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Suggested citation referring to the original publication:
Pain reports 9 (2017)
DOI http://dx.doi.org/10.1097/PR9.0000000000000623

Musculoskeletal
Research Paper

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PAIN REPORTS®

Development of a risk stratification and prevention index for stratified care in chronic low back pain. Focus: yellow flags (MiSpEx network)

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Abstract

Introduction: Chronic low back pain (LBP) is a major cause of disability; early diagnosis and stratification of care remain challenges.
Objectives: This article describes the development of a screening tool for the 1-year prognosis of patients with high chronic LBP risk (risk stratification index) and for treatment allocation according to treatment-modifiable yellow flag indicators (risk prevention indices, RPI-S).
Methods: Screening tools were derived from a multicentre longitudinal study (n = 1071, age >18, intermittent LBP). The greatest prognostic predictors of 4 flag domains ("pain," "distress," "social-environment," "medical care-environment") were determined using least absolute shrinkage and selection operator regression analysis. Internal validity and prognosis error were evaluated after 1-year follow-up. Receiver operating characteristic curves for discrimination (area under the curve) and cutoff values were determined.
Results: The risk stratification index identified persons with increased risk of chronic LBP and accurately estimated expected pain intensity and disability on the Pain Grade Questionnaire (0–100 points) up to 1 year later with an average prognosis error of 15 points. In addition, 3-risk classes were discerned with an accuracy of area under the curve = 0.74 (95% confidence interval 0.63–0.85). The RPI-S also distinguished persons with potentially modifiable prognostic indicators from 4 flag domains and stratified allocation to biopsychosocial treatments accordingly.
Conclusion: The screening tools, developed in compliance with the PROGRESS and TRIPOD statements, revealed good validation and prognostic strength. These tools improve on existing screening tools because of their utility for secondary preventions, incorporation of exercise effect modifiers, exact pain estimations, and personalized allocation to multimodal treatments.

Keywords: Back pain prognosis, Back pain diagnosis, Pain screening, PROGRESS/TRIPOD, Prediction of disability/intensity, Yellow flags, Exercise

1. Introduction

The lifetime prevalence of nonspecific chronic low back pain (LBP) in the general population is considerably high, 84%.[1] Many back pain episodes last only days and resolve spontaneously, but 44% to 78% of patients report renewed complaints within 1 year.[1] This results in higher health care costs,[10] which might have been preventable with early and individualized treatment strategies.

Cochrane Collaboration reviews show treatments such as exercise, physical therapy, and cognitive behavioral techniques are more successful in reducing pain and disability than usual

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PR9 00 (2017) e623

http://dx.doi.org/10.1097/PR9.0000000000000623

care.[13,18,19,21] Multimodal treatments including psychosocial interventions are also more efficient than unimodal approaches[25] because they address such factors as distress, subjective pain experience, social environment, and medical care. These factors have been categorized as yellow, orange, black, or blue flags according to their estimated impact on prognosis[32,56] and play a critical role in the chronification of LBP.[4,6,32,38,58] Furthermore, they have been found to moderate treatment effects.[47] However, because of their interindividual variability, these factors are difficult to integrate into routine clinical practice. Therefore, screening of patients' psychosocial risk factors and stratified allocation to treatment are required for evidence-based LBP guidelines.[53]

Existing screening tools in primary care either (1) classify patients into existing risk groups (eg, HKF-R 10[37] and INTERMED[49]) or (2) predict the risk of chronic pain or disability development (eg, RISC-BP,[16] PICKUP,[51,52] and ÖMPSQ[3]). The Keele STarT Back Decision Tool[22] is the only tool predicting risk, while designating patients to subgroups (high, medium, and low risk) for stratified care pathways.[26] It has shown noteworthy results in primary care interventions[14,23] but focuses solely on (1) yellow flag factors, (2) the risk of future chronicity (stratification based on group values), and (3) validation in primary care physical therapy settings.[32] Interventions for secondary prevention (eg, in persons with recurrent pain) are still lacking. Although especially exercise seems a promising treatment for this target group, prognostic flag factors may be modifying exercise treatment effects. These interactions were shown for pain,[9,12,50] depression,[35] distress,[33,59] and fear avoidance,[35] and should be respected in screening tool development.

