1.26	–0.02	0.797
Living alone[b]	–1.42	–0.06	0.392	–1.83	–0.05	0.462
Estimated travelling time to practitioner (minutes)	–0.02	–0.04	0.593	–0.05	–0.07	0.351
High education level[c]	–0.46	–0.02	0.775	2.27	0.07	0.349
Smoking	0.18	0.01	0.919	–1.35	–0.04	0.602
Treatment related factors						
Total number of medications	–1.11	–0.46	<0.001	–1.06	–0.30	<0.001
Serious side effects due to COPD medication[d]	–2.90	–0.13	0.080	–0.99	–0.03	0.690
Number of doctor visits (last year)	–0.18	–0.12	0.103	–0.24	–0.11	0.134
Participation at rehabilitation measures	–2.92	–0.15	0.036	–0.46	–0.02	0.826
Psychological factors						
HADS-A[e]						
Marginally noticeable	–1.40	–0.06	0.409	–13.83	–0.42	<0.001
Noticeable	–4.47	–0.21	0.008	–20.12	-0.62	<0.001
HADS-D[f]						
Marginally noticeable	–5.52	–0.23	0.002	–10.69	–0.30	<0.001
Noticeable	–8.07	–0.40	<0.001	–20.62	–0.68	<0.001

[a], no migration background; [b], living not alone; [c], low education level; [d], no serious side effects; [e], inconspicuous HADS-A; [f], inconspicuous HADS-D. CAT, COPD assessment test; FEV1, forced expiratory volume in 1 second; HADS-A, hospital anxiety and depression scale—anxiety scale; HADS-D, HADS–depression scale; SF-12, Short-Form 12; MCS-12, mental component of the SF-12; PCS-12, physical component of the SF-12.

HRQOL. Reporting symptoms of anxiety or depression show the strongest associations with MCS-12 score.

Disease-specific factors

CAT

The CAT has been developed as simple and reliable measure of health status in COPD patients (24) and can therefore be considered as a measure of COPD specific QOL. As far as we know the relationship of CAT with generic HRQOL has not been investigated before. If one takes a closer look at the content of the CAT, it becomes apparent that it enquires about symptoms (cough, phlegm/mucus, chest tightness, dyspnea) and functional limitations

Table 3 Multivariable analysis: regression coefficients (B, β) and 95% confidence intervals (CI) for the physical and mental part of the SF-12 separately [COPD patients (n=194)]

Independent variables	PCS-12 (R^2=0.57)				MCS-12 (R^2=0.54)			
	B	β	95% CI (B)	P	B	β	95% CI (B)	P
Constant	43.825		36.29; 51.36	<0.001	57.33		47.10; 67.55	<0.001
CAT	−0.54	−0.40	−0.76; −0.31	<0.001	−0.34	−0.19	−0.65; −0.03	0.033
FEV1 in % predicted	0.11	0.23	0.03; 0.18	0.006	0.006	0.009	−0.10; 0.11	0.908
Number of exacerbations during last year	−0.04	−0.01	−0.81; 0.74	0.925	−0.63	−0.01	−1.72; 0.46	0.256
Migration background [a]	3.45	0.06	−4.00; 10.90	0.361				
Total number of medications	−0.74	−0.28	−1.15; −0.33	0.001	−0.05	−0.01	−0.62; 0.53	0.876
Rehabilitation measure	1.41	0.07	−1.34; 4.16	0.312				
HADS-A[b] marginally noticeable					−7.74	−2.24	−12.49; −2.98	0.002
HADS-A[b] noticeable	1.84	0.08	−1.87; 5.56	0.327	−9.01	−2.28	−14.72; −3.30	0.002
HADS-D[c] marginally noticeable	−0.83	−0.03	−4.62; 2.95	0.663	−4.02	−0.11	−9.34; 1.31	0.138
HADS-D[c] noticeable	−2.30	−0.10	−6.46; 1.86	0.275	−11.12	−0.36	−17.07; −5.17	<0.001

[a], no migration background; [b], inconspicuous HADS-A; [c], inconspicuous HADS-D. CAT, COPD assessment test; FEV1, forced expiratory volume in 1 second; HADS-A, Hospital Anxiety and Depression Scale—anxiety scale; HADS-D, HADS–depression scale; MCS-12, mental component of the Short-Form 12 Questionnaire (SF-12); PCS-12, physical component of the SF-12.

(sleep disorders, domestic work, energy, confident leaving home). Therefore, an association with physical HRQOL was to be expected. However, the finding of a significant negative association between CAT and mental HRQOL is noteworthy and moreover the only significant relationship besides the association between MCS-12 score with psychological factors.

