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Original Scientific Paper

CHRONIC MULTIMORBIDITY OF LOW BACK PAIN OR OTHER CHRONIC BACK DISORDERS IN THE REPUBLIC OF CROATIA

Jelena Marunica Karšaj[1], Tomislav Benjak[2], Larisa Stojanovič[3], Frane Grubišić[1,4], Diana Balen[1] and Simeon Grazio[1,4]

[1]University Department of Rheumatology, Physical and Rehabilitation Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia;
[2]Croatian Institute of Public Health, Zagreb, Croatia;
[3]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia;
[4]School of Medicine, University of Zagreb, Zagreb, Croatia

SUMMARY – The aim was to assess the prevalence of chronic multimorbidity in patients with chronic low back pain or other chronic back disorders (BD). We analyzed data from the population-based cross-sectional European Health Interview Survey (EHIS) performed in the Republic of Croatia 2014-2015 by the Croatian Institute of Public Health. Outcome was the point-prevalence of chronic multimorbidity defined as having ≥2 chronic illnesses out of 14 contained in the EHIS questionnaire, after adjustment for ten sociodemographic, anthropometric and lifestyle confounders. Amoung fourteen targeted illnesses were asthma, allergies, hypertension, urinary incontinence, kidney diseases, coronary heart disease or angina pectoris, neck disorder, arthrosis, chronic obstructive pulmonary disease, diabetes mellitus, myocardial infarction, stroke, depression, and the common category "other". We analyzed data on 268 participants with BD and 511 without it. Participants with BD had a significantly higher relative risk of any chronic multimorbidity (RRadj=2.12; 95% CI 1.55, 2.99; p<0.001), as well as of non-musculoskeletal chronic multimorbidity (RRadj=2.29; 95% CI 1.70, 3.08; p=0.001) than participants without BD. All chronic comorbidities except for asthma and liver cirrhosis were significantly more prevalent in participants with BD than in participants without BD. In the population with BD, the participants with multimorbidity had three to four times higher odds for unfavorable self-reported health outcomes than the participants with no comorbid conditions, whereas the existence of only one comorbidity was not significantly associated with a worse outcome compared to the population with no comorbidities. In conclusion, the population suffering from BD has a higher prevalence of chronic multimorbidity than the population without BD and this multimorbidity is associated with unfavorable health outcomes.

Key words: *Low back pain; European Health Interview Survey; Comorbidity; Multimorbidity*

Introduction

Many risk factors for chronic low back pain or other chronic back disorders (BDs) including nonspecific low-back pain are shared with various other musculoskeletal disorders and conditions, as well as with different other noncommunicable chronic illnesses (NCI). For example, older age, smoking, insufficient physical activity, use of alcohol, and obesity increase the risk of BD, and of cardiovascular and metabolic diseases[1,2]; height loss with aging increases the risk of BD, and of gastroesophageal reflux disease[3]; delivery rank in women, hypertension or lower education increase the risk of BD and of urinary incontinence[4]; long-term

Correspondence to: *Professor Simeon Grazio, MD, PhD*, University Department of Rheumatology, Physical and Rehabilitation Medicine, Sestre milosrdnice University Hospital Center, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: simeon.grazio@kbcsm.hr

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smoking is a risk factor for BD and for chronic obstructive pulmonary disease (COPD)[2,5]. Furthermore, various NCIs themselves increase the risk of BD, for example, asthma or COPD[6], depression[7], urinary dysfunction[8], different conditions associated with chronic systemic inflammation[9], although the association of proinflammatory biomarkers and BD is not consistent across the literature[10]. In addition to similar risk factors and mutual causation, more comorbidity between BD and other NCIs may, of course, be caused by common etiologic factors or pathogenetic mechanisms, of which many do not necessarily have to be known. Finally, higher rates of comorbidity between particular BD and NCI may be caused by chance due to the high prevalence of any or both of them[11], as in the case of nonspecific low back pain and hypertension. Taking all this into account, elevated comorbidity rates of chronic back pain are to be expected, as well as elevated multimorbidity rates. Multimorbidity may be defined as having two or more chronic or long-term health conditions[12]. Such combinations of chronic conditions may have a multiplicative unfavorable effects on the health status, and particularly when the musculoskeletal or locomotor systems are included, as in BD[13].

Our primary objective was to assess the prevalence of chronic multimorbidity in patients with BD. Our hypothesis was that the population with self-reported BD have a higher prevalence of chronic multimorbidity than the population without self-reported BD. Our secondary objective was to compare the prevalence of particular NCIs in patients with and without BD. Our tertiary, exploratory objective was to investigate the association of chronic multimorbidity with four self-reported health outcomes in the population of patients with BD.

Subjects and Methods

Study design

We analyzed data collected in the population-based cross-sectional 2nd wave of the European Health Interview Survey (EHIS) performed in the Republic of Croatia from April 2014 to March 2015 by the Croatian Institute of Public Health using paper questionnaires and face-to-face interviewing. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) of 1975 as revised in 2013[14].

