

Health-related quality of life assessed by the EORTC QLQ-C30 questionnaire in the general Slovenian population

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Radiol Oncol 2017; 51(3): 342-350.

Received 15 January 2017

Accepted 17 March 2017

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Disclosure: No potential conflicts of interest were disclosed.

Background. The aim of our study was to obtain reference data of the EORTC QLQ-C30 quality of life dimensions for the general Slovenian population. We intend to provide the researchers and clinicians in our country with the expected mean health-related quality of life (HRQL) scores for distinctive socio-demographic population groups.

Methods. The EORTC QLQ-C30 questionnaire supplemented by a socio-demographic inquiry was mailed or distributed to 1,685 randomly selected individuals in the Slovenian population aged 18 – 90. Answers from 1,231 subjects representing socio-demographic diversity of the Slovenian population were collected and transformed into EORTC dimensions and symptoms. The impact of socio-demographic features on HRQL scores was assessed by multiple linear regression models.

Results. Gender, age and self-rated social class are the important confounders in the quality of life scores in our population. Men reported better quality of life on the majority of the specific scales and, at the same time, reported fewer symptoms. There was no gender-specific difference in cognitive functioning. The mean scores were consistently lower with age in both sexes.

Conclusions. This is the first study to report the normative EORTC QLQ-C30 scores for one of the south-eastern European populations. The reported expected mean scores allow Slovenian oncologists to estimate what the quality of life in cancer patients would be, had they not been ill. As they are derived by common methodology, our results can easily be included in any further international comparisons or in the calculation of European summarized HRQL scores.

Key words: health-related quality of life; EORTC QLQ-C30; normative values; socio-demographic determinants; reference data

Introduction

Cancer burden in Slovenia is increasing. There are approximately 14,000 new cancer patients annually (age standardized incidence rate (world) = 335/100,000), the life-time prevalence is almost 100,000. More than 10,000 patients are currently in the process of primary cancer treatment; almost 30,000 have recently completed a specific oncological treatment but have still been followed by oncologists.¹ Because of improvements in diagnostics

and treatment we are observing a constant increase in cancer patients' survival. Five-year relative survival is approaching 60%.² However, despite being widely recognised as a central endpoint in cancer research³, the health-related quality of life (HRQL) has not been used systematically as an outcome measure in clinical trials or oncological practice in our country so far.

Evaluation of quality of life is conducted by using the standardized questionnaires.⁴ The most widely used and generally accepted tool

for assessing HRQL in oncology is the questionnaire launched by the European Organization for Research and Treatment of Cancer (EORTC).⁵ The core questionnaire, which consists of 30 questions (EORTC QLQ-C30), is supplemented by disease-specific modules and is translated into 81 languages, including Slovene.⁶ To assist the overall interpretation of results from clinical research of HRQL the population-based reference values are used; the scores of the general population can be used as guidelines in the interpretation of HRQL scores from different patients' populations.

The normative (reference) values of the QLQ-C30 questionnaire for a generally healthy population are already available for some countries: Denmark – women⁷, Norway – both men and women⁸, Sweden^{9,10}, Germany^{11,12}, the Netherlands¹³ and again Denmark – both men and women.³ Outside Europe, they have obtained reference data for the EORTC QLQ-C30 in Columbia¹⁴ and South Korea.^{15,16} Recently, Hinz *et al.*¹⁷ published the European reference values of the EORTC QLQ-C30 by summarizing six European general population normative studies from four countries (Sweden, Norway, the Netherlands and Germany). Fayers compared reference data from Germany and the Scandinavian countries and noticed some differences, which can be attributable to differences in health status between these countries or to cultural differences.¹⁸ Similar conclusions were made by Scott *et al.* where they analysed the results of 106 clinical studies in order to assess international differences in response to the questionnaire EORTC QLQ-C30. Most response patterns were similar, but the largest variations were found in the results for Eastern Europe and East Asia.¹⁹

The aim of our study was to obtain reference data of the EORTC QLQ-C30 quality of life dimensions for the general Slovenian population. We intend to provide the researchers and clinicians in our country with the expected mean HRQL scores for distinctive socio-demographic population groups, which will allow them to estimate what the HRQL in cancer patients would be, had they not been ill.