Other criticisms of existing instruments include their accuracy (eg, sensitivity and specificity) and practical utility (eg, length),[26,32,56] which are limited by outdated actuarial and clinical methods used to develop them. Newer statistical methods are more applicable to high-dimensional data sets and allow combinations of actuarial and clinical methods,[30,38,51] assisting practitioners to predict future pain values and allocate individuals to stratified treatment pathways.

The study objectives were to develop 2 screening tools using modern statistical methods suitable for secondary prevention, whereby: (1) 1 tool should allow the prediction of the chronic LBP risk at 1-year follow-up (risk stratification index, RSI) and the other tool, a detection of modifiable prognostic indicators in 4 risk factor domains (risk prevention indices, RPI-S); further (2) the prognosis errors (internal validation) of the tools and (3) their optimal classification thresholds should be evaluated.

2. Material and methods

2.1. Development of risk stratification and prevention index

Objectives were pursued through a longitudinal multicenter study conducted by the German Network for Medicine in Spine Exercise (MiSpEx). The RSI and RPI-S were developed, a priori, with the Prognosis Research Strategy framework[24,42,48] and guidelines from the Transparent Reporting of a multivariable prediction model for Individual Prognosis and Diagnosis.[8] Risk stratification index and the risk prevention index are subsections of a planned final screening, which will also include biomechanical and functional parameters.

2.2. Design and procedure

Risk stratification index and RPI-S development was based on data collected over a 2-year multicentre longitudinal study (without treatment) conducted at 4 sites across Germany. Participants were invited to participate in 7 measurements: baseline (M1), 1-month (M2), 3-month (M3), 6-month (M4), 12-month (M5), 18-month (M6), and 24-month follow-ups (M7). At each measurement, trained study nurses administered a comprehensive questionnaire consisting of predictor and outcome variables. Furthermore, a physician or a physiotherapist performed a clinical examination with measurements of anthropometric and orthopedic data. For this reason, participants were asked to visit the same clinic at every measurement to receive the same assessment (**Fig. 1**).

2.3. Participants

Persons between the ages of 18 and 65 years were considered eligible if they fulfilled the following inclusion criteria: at least 1 episode (≥4 days) of nonspecific LBP in the past 12 months; able to understand the meaning of the study; and able to answer a questionnaire without help. Exclusion criteria were pregnancy, acute pain in the past 7 days, inability to stand upright, inability to share information regarding sick leave, or signs of red flag factors (inflammatory, traumatic, or systemic processes). Participants were referred to the study before their first consultation with a health care provider. All participants gave informed consent after receiving both written and oral information about the project.

2.4. Instruments

The main outcome (chronic) pain status was assessed using subscales from the Chronic Pain Grade questionnaire (CPG[55]), which measures subjective pain intensity (characteristic pain intensity [CPI]: 0 = "no pain" to 100 = "the worst pain imaginable") and pain disability (DISS: 0 = "no disability" to 100 = "I was incapable of doing anything") during the past 3 months. The predictors were modifiable psychosocial risk factors for pain recommended from the flag catalogue,[32,38,56] as well as protective factors (eg, social environment), which can also be of relevance within exercise treatment settings. The final predictor set depicts 4 domains: distress, pain experience, social environment, and medical care environment. The assessment uses standardized, psychometrically sound and validated German questionnaires: (1) Pain experience: anxiety and depression (HADS-D, Hospital Anxiety and Depression Scale—German version[20]), avoidance–endurance behavior (AEQ-PPS, Avoidance–Endurance-Questionnaire, Pain Persistence Scale[17]), self-efficacy (I-SEE, Inventory for the Measurement of Self-Efficacy and Externality[28]), and pain-related cognition (FABQ-D[40]). (2) Stress: chronic stress (TICS, Trier Inventory for Chronic Stress[44]), critical life events, perceived stress (PSS, Perceived Stress Scale[7]), vital exhaustion (VE, Maastricht Vital Exhaustion Questionnaire), and self-efficacy (I-SEE). (3) Social environment: social support (BSSS[45,46]), relationships (RQ-2, Relationship Questionnaire-2[2]), sociodemography (CASMIN Index[29]), lifestyle (alcohol, smoking, medication, sleep and health status), and physical activity (regular exercise per week). (4) Medical care environment: health insurance, urbanization level, distance to hospitals, and preventive medical check-ups. To reduce time burden during assessment, questionnaires were rotated in short form (**Fig. 1**).