Participants

The EHIS target population was general population aged ≥15 years, living in private households, and we further selected a subsample from the 18+ population living in the City of Zagreb and Zagreb County. Croatian Census 2011 was used as the frame for the two-stage stratified random sample designed by the Croatian Bureau of Statistics, with a household as the primary sampling unit. Interviews were performed with all members of >600 households and the response rate was 83%. Before analysis, we performed the power calculation under the following assumptions: targeted power of ≥80%, two-tail statistical significance set at 0.05, approximately 2:1 ratio of no-BD to BD group, and the expected chronic multimorbidity prevalence of 50% in the control population. To be able to significantly detect a difference of 15 percentage points that we considered clinically relevant, we needed 133 subjects with BD and 266 subjects without it. Available sample size met this requirement, so testing of our hypothesis was properly powered.

Outcomes

The primary outcome was the prevalence of chronic multimorbidity defined as having ≥2 NCIs[12]. We defined NCI in two steps. In the first step, we counted the following 14 specific self-reported chronic medical conditions from the EHIS questionnaire: (a) asthma, including allergic asthma, chronic bronchitis; (b) chronic obstructive pulmonary disease, emphysema; (c) myocardial infarction or chronic consequences of myocardial infarction; (d) coronary heart disease or angina pectoris; (e) high blood pressure (hypertension); (f) stroke (cerebral hemorrhage, cerebral thrombosis) or chronic consequences of stroke; (g) arthrosis, arthritis excluded; (i) neck pain or other chronic neck disorder; (j) diabetes mellitus; (k) allergy, such as rhinitis, hay fever, eye inflammation, dermatitis, food allergy or other allergies excluding allergic asthma; (l) cirrhosis of the liver; (m) urinary incontinence, problems in controlling the bladder; (n) kidney diseases; and (o) depression. The ordinal letters we used here to denote individual NCIs follow the coding from the original EHIS questionnaire. In the second step, we added the "other" category defined by the EHIS question: "HS2 Do you have any long-standing illness or (long-standing) health problem? By long-standing I mean an illness or health problem that has lasted or is expected to last six months or longer." We counted affirmative answer to this question as an additional NCI only to participants who did not list any of the 14 diseases specifically listed previously. The secondary outcome was the relative risk for each particular NCI in the popula-

tion with BD compared to the population without BD adjusted for ten confounding variables. The tertiary, exploratory outcomes were the following four general health indicators: self-reported long-standing moderate or severe limitation of activities, moderate to severe chronic body pain, moderate or severe interference of bodily pain with normal work, and self-perception of general health as average, bad or very bad.

Exposure

The exposure was the self-reported low back pain or other chronic BDs as defined by the EHIS questionnaire[15].

Possible confounders controlled as covariates

Ten variables the presumed confounding effect of which we wanted to control were age, sex, education, degree of urbanization, marital status, number of household members, work status, body mass index (kg/m^2), regular smoking and alcohol consumption. We defined the degree of urbanization in accordance with the EHIS methodological manual as the type of local administrative unit being densely-populated (city), intermediate-populated (town or suburb), or thinly-populated (rural)[15].

Statistical analysis

We used 15 variables to compute our primary outcome composite variable. These 15 variables were 14 binary variables indicating specific NCIs and the one indicating all other NCIs not specifically mentioned in the EHIS questionnaire. In all these 15 variables and in the exposure variable "self-reported low back pain or other chronic back disorder (BD)" we recoded the answers "I don't know/I refuse to answer" into "0" meaning: "this particular NCI was not self-reported". We computed the primary outcome composite variable by counting these 15 variables, and then categorized the new variable into three groups: no NCI, one NCI, chronic multimorbidity (≥2 NCIs), as our primary outcome. We performed direct age-standardization of multimorbidity and NCI point-prevalence to the Standard European Population[16] using a five-year wide age categories, and presented these age-standardized prevalence (ASP). We calculated the absolute risk difference between the populations with and without BD, and risk ratios with their 95% confidence interval (CI) and statistical significance. We presented the crude rates, standard-European age-standardized rates (ASP), risk differences (RD^{adj}) and risk ratios (RR_{adj}) adjusted for ten confounders by multivariable logistic regression and transformation to predicted probabilities and standard errors estimated by delta-method. Because there was a relevant number of missing data on two important confounders, body mass index and consumption of alcohol, we performed sensitivity analysis for our hypothesis test. In the sensitivity-analysis data set we imputed the missing data in a way that promoted null hypothesis. For participants with BD, we imputed the missing data on body mass index at 14 kg/m^2, which was the lowest value in the complete data set, and alcohol consumption at "weekly". For participants without BD, we imputed body mass index at 59 kg/m^2, the highest value in complete data set, and alcohol consumption at "never". In the analysis of tertiary, exploratory outcomes, we used binary logistic regression and presented odds ratios (OR) with their 95% CI. We performed the analysis on the unweighted samples because the BD population parameter structure was unknown. We set two-tailed statistical significance at $p<0.05$ and calculated all CI at the 95% level. We categorized body mass index only for descriptive purposes, but for the control of this possible confounder, we used the original, interval data. We controlled the false positive rate using the Benjamini-Hochberg procedure with the false discovery rate (FDR) set in advance at FDR<5%, and taking all statistical testing into account regardless of whether it was a primary, secondary or exploratory analysis. We performed the statistical data analysis using StataCorp 2019 (Stata Statistical Software: Release 16, StataCorp LLC, College Station, TX, USA).