Patients and methods

Population sample

The study was conducted in the year 2011 and the first half of the year 2012. The healthy individuals were sampled from the Slovenian adult population, aged between 18 and 90 years. All the participants have provided an informed consent for participa-

tion in the study. All procedures performed in our study were in accordance with, and with the approval of, the National Medical Ethics Committee (No. 134/09/09, from 5.11.2009) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The random sample from the target population of 1,650,000 was collected from two data sources: (1) the copy of the Central Population Registry for the age groups 50 – 69 kept by the Registry of the National colorectal screening program SVIT (the questionnaire was sent by ordinary mail together with the screening invitation) and (2) the list of visitors to the outpatient clinic at the Institute of Oncology in Ljubljana (the questionnaires were distributed to the relatives or companions of the cancer patients).

The response rate in the first data source was 63%; 566 subjects returned the questionnaire out of 898 selected. By the second approach, 787 questionnaires had been distributed to the relatives or companions of the cancer patients, of which 731 answered questionnaires were returned (response rate 93%). In total we collected 1,297 questionnaires, of which 66 were not included in the study because some answers were missing or were not clear. The final sample consists of 1,231 subjects. The comparison with the national data provided by the Statistical Office of the Republic of Slovenia²⁰ shows that the collected sample is representative for the general Slovenian population in respect of age ($p = 0.140$) and gender ($p = 0.582$) (Table 1). To check the representativeness by socio-demographic variables our sample was compared with the population-based socio-economic variables obtained in the Countrywide Integrated Noncommunicable Diseases Intervention (CINDI) research, which was conducted in Slovenia investigating the socio-economic and geographic determinants in correlation with the incidence of chronic non-infectious disease or unhealthy lifestyle.²¹ Our sample is representative for the general population in respect of education ($p = 0.054$), employment ($p = 0.100$), living environment ($p = 0.103$) and geographical area ($p = 0.260$), but it is not comparable for marital status ($p < 0.000$) or social class ($p < 0.000$) (Table 1).

Questionnaires

The EORTC QLQ-C30 is a questionnaire assessing individual HRQL during the previous week. The EORTC QLQ-C30 has 30 items arranged into nine scales (dimensions) and six single items. The scales are divided into five function scales (physi-

TABLE 1. Socio-demographic characteristics of the sample by gender and its comparisons with national averages^{21,20}

	Men Number (%)	Women Number (%)	Total Number (%)	National reference (S,C)* (%)	p (chi square)
Gender					0.582
Men	619 (50.3)			49.51 ^s	
Women		612 (49.7)		50.5 ^s	
Age category					0.140
18-39 years	224 (36.2)	188 (30.7)	412 (33.5)	35.7 ^s	
40-59 years	230 (37.2)	262 (42.8)	492 (40.0)	37.4 ^s	
60-90 years	165 (26.7)	162 (26.5)	327 (26.6)	26.9 ^s	
Marital status					<0.000
With a partner	441 (71.2)	439 (71.2)	880 (71.5)	76.7 ^c	
Single	178 (28.8)	173 (28.3)	351 (28.5)	23.3 ^c	
Education					0.054
Elementary or less	107 (17.3)	101 (16.5)	208 (16.9)	16.7 ^c	
Secondary school	346 (55.9)	298 (48.7)	644 (52.3)	55.4 ^c	
More than secondary school	166 (26.8)	213 (34.8)	379 (30.8)	27.9 ^c	
Employment					0.100
Employed	338 (54.6)	325 (53.1)	663 (53.9)	53.5 ^c	
Unemployed	39 (6.3)	45 (7.4)	84 (6.8)	8.5 ^c	
Not active	242 (39.1)	242 (39.5)	484 (39.3)	38.1 ^c	
Living environment					0.103
Urban	187 (30.2)	235 (28.4)	422 (34.3)	31.5 ^c	
Suburban	119 (19.2)	150 (24.5)	269 (21.9)	23.2 ^c	
Rural	313 (50.6)	227 (37.1)	540 (43.9)	45.3 ^c	
Geographical area					0.230
West	125 (20.2)	170 (27.8)	295 (24.0)	22.3 ^c	
Central	179 (28.9)	194 (28.9)	373 (30.3)	29.9 ^c	
East	315 (50.9)	248 (40.5)	563 (45.7)	47.8 ^c	
Social class					<0.000
Lower	214 (34.6)	189 (30.9)	403 (32.7)	42.2 ^c	
Middle	340 (54.9)	351 (57.4)	691 (56.1)	47.9 ^c	
Upper	65 (10.5)	72 (11.8)	137 (11.1)	9.9 ^c	

*As a national reference the data from Statistical Office of the Republic Slovenia (S) and Countrywide Integrated Noncommunicable Diseases Intervention in Slovenia (C) is applied.