2.5. Statistics and data analysis

After descriptive analysis using IBM SPSS Statistics 23.0, development and validation of the RSI and RPI-S were

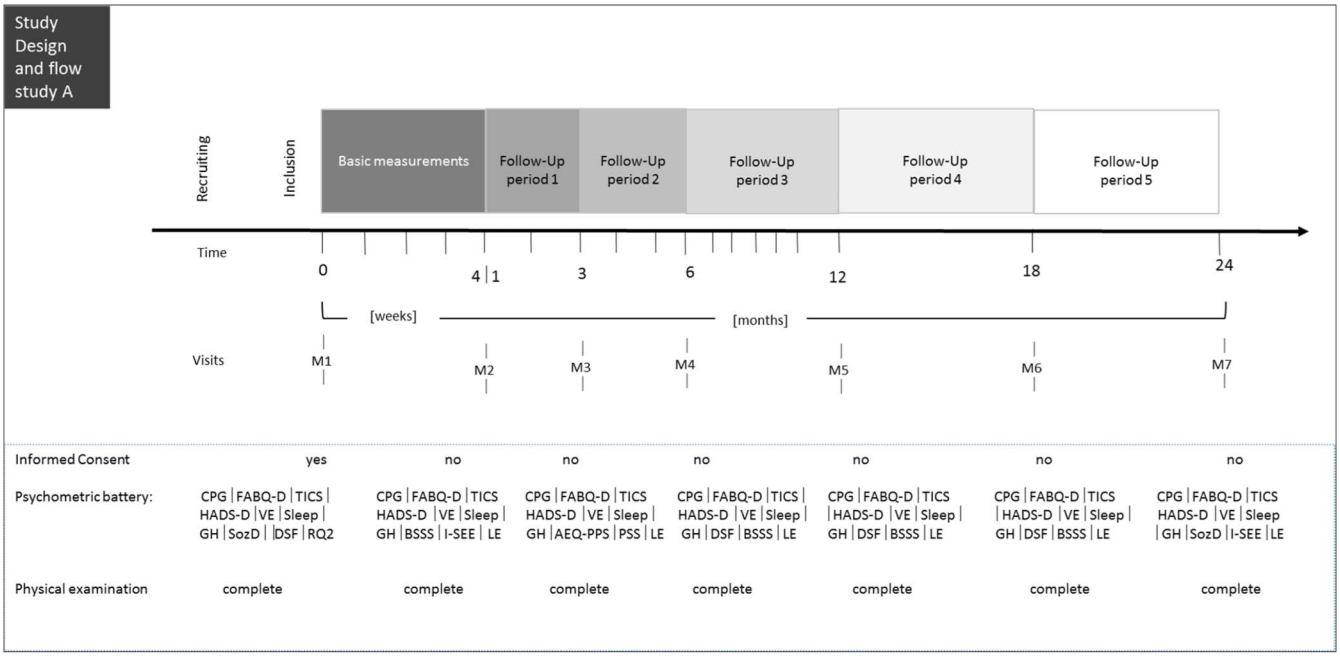

Figure 1. Psychometric battery (content and rotation).