Results

Description of participants

There were 861 participants enrolled in the 2nd wave of EHIS study in the City of Zagreb and Zagreb County. We excluded 24 patients who were younger than 18 and were not our target population, leaving 837 subjects in the sample. This was the total sample we used for assessment of the overall prevalence of multimorbidity and for sensitivity analysis. For the main analysis, we further excluded 20/288 (6.9%) participants with BD, and 38/549 (6.9%) participants without BD in whom data were missing on body mass index or alcohol consumption, the only two covariates with missing data. Participants excluded from the analysis were somewhat younger. In the BD population, median (interquartile range, IQR) age of excluded and remained was 54 (42-74) and 60 (49-73) years, respectively. In the population without BD, me-

Table 1. Participant characteristics

	Back disorders (n=268)		No back disorders (n=511)	
Age (years), median (IQR)	60	(49-73)	46	(30-60)
Gender:				
men	110	(41.0)	247	(48.3)
women	158	(59.0)	264	(51.7)
Degree of urbanization:				
city	135	(50.4)	257	(50.3)
town and suburbs	65	(24.3)	168	(32.9)
rural	68	(25.4)	86	(16.8)
Education:				
elementary school	68	(25.4)	59	(11.6)
secondary school	143	(53.4)	282	(55.2)
college/university	57	(21.3)	170	(33.3)
Marital status:				
married	180	(67.2)	306	(60.0)
never married	21	(7.8)	154	(30.1)
widow or divorced and single	67	(25.0)	51	(10.0)
Number of household members, median (IQR)	3	(2-4)	4	(3-5)
Work status:				
employed or student	84	(31.3)	305	(59.7)
unemployed	17	(6.3)	62	(12.1)
retired/housewife or inactive	167	(62.3)	144	(28.2)
Body mass index (kg/m^2), median (IQR)	27	(24-30)	25	(22-28)
Body mass index categorized (kg/m^2):				
healthy (<25.0)	81	(30.5)	245	(48.8)
overweight (25.0-29.9)	109	(41.0)	179	(35.7)
obese (≥30.0)	76	(28.6)	78	(15.5)
Smoking	68	(25.4)	171	(33.5)
Consumption of alcohol:				
never	76	(28.4)	147	(28.8)
less often than once a month	74	(27.6)	112	(21.9)
monthly	53	(18.8)	127	(24.9)
weekly	65	(24.3)	125	(24.5)
Self-reported long-standing activity limitations:				
no limitations	109	(41.8)	389	(82.6)
moderate or severe limitations	152	(58.2)	82	(17.4)
Chronic body pain:				
none or mild	136	(50.8)	461	(90.4)
moderate or severe	132	(49.3)	49	(9.6)
Interference of bodily pain with normal work:	124	(47.0)	38	(7.7)
none or little	140	(53.0)	459	(92.4)
moderate or severe	124	(47.0)	38	(7.7)
Self-perceived general health:				
good or very good	75	(28.0)	393	(78.0)
average, bad or very bad	193	(72.0)	111	(22.0)

Data are presented as number (percentage) of participants if not stated otherwise; IQR = interquartile range

dian (IQR) age was 34 (28-52) and 46 (30-60) years, respectively. Excluded participants compared to those who remained in the analysis were more often women (63% *vs*. 52%), more often residing in city (93% vs 50%) than in small town, suburbs or in rural settlements, more often employed (66% *vs*. 50%), more often with healthy body mass index (50% *vs*. 42%), nonsmokers (79% *vs*. 69%), nonusers of alcohol (43%

Table 2. Prevalence of chronic illnesses and multimorbidity (not counting chronic back disorder) in population with and without chronic back disorders