cal, role, cognitive, emotional and social functions); three symptom scales (fatigue, pain, nausea or vomiting) and one global health-status/quality of life dimension. The six single items address specific symptoms: dyspnoea, appetite loss, insomnia, constipation, diarrhoea and a question addressing the financial impact of the disease. Each item has four response alternatives: 1) "not at all", 2) "a little" 3) "quite a bit" 4) "very much" except for the global health-status/quality of life scale, which has response options ranging from 1) "very poor" to 7)

"excellent". The questionnaire was officially translated into the Slovenian language.^{5,6,22}

The subjects in our research also received a questionnaire on their socio-demographic data, including gender, age, marital status, education, employment, social class, living environment and geographical area. The categories of socio-demographic variables were adapted from the Slovenian CINDI research.²¹ To facilitate the analysis some of the categories were merged – the applied response categories are presented in Table 1.

TABLE 2. Mean scores (MS) with standard deviations (SD) for all scales and items by gender

	Total		Men		Women		p (t-test)
	MS	SD	MS	SD	MS	SD	
Global health status/quality of life	71.1	21.4	72.5	21.4	69.7	21.3	0.882
Physical functioning	91.8	14.0	93.3	12.6	90.3	15.1	<0.000
Role functioning	88.7	20.1	90.0	19.3	87.5	20.9	0.056
Emotional functioning	82.0	18.5	83.6	18.4	80.4	18.5	0.686
Cognitive functioning	90.2	16.0	90.2	16.3	90.2	15.7	0.760
Social functioning	90.9	17.3	91.6	16.9	90.2	17.8	0.094
Fatigue	19.8	19.8	17.4	19.3	22.2	20.0	0.769
Nausea/vomiting	3.3	10.6	3.0	10.2	3.5	11.0	0.116
Pain	14.5	20.2	13.1	19.6	16.0	20.8	0.134
Dispnea	5.3	15.3	5.0	14.7	5.7	15.8	0.087
Insomnia	19.8	25.1	16.8	23.9	22.8	25.9	0.056
Appetite loss	5.3	15.5	5.3	16.0	5.2	15.1	0.795
Constipation	6.9	16.9	4.6	13.8	9.2	19.3	<0.000
Diarrhoea	4.2	13.6	4.4	14.1	4.0	13.0	0.247
Financial problems	6.6	17.5	6.4	17.2	6.9	17.9	0.385

Statistical analysis

The answers recorded by the EORTC QLQ-C30 questionnaire were transformed into dimensions ranged 0 – 100 according to the EORTC scoring instructions.²² In all dimensions, where the linear transformation includes multiple answers, internal consistency was proved adequate by a high Cronbach alpha coefficient of reliability. The coefficients for the scales were as follows: global health-status / quality of life 0.89, social functioning 0.86, emotional functioning 0.83, physical functioning 0.80, role functioning 0.80, cognitive functioning 0.64, fatigue 0.80, nausea/vomiting 0.69 and pain 0.70.

The dimensions were considered as numerical variables and presented by mean and standard deviations. Socio-demographic characteristics were analysed as categorical variables. The differences between genders in all scales were tested by Student's t test. The chi-square test was applied to check if the collected sample is representative for the general Slovenian population. The impact of socio-demographic features on HRQL was assessed by multiple linear regression models as suggested by Hjermstadt.²³ A separate model has been constructed for each dimension. The model constants and the regression coefficients have been applied in the calculation of the expected mean scores for

each socio-demographic population group using equation 1:

$$\text{Dimension score} = n + \sum_{i=1}^I b_i X_i, \quad [\text{Equation 1}]$$

where X_i ($i = 1, \dots, I$) represents a particular socio-demographic feature (expressed as dummy variables), b_i represents the regression coefficient for the i -th socio-demographic feature and n is the model constant.

The values of $p < 0.05$ were considered as statistically significant. All statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 21).

Results

There were 1,231 questionnaires eligible for analysis. The subjects were made up of 50.3% men (619 persons) and 49.7% women (612 persons). Table 1 shows the socio-demographic data of the sample divided by gender. The mean age was 48 (range 19 to 90 years). As in the general Slovenian population, the majority of the subjects in the sample were employed, had a secondary school education and were living in the rural environment of Eastern Slovenia. In comparison with the general population in our sample, the individuals, on average, reported a higher social class and there were significantly more single living persons in our sample in comparison with the national averages.