performed in 3 steps with the R-package penalized[15]: (1) least absolute shrinkage and selection operator (LASSO) regression analysis to select predictors with high potential; (2) root-mean-squared error (RMSE) analysis to calculate RSI and RPI-S error between predicted and observed values; and (3) receiver operating characteristic (ROC) curve analysis to determine discriminant validity and establish RSI and RPI-S cutoff values. Two-sided tests were used with significance level set to $p = 0.05$. The screening tools were designed for a 1-year follow-up time, which is different from other tools focusing on shorter follow-ups (3–6 months). Psychosocial risk increases with the duration of LBP (>1 month, prevalence = 5%; >3 months, prevalence = 35%), meaning the positive predictive value of the test increases with prevalence.[27] Furthermore, persons affected by intermittent pain show high variability in intensity during episodes and pain-free phases, up to months and years later.[54] If the aim is secondary prevention, a longer-term prognosis would then seem more appropriate than those constructed for primary and clinical care management.

2.5.1. Step 1: selection and development of risk stratification index and risk prevention index

High-potential predictors from the LASSO regression analysis (10-fold cross-validation) were selected. This method was chosen because it enables calculation of more predictors within a small sample, while avoiding an over fitting of the data. After LASSO calculation (and refitting of biased coefficients with linear regression models), the unbiased coefficients served as weights for the calculation of RSI and RPI-S values. Finally, a subgroup, n = 588 participants, having no missing values in predictor and outcome variables (each item) at baseline and 1-year follow-up were available for LASSO calculation.

The RSI was derived through 1 LASSO calculation model containing predictors from all flag domains (full model; number

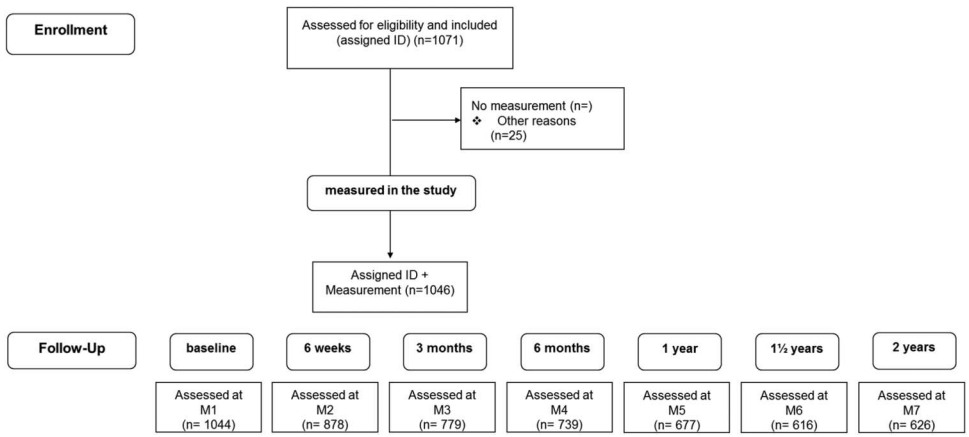

Figure 2. Enrollment of participants measured by psychometric battery within the study.

Table 1

Characteristics of participants in the study (development sample).