	Back disorders (n=268)			No back disorders (n=511)			RD_{adj}	RR_{adj}	(95% CI)	p
	n	(%)	[ASP]	n	(%)	[ASP]				
Any NCI										
NCI	240	(89.6)	[85.3]	227	(44.4)	[47.0]	22.8	2.07	(1.80, 2.39)	<0.001*
Number, mean (SD)†	2.8	(1.99)	[2.9]	1.5	(0.91)	[1.5]				
Number of NCI:										
none	28	(10.5)	[13.6]	284	(55.6)	[52.0]	-22.4	0.63	(0.52, 0.75)	<0.001*
one	56	(20.9)	[24.4]	155	(30.3)	[30.6]	7.0	1.27	(0.99, 1.62)	0.068
multimorbidity	184	(68.7)	[61.1]	72	(14.1)	[16.2]	15.4	2.12	(1.55, 2.88)	<0.001*
Non musculoskeletal NCI										
NCI	203	(75.8)	[66.0]	183	(35.8)	[38.3]	25.0	1.60	(1.39, 1.84)	<0.001*
Number, mean (SD)†	2.2	(1.75)	[1.9]	1.5	(0.80)	[1.1]				
Number of NCI:										
none	65	(24.3)	[33.0]	328	(64.2)	[60.8]	-24.5	0.58	(0.48, 0.71)	<0.001*
one	95	(35.5)	[30.3]	127	(24.9)	[25.5]	6.4	1.23	(0.97, 1.56)	0.083
multimorbidity	108	(40.3)	[35.7]	56	(11.0)	[12.7]	18.1	2.29	(1.70, 3.08)	0.001*
Particular NCI:										
Neck disorder	176	(65.7)	[63.4]	34	(6.7)	[7.8]	50.5	7.60	(5.36, 10.75)	<0.001*
Allergies	64	(23.9)	[26.0]	67	(13.1)	[12.6]	14.0	2.11	(1.51, 2.96)	<0.001*
Arthrosis	53	(19.8)	[21.5]	17	(3.3)	[3.6]	10.5	3.46	(1.99, 6.00)	<0.001*
Hypertension	115	(42.9)	[35.4]	92	(18.0)	[20.1]	10.3	1.46	(1.16, 1.84)	0.001*
Urinary incontinence	51	(19.0)	[16.5]	12	(2.4)	[2.5]	10.0	4.11	(2.23, 7.59)	<0.001*
Kidney problems	34	(12.7)	[13.3]	9	(1.8)	[2.1]	7.7	4.59	(2.10, 10.04)	<0.001*
CHD	35	(13.1)	[15.4]	11	(2.2)	[3.0]	6.7	3.39	(1.70, 6.73)	<0.001*
Depression	32	(11.9)	[13.9]	13	(2.5)	[2.8]	6.0	2.88	(1.48, 5.60)	0.002*
COPD	28	(10.5)	[13.4]	16	(3.1)	[4.3]	5.3	2.48	(1.31, 4.68)	0.007*
Diabetes mellitus	38	(14.2)	[13.7]	25	(4.9)	[5.5]	5.0	1.84	(1.10, 3.08)	0.023*
Myocardial infarction	18	(6.7)	[8.4]	3	(0.6)	[0.7]	5.0	5.85	(1.64, 20.77)	0.001*
CVI	22	(8.2)	[9.2]	7	(1.4)	[1.5]	3.7	2.95	(1.24, 7.02)	0.001*
Asthma	9	(3.4)	[7.1]	10	(2.0)	[2.5]	2.4	1.98	(0.72, 5.43)	0.237
Cirrhosis of the liver	5	(1.9)	[5.4]	3	(0.6)	[0.9]	2.3	3.17	(0.67, 15.11)	0.204

Data are presented as number (percentage) of participants if not stated otherwise; data are sorted in the order of absolute risk difference; ASP = prevalence direct age-standardized to the standard European population; RDadj = absolute risk difference adjusted for all confounders; RRadj = risk ratio adjusted for all confounders; ARD = risk difference adjusted for all confounders: age, sex, education, degree of urbanization, marital status, number of household members, work status, body mass index, smoking and alcohol consumption; p = statistical significance of differences between participants with and without chronic back disorder adjusted for all confounders using logistic regression, transformation to probabilities and delta-method standard errors; NCI = noncommunicable chronic illness; BMI = body mass index; COPD = chronic bronchitis, chronic obstructive pulmonary disease, emphysema; CVI = cerebrovascular insult, stroke (cerebral hemorrhage, cerebral thrombosis) or chronic consequences of stroke; CHD = coronary heart disease or angina pectoris; n.c. = not calculable; †number of any NCI only in the subpopulation of participants with at least one of the monitored chronic illnesses; *false discovery rate <5%

vs. 29%), and with good or very good self-perception of the general health (70% *vs*. 61%). They were comparable according to education, marital status, and number of household members. Excluded and remained participants differed in our primary outcome. Those who were excluded from the population with BD had multimorbidity in 11/20 (55.0%), and those who remained in 184/268 (68.7%) cases. In the population of participants without BD, those excluded had multimorbidity in 4/38 (10.5%) and the remained in 72/511 (14.1%) cases. These differences indicated that data on confounding variables were not missing at random and therefore should not be just excluded without further sensitivity analysis. The remaining sample that we used in the main analysis included 268 participants with BD and 511 without it. Median (IQR) age of the participants with BD was 60 (49-73) years and of those without BD 46 (30-60) years (Table 1). Samples from our target (BD) and control (non-BD) populations were different on almost all confounders (Table 1), which implied no serious errors in their measurements and correct selection.