TABLE 3. Regression coefficients with constants for all scales and items applied in the calculation of the expected mean scores according to gender, age and social class in Slovenian population

	Men	18-39 years	40-59 years	Lower social class	Middle social class	Constant
Global health status/quality of life	-0.07	0.30	0.21	0.30	- 0.12	71.5
Physical functioning	-0.11	0.42	0.29	-0.25	- 0.08	89.6
Role functioning	-0.07	0.10	0.06	0.20	- 0.05	91.6
Emotional functioning	-0.09	0.04	0.06	-0.11	0.00	83.7
Cognitive functioning	0.00	0.21	0.16	-0.15	- 0.06	88.6
Social functioning	-0.04	0.17	0.12	-0.17	- 0.03	90.6
Fatigue	0.13	-0.10	-0.12	0.19	0.05	16.8
Nausea/vomiting	0.03	0.03	-0.06	0.02	-0.08	4.5
Pain	0.07	- 0.26	-0.17	0.19	0.05	15.7
Dispnea	0.02	-0.22	-0.15	0.09	-0.01	8.4
Insomnia	0.12	-0.18	-0.16	0.08	-0.01	21.9
Appetite loss	0.01	0.05	-0.04	0.09	-0.07	5.3
Constipation	0.13	-0.10	-0.05	0.08	0.05	4.8
Diarrhoea	-0.02	-0.05	-0.02	0.00	-0.04	5.8
Financial problems	0.02	-0.08	-0.02	0.23	0.03	4.3

Scale and item scores

Table 2 shows mean values of EORTC QLQ-C30 scores for all scales and items. The distribution of means is highly skewed since most subjects reported no symptoms and the best functioning. Men reported better global quality of life as well as better physical, role, emotional and social functioning. On the cognitive functioning scale there is no difference between genders. Men also reported less fatigue, nausea or vomiting, pain, dyspnoea, insomnia, constipation and financial impact. Women reported less diarrhoea and loss of appetite. The described differences are not statistically significant except for physical functioning, which is significantly higher in men and obstipation, which is significantly more prevalent in women. However, as presented graphically in Figure 1, the differences between genders are more prominent in older age groups. The mean scores of the global health-status/quality of life and specific functional scales are consistently lower with age in both sexes. However the decrease of mean scores with age, is the highest in women evaluating physical and role functioning. The mean scores of symptom scales and single items increase with age. We observed the highest increase in the mean score for women when evaluating fatigue and pain. The mean score

of nausea/vomiting, appetite loss and diarrhoea did not change much with age.

The impact of socio-demographic features

The impact of socio-demographic features on all scales of HRQL was assessed by multiple linear regression models. In our population gender, age and social class have a critical impact on HRQL. A separate model has been constructed for each dimension; gender had an impact on 8 scales of HRQL, age on 9 scales, education on 3 scales, employment on 2 scales, living environment on 1 scale, marital status and geographical area on no scale and social class on 10 scales.

Table 3 shows the regression coefficients with model constants for all scales in relation to gender, age and social class. These statistics are the inputs in the calculation of the expected mean score of each scale according to gender, age and social class. The universal model fitted is described by equation 1. As an empirical example for the calculation of expected mean scores for a particular socio-demographic population group we apply the case of women, aged 65 from the middle social class. Their expected score for the scale physical functioning is 89.52:

$$\text{Physical functioning score} = -0.11 \times 0 + 0.42 \times 0 + 0.29 \times 0 - 0.25 \times 0 - 0.08 \times 1 + 89.60 = 89.52$$

Values for dummies included in the model are as follows: gender: men = 1, age1: 18 – 39 years = 1, age2: 40 – 59 years = 1, social class 1: lower class = 1, social class 2: middle class = 1.

Discussion

In this study we present the reference data of the EORTC QLQ-C30 quality of life dimensions for the general Slovenian population. The collected raw questionnaire data are transformed into expected mean HRQL scores for distinctive socio-demographic population groups. In the results we reveal the expected mean score of only one single empirical example (women, 65, middle social class: 89.52) - the complete table of all expected mean HRQL scores for all significant socio-demographic population groups is too complex and was, in order to keep the focus on the primary aim of the study, deliberately not added to the paper. Still, as a part of our entire research project, all the expected mean HRQL scores for any significant socio-demographic population group were prepared and are freely available to Slovenian oncologists in a suitable format to be used in everyday practice.