FEV1

FEV1 is the most commonly used way to express functional impairment. Although it is quite difficult to compare or summarize results, due to heterogeneity in outcome measures and instruments used, our results are comparable to previous studies (32). According to results of Garrido *et al.*, who found a higher correlation between FEV1 and PCS-12 score (20), predicted FEV1% was only significantly associated with PCS-12 score in the multivariable analysis of this study. Bentsen *et al.* demonstrated that subjective health status in COPD patients is determined more by symptoms, particular breathlessness as well as anxiety and depression, than demographics or physiological variables like predicted FEV1% (33). In a study of Janson *et al.* (13) lower FEV1 was associated with a lower PCS-12 score, but there was no significant association between FEV1 and the mental part of QOL. The strong association in our univariate analysis is possibly explainable by the high number of severe and even very severe COPD patients in our study population. Often patients with COPD stage IV are underrepresented in studies due to time consuming test batteries which impose a burden to patients. In a study of Pereira *et al.* (34) 57.1% of patients were classified as having severe or extremely severe COPD. In this study, FEV1 was the parameter that best correlated with the St Georges Respiratory Questionnaire (SGRQ), another disease-specific measure of HRQOL for chronic respiratory illness, total score and the only respiratory function parameter that correlated with PCS-36 score.

Treatment related factors

In our study, poorer physical HRQOL was associated with a higher number of total medications in multivariable analysis. In reviewing the literature, a study with 611 COPD patients (43.7% with COPD GOLD III) found that patients who took two or more medications to treat their COPD compared to patients without any medication had a clinically relevant decrease in their HRQOL measured with SGRQ (35). Furthermore, Miravitlles *et al.* showed in

a cross-sectional study with 441 COPD patients, that the PCS-12 score was significantly associated with the number of different drugs (36). Since in our study no differentiation was made between medications for treating COPD and other medications, a direct comparison with these studies is not possible. However, a similar trend can be observed. Since there is only a significant association with the physical QOL, the total number of medications taken could potentially represent a proxy measure for the number of comorbidities.

Psychological factors

In this study, about one third of the patients reported a noticeable amount of depressive symptoms and about 20 % were grouped as having marginally noticeable depressive symptoms. Having marginally noticeable symptoms of anxiety is true for about 25% in our study. Our finding is comparable to the prevalence of clinically significant depressive symptoms in COPD patients revealed in a meta-analysis study by Zhang *et al.* (37). Together HADS-A and HADS-D explain the majority of variance in the mental component of HRQOL in our study. In contrast to the significantly negative associations between HADS and MCS-12 score, our study found no association between the different categories of the HADS and the physical component of the SF-12 questionnaire. A review and meta-analysis of Tsiligianni *et al.* (7) has shown a persisting association between depression or rather anxiety with QOL, when using different questionnaires. Looking at the SF-36, the long form of the SF-12 questionnaire used in our study, a cross-sectional study revealed that COPD patients without significant depressive symptoms had significantly higher scores in all sub-scales of the SF-36 compared to those with depressive symptoms (38). Even across multiple study designs the relationship between anxiety and depression with HRQOL remains the same (39). Moreover, when depression and anxiety are considered as comorbidities, a strong association with HRQOL can be found in literature (18). A clear association between depressive or anxious symptoms and HRQOL can therefore be assumed. However, it has to be noted, that both HADS and MCS-12 tap into related constructs which means that a correlation can be expected to some extent.

Strengths and weaknesses

To interpret the findings of the study correctly, some limitations should be acknowledged. Due to the cross-sectional design of our study, no causal relationships could be revealed as we are unable to disentangle the time sequence of events. Furthermore, HRQOL was obtained as a self-reported outcome, which means that for example daily sensitivities like stress or bad mood may influence the answers as there are included retrospective questions. However, self-reported outcome measures are considered important measuring tools in clinical research when it comes to HRQOL (40). Even if there was no random selection of participating physicians, we aimed to cover a wide range of different recruitment sites in order to get a most generalizable COPD population. Despite the attempt we made to recruit a broad range of severities from different recruitment sites, we did end up with a sample that has a higher proportion of severe and very severe stages of COPD compared to the general COPD population in Europe (41). A further strength is the broad approach with different spheres of influence analyzed, as living with COPD is complex and there are various domains that possibly affect HRQOL. Furthermore, the use of standardized and validated measurement instruments for our main outcome and most of our independent variables is a strength of our study.

Conclusions

Depending on the component of QOL, HRQOL is associated with a number of factors. The strongest of which are COPD-specific HRQOL for generic physical HRQOL and reporting symptoms of depression and/or anxiety for generic mental HRQOL. In clinical practice screening for depression and anxiety and referring potentially affected patients to psychiatric assessment may be promising approaches to enhance the QOL of COPD patients. Furthermore, the conduct of robust interventional studies is warranted.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Prior to the investigation, ethical clearance was obtained from the local ethics committee on 16 May 2013 (reference number: 13-101-0091). Informed consent was obtained from all individual participants included in the study.

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