Primary analysis

In the total sample of 837 subjects regardless of BP, the crude prevalence of multimorbidity was 32.4% (95% CI 29.3, 35.6), or 30.4% direct age-standardized to the European standard population. In the main analysis set of 779 participants, the prevalence of chronic multimorbidity was significantly higher in the participants with BD than in those without it (Table 2). Counting all NCIs from the EHIS questionnaire, participants with BD had more than two times higher relative risk of chronic multimorbidity than participants without BD after the adjustment for all confounders (RR_{adj}=2.12; 95% CI 1.55, 2.99; p<0.001; FDR <5%) (Table 2). Direct age-standardized to the European standard population, the prevalence of chronic multimorbidity was 61.1% in subjects with and 16.2% in subjects without BD. The prevalence of multimorbidity was significantly higher in the participants with BD, after adjustment for all covariates, even when counting only non-musculoskeletal NCIs (RRadj=2.29; 95% CI 1.70, 3.08; p=0.001; FDR <5%).

Secondary analysis

All NCIs except for asthma and cirrhosis of the liver were significantly more prevalent in the participants with BD than in those without BD (Table 2, Fig. 1). The most prevalent NCIs in the participants with BD were neck disorder, hypertension, allergies, arthrosis, and urinary incontinence. After adjustment for all confounders, the relative difference between BD and non-BD population was largest in neck disorders (RR=7.60; 95% CI 5.36, 10.75; p<0.001; FDR <5%), myocardial infarction (RR=5.85; 95% CI 1.64, 20.77; p=0.001; FDR <5%), kidney problems (RR=4.59; 95% CI 2.10, 10.04; p<0.001; FDR <5%), urinary incontinence (RR=4.11; 95% CI 2.23, 7.59; p<0.001; FDR <5%), arthrosis (RR=3.46; 95% CI 1.99, 6.00; p<0.001;

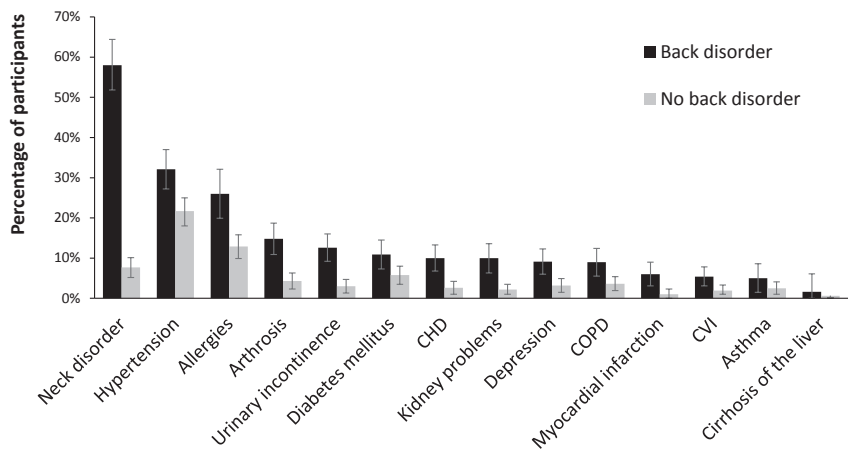

Fig. 1. Point prevalence of a self-reported chronic illnesses, direct age-standardized to the standard European population; error lines represent 95% confidence intervals; illnesses are sorted by the prevalence in the population with back disorders.

CHD = chronic heart disease; COPD = chronic obstructive pulmonary disease; CVI = cerebrovascular insult

Table 3. Association of chronic multimorbidity with different health outcomes in patients with back disorders (N=268)