The suggested comparison of scores measured in cancer patients and the obtained Slovenian average values will enable better clinical interpretation of disease progress and treatment effects. The quality of life in Slovenian cancer patients could be monitored objectively, excluding the impact of important socio-demographic factors. As established in several papers so far^{18,19}, to avoid over- or underestimation of the mean score difference it is essential to use the population-specific norms incorporating each country's socio-economic characteristics. Alternatively, the expected mean scores could be used in a clinical practice as baseline individual HRQL scores, since newly diagnosed patients can already have disease symptoms and psychological problems affecting the results of the questionnaire.¹²

The expected mean scores have been calculated by identical multiple linear regression models as described in equation 1 and as already proposed by Hjermstad.²³ The relationship between the variables and scale or item scores in our data was generally linear. There were some non-linear components in the age/fatigue and age/pain association which could be expressed in an additional Age² component in the regression models as suggested

by Schwartz.¹¹ For simplicity and clarity reasons we decided to omit this quadratic term and further on to assume equal independent variables (the socio-demographic feature) for all scales, even though some of the factors do not contribute to some of the scales at all. However, for the final linear model, only the three most influential variables were selected: gender, age and social class.

The results of our study considering age and gender distribution were similar to the results conducted in the other European countries and elsewhere in the world.^{3,7-16} Some important but mostly statistically insignificant gender differences were identified in Slovenian population: men reported better quality of life on the majority of the specific scales and, at the same time, reported fewer symptoms. On the other hand, women reported less appetite loss and diarrhoea. We didn't observe any gender-specific difference on cognitive functioning. In the Norwegian study, which was the first to be conducted on a sample of the general population, men reported better quality of life on all scales and fewer symptoms.⁸ Similar results were observed in the German study – men reported better quality of life on all scales and fewer symptoms in comparison to women.¹¹ In the last study from Denmark, which was published in 2014, the better quality of life assessed by men was not so obvious. Men reported better physical functioning, less insomnia and constipation, whereas women reported better social functioning and less dyspnoea.³

In our study we observed that all scales deteriorated with age. Older subjects also reported more symptoms. The only exception is emotional functioning where there was no age-dependent fall. Similarly, emotional functioning was not age-dependent also in three Scandinavian studies^{3,9,8}, but in the German population there was a slight decrease of emotional functioning in the older age groups.¹¹ In the comparison of the German, Norwegian and Sweden HRQL scores Fayers¹⁸ noticed that in Germany there is a steeper age-dependent decline in the mean score for the global quality of life, ending at far lower scores in older patients, compared to the Scandinavian results. A similar difference was noticed with the fatigue scale. In the Slovenian population we noticed a similar fall in the mean score of the global health-status/quality of life scale and a similar increase of the mean score of the fatigue scale as in the German study. As the Slovenian scores of most scales are more similar to the German results, we can assume