Baseline characteristics	Baseline (total n = 1046); development RSI, RPI-S	1-y follow-up (n = 677); validation RSI, RPI-S
Age, y, mean ± SD	40.4 ± 13.4	39.8 ± 13.4
Sex, female, n (%)	596 (57)	—
Smoking, yes, n (%)	90 (9)	65 (10)
Alcohol, yes, n (%)	610 (58)	481 (71)
Medication (M), yes, n (%)	330 (31)	223 (33)
Pain medication (PM), yes, n (%)	187 (21)	110 (16)
Outcome criteria, CPI and DISS		
CPG CPI characteristic pain intensity past 3 mo, mean ± SD	28.9 ± 19.1	22.7 ± 18.3
CPG DISS subjective pain disability past 3 mo, mean ± SD	16.2 ± 19.2	10.1 ± 15.6
Pain experience M_P		
HADS-D anxiety, mean ± SD	6.3 ± 3.5	6.0 ± 3.6
HADS-D depression, mean ± SD	3.7 ± 3.1	3.6 ± 3.4
FABQ-D, work prognosis, mean ± SD	1.4 ± 3.5	1.2 ± 3.2
FABQ-D, physical activity, mean ± SD	11.4 ± 6.6	9.5 ± 6.8
FABQ-D work as cause, mean ± SD	7.5 ± 7.0	6.2 ± 6.5
AEQ pain persistence scale, mean ± SD	3.3 ± 1.2	3.3 ± 1.2
I-SEE general self-concept on personal skills and abilities, mean ± SD	33.8 ± 5.3	34.4 ± 5.2
I-SEE internal attribution in general control beliefs, mean ± SD	34.1 ± 4.3	34.1 ± 5.2
I-SEE socially caused externality, mean ± SD	24.8 ± 4.9	24.2 ± 5.0
I-SEE fatalistic externality, mean ± SD	22.8 ± 5.1	22.1 ± 3.6
distress M_S		
VE, mean ± SD	7.2 ± 4.9	6.6 ± 5.3
TICS work overload, mean ± SD	13.5 ± 6.2	12.8 ± 6.2
TICS social overload, mean ± SD	8.8 ± 5.0	9.1 ± 4.8
TICS pressure to perform, mean ± SD	15.5 ± 6.5	16.0 ± 6.9
TICS work discontent, mean ± SD	9.4 ± 5.1	9.2 ± 5.1
TICS excessive demands at work, mean ± SD	5.5 ± 3.7	5.3 ± 3.7
TICS lack of social recognition, mean ± SD	4.8 ± 3.3	4.9 ± 3.1
TICS social tensions, mean ± SD	5.8 ± 3.7	5.7 ± 3.8
TICS social isolation, mean ± SD	6.0 ± 4.6	5.7 ± 4.6
TICS chronic worrying, mean ± SD	5.7 ± 3.4	5.0 ± 3.5
PSS, mean ± SD	5.8 ± 2.8	5.7 ± 2.8
Critical life events, yes, n (%)	37 (3.5)	43 (4)
Social environment M_{SE}		
Days off work in past 3 mo, mean ± SD	1.3 ± 6.6	0.3 ± 2.2
BSSS social support perceived, mean ± SD	3.6 ± 0.5	3.7 ± 0.5
BSSS social support received, mean ± SD	3.2 ± 0.5	3.3 ± 0.5
RQ-2 others, mean ± SD	1.3 ± 3.7	—
RQ-2 self, mean ± SD	3.9 ± 4.1	—
College degree or higher education, n (%)	757 (73)	—
Medical care context M_{MC}		
Health insurance, public, n (%)	794 (76)	—
Health care providers, distance to specialist, km, mean ± SD	7.3 ± 8.4	—
Medical care level (urbanisation) >100,000 inhabitants, n (%)	658 (63)	—

RPI-S, risk prevention index; RSI, risk stratification index.

of predictors [**P**] = 208). As control variables, baseline pain, age, sex, and study center were included unpenalized. The RPI-S was derived within 4 LASSO calculation models (partial models) for each flag domain (pain experience M_P, **P** = 88; distress M_S, **P** = 116; social environment/life context M_{SE}, **P** = 41; and medical care environment M_{MC}, **P** = 31). Self-efficacy is known to play a role both in stress management and pain experience and was therefore incorporated in both calculations. For the RPI-S, baseline pain, age, sex, study center, physical activity, and lifestyle (eg, smoking, alcohol, sleep, and medications) were included as control variables (unpenalized) in each model. Although the RPI-S should be appropriate for stratified exercise treatment allocation, the physical activity status before as well as its interaction with flag factors during the intervention are respected as treatment effect modifiers.