	n	(%)	OR	(95% CI)	p
Moderately or severely limited activities					
Bivariable, unadjusted analysis					
no NCI	8	(29.6)	1		
one NCI	23	(44.2)	1.88	(0.70, 5.07)	0.210
multimorbidity (≥2 NCI)	121	(66.5)	4.71	(1.95, 11.38)	0.001*
Multivariable, adjusted analysis†					
no NCI	(38.8)	(20.2, 57.5)	1		
one NCI	(55.1)	(41.9, 68.4)	2.21	(0.74, 6.61)	0.155
multimorbidity (≥2 NCI)	(61.7)	(54.7, 68.7)	3.06	(1.11, 8.44)	0.031*
Moderate to severe chronic body pain					
Bivariable, unadjusted analysis					
no NCI	8	(28.6)	1		
one NCI	17	(30.4)	1.09	(0.40, 2.96)	0.866
multimorbidity (≥2 NCI)	107	(58.2)	3.47	(1.45, 8.30)	0.005*
Multivariable, adjusted analysis†					
no NCI	(31.3)	(13.3, 49.3)	1		
one NCI	(36.0)	(22.5, 49.5)	1.26	(0.43, 3.66)	0.675
multimorbidity (≥2 NCI)	(56.4)	(49.1, 63.7)	3.12	(1.17, 8.31)	0.023*
Moderate or severe interference of body pain with normal work					
Bivariable, unadjusted analysis					
no NCI	7	(25.0)	1		
one NCI	13	(23.6)	0.92	(0.32, 2.67)	0.891
multimorbidity (≥2 NCI)	104	(57.5)	4.05	(1.64, 10.01)	0.002*
Multivariable, adjusted analysis†					
no NCI	(29.3)	(11.2, 47.4)	1		
one NCI	(29.2)	(15.9, 42.5)	0.99	(0.32, 3.05)	0.992
multimorbidity (≥2 NCI)	(55.1)	(47.6, 62.5)	3.21	(1.18, 8.74)	0.022*
Average, bad or very bad self-perceived general health					
Bivariable, unadjusted analysis					
no NCI	12	(42.9)	1		
one NCI	24	(42.9)	1.00	(0.40, 2.50)	>0.999
multimorbidity (≥2 NCI)	157	(85.3)	7.75	(3.31, 18.19)	<0.001*
Multivariable, adjusted analysis†					
no NCI	(55.9)	(37.6, 74.1)	1		
one NCI	(52.5)	(39.2, 65.9)	0.84	(0.28, 2.56)	0.764
multimorbidity (≥2 NCI)	(81.1)	(75.2, 87.0)	4.64	(1.62, 13.33)	0.004*

In bivariable, unadjusted analysis data are presented as number (percentage) or participants with targeted outcome if not stated otherwise; in multivariable, adjusted analysis data are presented as estimated, adjusted percentages of the targeted outcome and 95% confidence intervals if not stated otherwise; OR = odds ratio; CI = confidence interval; p = statistical significance calculated using binary logistic regression; NCI = noncommunicable chronic illness; †analysis was adjusted for age, sex, education, degree of urbanization, marital status, number of household members, work status, body mass index, smoking and alcohol consumption; *false discovery rate <5%

FDR <5%), and coronary heart disease or angina pectoris (RR=3.39; 95% CI 1.70, 6.73; p<0.001; FDR <5%). The most frequent multimorbidity in the participants with BD were neck disorder and hypertension (8.2%), neck disorder and allergies (2.6%), neck disorder and arthrosis (2.6%), neck disorder, arthrosis, and hypertension (2.2%), neck disorder and depression (1.5%), and neck disorder and urinary incontinence (1.5%). In subjects with no BD, the most frequent multimorbidity were hypertension and diabetes mellitus (1.4%), and neck disorder and hypertension (1.2%).

Tertiary, exploratory analysis

In the population with BD, all four self-reported outcomes were unfavorably associated with multimorbidity (Table 3). Compared to the participants with no comorbid conditions, after adjustment for all confounders, participants with multimorbidity had three times higher odds for moderately or severely limited activities of daily life (OR=3.06; 95% CI 1.11, 8.44; p=0.031; FDR <5%), moderate to severe chronic body pain (OR=3.12; 95% CI 1.17, 8.31; p=0.023; FDR <5%), moderate or severe interference of body pain with normal work (OR=3.21; 95% CI 1.18, 8.74), and more than four times higher odds for the average, bad or very bad self-perceived general heath as opposed to good or very good self-perception of general health (OR=4.64; 95% CI 1.62, 13.33; p=0.004; FDR <5%). In none of these four outcomes, the existence of only one comorbidity was associated with significantly worse outcomes compared to the population with no comorbidities.

Sensitivity analysis

In the sensitivity analysis with the imputed missing data for body mass index and consumption of alcohol, we used samples of 284 participants with BD and 545 participants without BD. The imputed data represented the 'worst-case' scenario, namely, the values that promoted the null hypothesis of no difference between BD and non-BD in the prevalence of multimorbidity. In this data set, the crude prevalence of multimorbidity was 193/284 (68.0%) in the participants with BD and 76/545 (13.9%) in the participants without BD. In both populations, the unadjusted difference to the main analysis results was within 1%. After adjustment for all confounders, the relative risk of any multimorbidity in the participants with BD was RR_{adj}=3.26; 95% CI 2.61, 4.06; p<0.001; FDR <5%, and for non-musculoskeletal multimorbidity RR_{adj}=2.39; 95% CI 1.79, 3.19; p<0.001; FDR <5%. In both cases, the relative risk of multimorbidity was larger in the sensitivity analysis data set than in the original one. Therefore, our test of the hypothesis was robust to the missing data on the two important confounders.