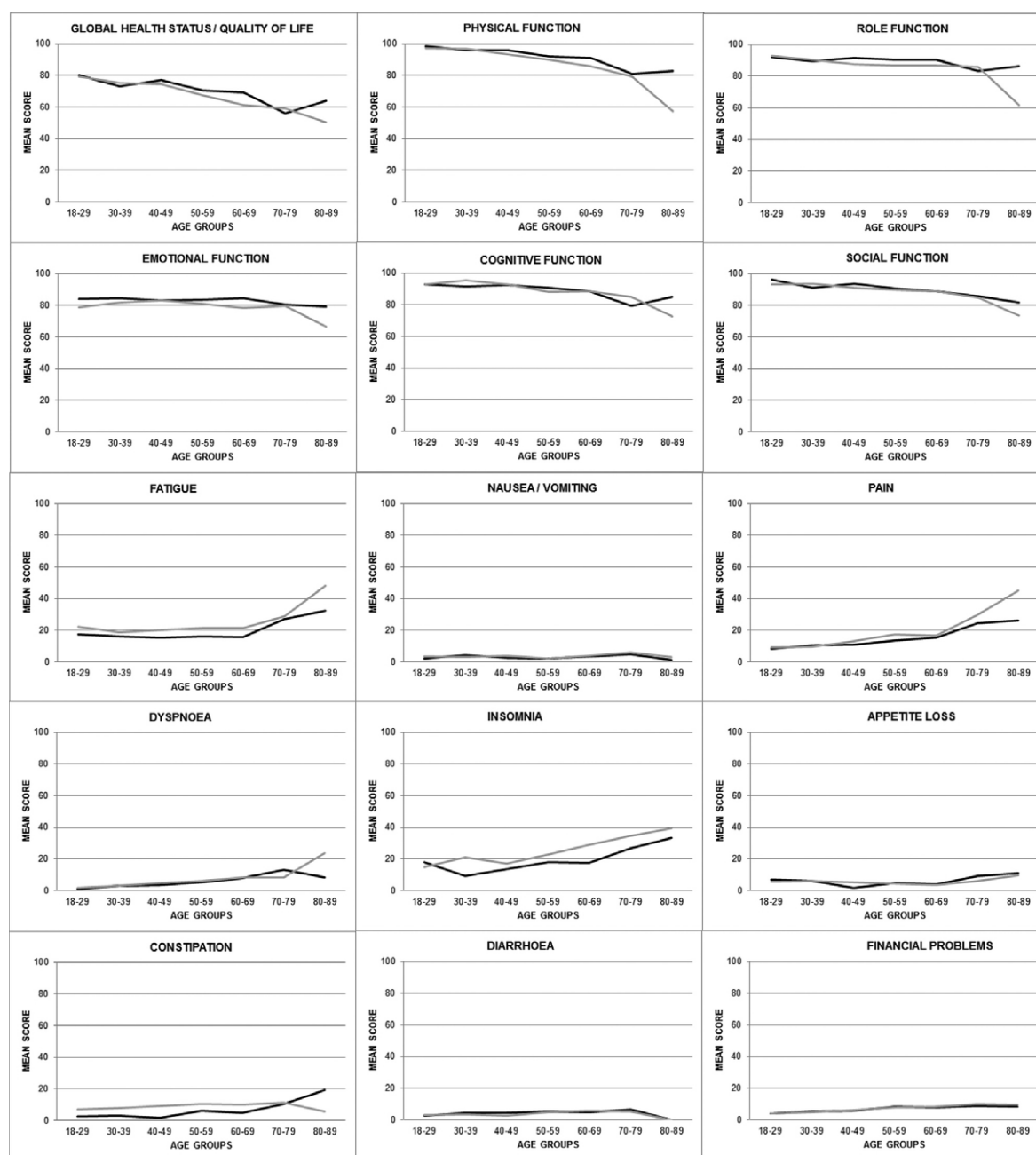


FIGURE 1. Mean scores of all scales divided by sex (grey – women, black – men).

our cultural environment and health status is more similar to the Germans than to the Scandinavians.

In Slovenia we have been following the impact of demographic, socio-economic and geographic features on the incidence of chronic non-infectious diseases and health-related lifestyle for more than a decade.²¹ Furthermore we have investigated the

impact of the socio-demographic determinants on the cancer incidence in Slovenia – in the socio-economically more deprived regions in the eastern part of the country there is higher incidence of head and neck tumours but less female skin melanoma and breast cancer.²⁴ Yet another study in Slovenia confirmed the higher prevalence of poor self-rated

health in individuals from lower self-assessed social class.²⁵ As, when resuming all this research, the socio-demographic determinants have an impact on the incidence of non-infectious disease, cancer and on self-rated health in Slovenia, we assumed that determinants could also affect the HRQL. Besides gender and age we have tested the influence of six additional socio-demographic variables on HRQL in the general Slovenian population – it turned out that only self-assessed social class has a significant impact on HRQL in our population. On the contrary, Hjermstad and Juul showed that education, employment status, marital status and living environment have a significant influence on at least some HRQL scores in the Norwegian and Danish populations respectively.^{3,8}

Although gender, age and other socio-demographic features are important confounders in normative as well as in clinical quality of life scores it seems that morbidity has a distinct impact on all functional scales and should be considered as a strong confounder in all quality of life evaluations.³ The impact of associated health problems on HRQL can sometimes be higher than late treatment effect in cancer patients.²⁶ In this study we have not investigated whether HRQL in the general Slovenian population depends on morbidity. However we believe that worsening of HRQL with age should be explained by the fact that physical strength and vital function deteriorate with age as the elderly have more pain, insomnia and dispnea which all are a consequence of more morbidity. Surely the impact of morbidity on HRQL in our population will be the field of our further surveys.

In conclusion, in this study we have derived, by common methodology, the Slovenian HRQL normative values. Gender, age and self-rated social class are the important confounders in the quality of life scores in our population. The expected mean scores reported could be used as a reference in the clinical interpretation of disease progress and treatment effects. Finally, our study is the first to report the normative EORTC QLQ-C30 scores for one of the south-eastern European populations and can easily be included in any further international comparisons or in the calculation of European summarized scores.

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