2.5.2. Step 2: internal validity and prognosis error of risk stratification index and risk prevention index

Although the instruments allow for accurate future estimation of CPG-CPI and CPG-DISS, it is necessary to quantify the prognosis error between predicted and observed values using the mean squared error, ie, its RMSE.[43] This internal validity check was performed for a 1-year prognosis (baseline to 1-year follow-up) using the subset of n = 588.

2.5.3. Step 3: discriminant validity

After construction of the basic RSI and RPI-S, each tool was tested for discriminant validity using ROC curves[36] by calculating the area under the curve (AUC) of overall screening tool cutoff values. Optimal classification thresholds of the RPI-S were essential for treatment allocation, but not necessary for the RSI,

which allowed an accurate CPG estimation while still respecting all risk factor domains. These analyses were derived from the same data set as Step 2. Optimal cutoffs by means of ROC analysis require previous sorting of subjects according to a specific criterion, thus these analyses were geared to risk subgroups based on both CPG scales (CPI and DISS).[55] Finally, optimal cutoffs for both RSI and RPI-S were determined with the Youden's index.[60] In line with Metz,[34] a strength of discrimination between 0.7 and 0.8 was classified as acceptable discrimination, from 0.8 to 0.9 as excellent, and more than 0.9 as outstanding.

3. Results

3.1. Sample

At baseline, n = 1071 (age: mean = 40.4 years, SD = 13.4 years, *f* = 57%) participants were enrolled over a period of 18 months; n = 25 persons declined participation (participation rate: 97%). Of those who participated at baseline, n = 677 (65%) completed questionnaires at 1-year follow-up (**Figure 2**). There were no differences between participants who completed and those who did not. Reported reasons for dropout were, eg, upcoming pregnancy, illness, or relocation (sample characteristics; **Table 1**). Instrument development was derived from a subset of n = 588 subjects with no missing data at baseline and follow-up.

3.2. Step 1: selection and development of risk stratification index and risk prevention index

3.2.1. Risk stratification index (full model)

Least absolute shrinkage and selection operator selection reduced the number of predictors from 205 to 17 for pain intensity and from 205 to 8 for pain disability. Thus, care providers would need 17 predictors for a 1-year prognosis of expected pain intensity and 8 predictors for expected pain disability. The screening tool contains questions concerning pain at baseline, pain endurance, sleep problems, unhappiness, chronic worry, misfortune, work dissatisfaction, social support, social status, and health care–related topics (eg, pharmaceutical and physical therapy). **Figure 3** shows the immense reduction of predictors achieved by applying LASSO. The remaining coefficients from the CPI and DISS predictions are listed in **Table 2**.

3.2.2. Risk prevention index (partial models)

To summarize the different RPI-S domains, a minimum of 3 up to a maximum of 16 predictors would allow health care providers to individualized treatment allocation, while respecting the heterogeneity of their patients. The selected predictors partially overlap with RSI predictors and therefore refer to similar items. In detail, 12 CPI predictors and 6 DISS predictors were selected for the domain pain experience (RPI-S_P). Ten CPI predictors and 9 DISS predictors were selected for the domain distress (RPI-S_S). Fourteen CPI predictors and 16 DISS predictors were selected for the domain social environment (RPI-S_{SE}). Seven CPI predictors and 3 DISS predictors were selected for the domain medical care environment (RPI-S_{MC}). In all models, baseline pain values showed strong influence.

3.3. Step 2: internal validity and prognosis error of risk stratification index and risk prevention index

3.3.1. Risk stratification index

The validity check of the RSI model for pain intensity resulted in a prognosis error (RMSE) of 16.87. The model for pain disability showed an all-observation RMSE = 15.45. This means that a 1-year prognosis of estimated disability from pain value can vary per patient an average of 15 points on the 0- to 100-point CPG scales.

3.3.2. Risk prevention index

The 4 partial models had a prediction validity for pain intensity ranging from RMSE = 15.44 to 17.05, with similar results for RSI pain intensity prediction. The RMSE for pain disability was found to be between 13.02 and 16.20 (see all values in **Table 3**).