Discussion

We confirmed the hypothesis that the population with self-reported BD have a higher prevalence of chronic comorbidities than the population without self-reported BD. All NCIs except for asthma and cirrhosis of the liver were significantly more prevalent in the participants with BD than in those without BD. In the population with BD, the participants with multimorbidity had three to four times higher odds for unfavorable self-reported health outcomes than the participants with no comorbid conditions, whereas the existence of only one comorbidity was not significantly associated with worse outcomes compared to the population with no comorbidities.

Our finding on the prevalence of multimorbidity in the total sample regardless of BD (direct age-standardized to the European standard population, 30.4%) was in line with many other studies[13,17,18], but different from many other as well[19-21]. The estimated prevalence of multimorbidity varies with regards to the included conditions, definition of multimorbidity (≥2 and ≥3 comorbid conditions, being the most often ones), target population and particularly target age range, type of data source, methods of verification of diagnosis, and stratification or standardization for sex and age[11,22]. Surprisingly, the age and sex standardization to some standard population is a relatively rare practice. A systematic review of studies on multimorbidity in primary care published between 1961 and 2013[23], and the scoping review of literature on multimorbidity up to March 8, 2020[22] revealed large variation in the prevalence of multimorbidity (defined as in our study as ≥2 chronic conditions) ranging from <15% to >95%. The two reviews identified studies including from 5 to 335 conditions over more than 20 disease categories. Not surprisingly, the larger the number of conditions analyzed, the higher is the prevalence estimate of multimorbidity. If BD has such a high potential for multimorbidity, as our study indicated (direct age-standardized to the European standard population, 61.1%), its effective treatment may probably have additional beneficial consequences. Improvement of mobility and reduction of pain interference with everyday activities may improve the prevention and probably even

treatment of different other chronic conditions[13]. This way, the treatment of BD may synergistically lower the overall multimorbidity. Based on this cross-sectional study, we could not test any causal hypothesis, but if there is a reverse or bi-directional causation between BD and, for example, depression or diabetes, treatment of BD should be considered within a broader scope of treatment planning for these conditions. Conversely, it is possible that comorbid and poorly controlled BD reduces the effects of primary treatment of these other conditions. Our results on the association of multimorbidity in BD population with the less favorable health outcomes were in line with the results of other studies that prospectively found the association of multimorbidity with an increased risk of disability[24] or increased mortality[25].

A specific and very difficult problem with such a high level of multimorbidity in BD patients is the fact that multiple conditions are regularly considered as non-inclusion and exclusion criteria in randomized controlled trials (RCT) of new treatments and therapies[26]. This is most often done intentionally to improve the interval validity of the study, but one of the consequences is lower external validity, or limited generalizability to the population with multimorbidity. These two premises, i.e., a large prevalence of multimorbidity in the population with BD and only a single chronic condition allowed in RCT target population might result in a relatively lower level of evidence for the specific treatment targeted at BD in comparison to the level of evidence for the treatment of conditions with a lower potential for multimorbidity such as multiple sclerosis, breast or prostate cancer[13]. Whether this is indeed the case, should be tested by future studies. Furthermore, even when RCT includes the population with multimorbidity, it is not clear how the studied effects should be analyzed and reported for specific combinations of conditions. Simple post-hoc analysis within each of the comorbidity combinations is most often not a plausible solution due to the insufficient power[26]. As our analysis has shown, the fuel for the problem is provided by the fact that in the general 18+ population living in private households, as much as one-third may suffer from multiple medical conditions. The prevalence of multimorbidity is probably even higher in many subpopulations diagnosed with a particular chronic condition. What has been said for RCT aimed at new treatment effects and safety, may partially be true for diagnostic, prognostic, and etiologic studies as well. Although the described weaknesses of RCT aimed at the efficacy and safety of a new treatment are probably less frequent in diagnostic, prognostic, or etiologic research, and although the immediate clinical consequences are certainly smaller in these types of studies, the theoretical, scientific, and long-term clinical consequences can be worse. The problem should be taken seriously. Traditionally, multimorbidity was analyzed by counting the conditions[27], multiplying them into the composite indices such as Charlson Comorbidity Index[28], Elixhauser Comorbidity Index[29], Index of Coexistent Diseases[30], Chronic Disease Score[31], John Hopkins' Aggregated Diagnosis Groups, and similar, or by analysis of condition dyads, triads, tetrads[32], when usually the size of the sample would not allow continuation to the more complex combinations. However, even when such an analysis is possible, for example, on samples from a huge insurance databases, medical electronic documentation or similar sources, analyzing each individual combination actually hides the interactions of conditions within multimorbidity[33] and again fails to note the specific effects of different condition combinations. In 2017, Larsen *et al*. proposed a solution, i.e., analysis of specific comorbidity patterns. It is certainly improvement over the traditional approach, but this concept also contains an error and should be refined. Phenotypes or clusters or latent classes/profiles or latent dimensions/factors/principal components or whatever the name of these constructs is or may be, the proposal by Larsen *et al*. ignores the underlying associative mechanisms of multimorbidity, as we described them in the introduction of this manuscript, including common etiologic factors or pathogenetic mechanisms, mutual causation, common risk factors, or simply chance due to the high prevalence of any of the included conditions[33]. Thus, the logical first next step in advancing their proposal is to introduce the associative mechanism described as a covariate in latent class analysis (or some other comparable technique) in multimorbidity profile analysis.

Strengths and limitations of the study

The main strength of our analysis was that it was performed on the sample from the general and not from the hospitalized population or the population examined in a primary care practice. Therefore, our results were not subject to Berkson's or admission rate bias. The main limitation of our study was that our primary outcome was based on the self-reported chronic medical conditions. Therefore, we included only the

detected and diagnosed conditions, and only conditions that participants were able to recall and report. The bias induced by differences in the detection/diagnosis and recall probably was larger in the conditions with less severe symptoms such as hypertension or diabetes than in the conditions with more severe symptoms such as myocardial infarction, stroke, urinary incontinence or COPD. While it is not clear what the magnitude of the bias induced this way is, its direction is probably against the null hypothesis because the participants with BD have better chances to detect a medical condition due to their more frequent use of healthcare services than participants without any chronic condition. As far as this limitation is concerned, the difference in the prevalence of multimorbidity between participants with and without BD is probably somewhat overestimated. The ultimate solution to this problem would be a study with medical examination done precisely for the purposes of the study, but such a design is hardly plausible. We did not have data on the severity or duration of chronic illnesses that were included into our primary outcome, but we cannot speculate on the direction or magnitude of this limitation. Our exposure was defined broadly, in accordance with the EHIS questionnaire. It probably includes mostly nonspecific low-back pain due to its high prevalence but to an unknown extent also various other back and spine disorders. One of the important limitations of our study may be seen as a strength as well. Namely, we analyzed conditions that were used and described in the EHIS questionnaire. While this list is very far from being comprehensive, its advantage is that it was used in a comparable way in 28 EU Member States and in Norway, Iceland and Turkey, in 2013-2015, and that it will be continuously used in the future.

Conclusion

The population suffering from BD has a higher prevalence of chronic multimorbidity than the population without BD and multimorbidity is associated with unfavorable health outcomes.

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Sažetak

KRONIČNI MULTIMORBIDITET KOD KRIŽOBOLJE ILI DRUGIH KRONIČNIH POREMEĆAJA U LEĐIMA U REPUBLICI HRVATSKOJ

J. Marunica Karšaj, T. Benjak, L. Stojanovič, F. Grubišić, D. Balen i *S. Grazio*

Cilj je bio procijeniti prevalenciju kroničnog multimorbiditeta u bolesnika s križoboljom ili drugim kroničnim poremećajima u leđima (KPL). Analizirali smo podatke populacijske presječne Europske zdravstvene ankete (EHIS) koju je u Republici Hrvatskoj tijekom 2014. i 2015. godine proveo Hrvatski zavod za javno zdravstvo. Ishod je bila trenutna prevalencija kroničnog multimorbiditeta, definiranog prisutnošću s dvije ili više kroničnih bolesti od ukupno četrnaest sadržanih u EHIS upitniku, nakon prilagodbe za deset sociodemografskih, antropometrijskih i poremećujućih varijabla povezanih sa životnim stilom. Između četrnaest ciljanih bolesti bile su obuhvaćene astma, alergije, hipertenzija, urinarna inkontinencija, bubrežne bolesti, koronarna bolest ili angina pectoris, vratobolja, artroza, kronična opstruktivna plućna bolest, moždani udar, šećerna bolest, srčani udar, depresija i zajednička kategorija „ostalo". Analizirali smo podatke o 268 sudionika s KPL i 511 bez njih. Sudionici s KPL imali su značajno veći relativni rizik za bilo koji kronični multimorbiditet (RRadj = 2,12; 95% CI 1,55; 2,99; p<0,001) kao i za kronični ne-muskuloskeletni multimobiditet (RRadj = 2,29; 95% CI 1,70, 3,08; p=0,001) od sudionika bez KPL. Svi kronični komorbiditeti osim astme i ciroze jetre, bili su značajno zastupljeniji u sudionika s KPL nego u sudionika bez KPL. U populaciji s KPL, sudionici s multimorbiditetom imali su tri do četiri puta veće izglede za samoprijavljene nepovoljne zdravstvene ishode, nego sudionici bez komorbidnih stanja, dok postojanje samo jednog komorbiditeta nije bilo značajno povezano s lošijim ishodima u usporedbi s populacijom bez kroničnih komorbiditeta.

Zaključno, populacija s KPL ima veću prevalenciju kroničnog multimorbiditeta nego populacija bez KPL i taj je multimorbiditet povezan s nepovoljnim zdravstvenim ishodima.

Ključne riječi: *Bol u donjem dijelu leđa; Europska zdravstvena anketa; Komorbiditet; Multimorbiditet*