3.4. Step 3: discriminant validity

The evaluation of each screening tools' discriminant validity extracted from the development sample is presented in **Tables 4 and 5**. In all approaches, the discriminant power decreased with increasing severity of chronic pain. This resulted in small sample sizes for patients with high pain intensity and disability. **Tables 6 and 7** contain sensitivity, specificity, and negative as well as positive likelihood ratios (LRs) obtained for the RSI and the 4 RPI-S based on pain intensity and pain disability (baseline to 1-year follow-up).

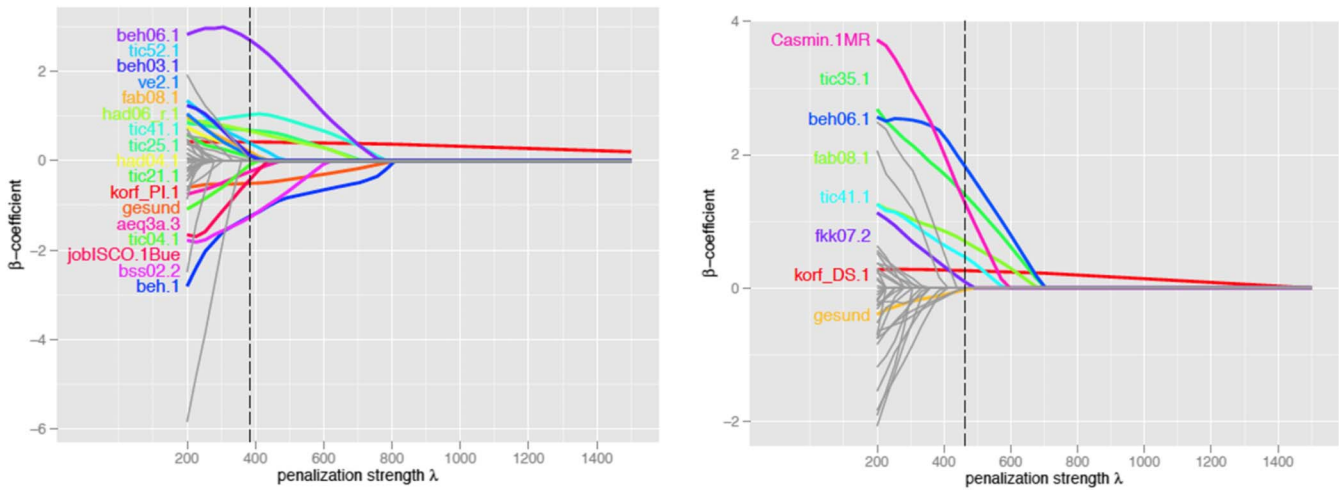

Figure 3. Least absolute shrinkage and selection operator selection graph.

Table 2

Selected predictors for the RSI (full LASSO model) and the RPI-S on the 4 yellow flag domains—pain experience, distress, social environment, and medical care context (partial LASSO models).

Outcome	M_F full model (RSI)		M_P pain experience (RPI-S_P)		M_S distress (RPI-S_S)		M_{SE} social environment (RPI-S_{SE})		M_{MC} medical care environment (RPI-S_{MC})	
	CPI	DISS	CPI	DISS	CPI	DISS	CPI	DISS	CPI	DISS
Coefficients	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*
Intercept	31.681/11.360	−6.494/6.191	12.101/5.712	−4.082/4.785	6.400/4.758	6.792/9.529	30.193/7.848	19.545/11.556	13.252/4.566	15.377/8.265
Baseline CPI/DISS	0.426/0.052/**0.000**	0.323/0.061/**0.000**	0.469/0.044/**0.000**	0.228/0.045/**0.000**	0.483/0.041/**0.000**	0.248/0.041/**0.000**	0.523/0.042/**0.000**	0.334/0.044/**0.000**	0.477/0.044/**0.000**	0.344/0.046/**0.000**
Sex	−2.716/1.919/0.524	0.041/1.800/0.738	−1.327/1.453/0.519	−0.391/1.439/0.811	1.445/1.448/0.495	0.889/1.379/0.876	−0.771/1.614/0.447	−0.571/1.679/0.703	−0.231/1.456/0.817	−1.297/1.467/0.341
Age	0.015/0.80/0.191	0.099/0.079/0.012	0.055/0.060/0.216	0.120/0.059/0.005	0.101/0.060/0.018	0.198/0.071/0.000	0.078/0.073/0.138	0.137/0.081/0.029	0.020/0.062/0.247	0.146/0.074/0.015
Center B	−3.668/3.353/0.367	−1.380/3.422/0.297	−2.453/2.297/0.311	−1.294/2.232/0.363	−4.410/2.354/0.112	−3.227/2.247/0.109	−2.742/2.596/0.292	−1.693/2.705/0.364	−3.951/2.500/0.124	−3.117/2.537/0.207
Center H	1.925/2.452/0.300	0.664/2.582/0.144	1.096/2.099/0.325	1.776/2.093/0.202	1.119/2.071/0.224	2.655/1.986/0.148	−0.004/2.078/0.908	−0.241/2.172/0.922	−0.170/2.070/0.698	1.077/2.086/0.527
Center P	2.066/2.078/0.191	0.188/2.204/0.778	0.245/1.723/0.520	0.011/1.722/0.934	0.437/1.716/0.644	0.280/1.645/0.900	1.304/1.800/0.0378	1.081/1.867/0.777	0.059/1.758/0.690	0.559/1.771/0.808
M_P pain experience										
M_P item 1 (fabq)	1.837/1.006/**0.032**	2.062/1.067/**0.008**	2.302/0846/**0.013**	3.001/0.864/**0.001**						
M_P item 2 (hads)				1.554/1.059/0.298						
M_P item 3 (hads)	1.491/1.665/**0.050**		0.971/1.355/0.122							
M_P item 4 (hads)			1.200/1.046/0.277							
M_P item 5 (hads)	1.293/1.600/0.095		1.349/1.286/0.097							
M_P item 6 (hads)				1.157/1.274/0.143						
M_P item 7 (hads)			2.127/1.301/0.156							
M_P item 8 (i-see)		1.810/0.834/0.207	0.720/0.689/0.231	1.226/0.656/0.141						
M_P item 9 (i-see)			0.766/0.718/0.066							
M_P item 10 (aeq)	−1.386/0.583/**0.025**		−1.397/0.479/**0.006**							
M_P item 11 (aeq)			0.854/0.463/**0.031**							
M_S distress										
M_S item 1 (tics)	−2.499/0.876/**0.029**					−1.749/0.726/0.057				
M_S item 2 (tics)						0.820/1.004/0.208				
M_S item 3 (tics)	0.815/1.383/0.069									
M_S item 4 (tics)	1.252/1.119/**0.006**				2.117/0.900/**0.001**	2.160/0.853/**0.007**				
M_S item 5 (tics)						0.820/0.867/0.263				
M_S item 6 (tics)		3.761/1.334/**0.006**								
M_S item 7 (tics)	0.483/1.442/**0.031**	1.923/1.133/0.067			1.501/1.065/0.094	0.737/1.181/0.110				
M_S item 8 (tics)					1.307/0857/**0.016**					
M_S item 9 (tics)	2.096/1.360/0.052									
M_S item 10 (tics)					0.179/0.936/0.078					
M_S item 11 (ve)										
M_S item 12 (ve)	1.290/1.230/0.098									
M_S item 13 (ve)					0.941/1.029/0.153					
M_S item 14 (i-see)						0.616/0.704/0.196				
M_S item 15 (i-see)						1.723/0.726/**0.042**				
M_S item 16 (pss)					−1.669/0.822/**0.016**					
M_{SE} social environment										
M_{SE} item 1 (income)					−1.039/1.210/0.170			−1.548/1.292/0.194	−2.271/1.250/**0.028**	
M_{SE} item 2 (smoke)							3.762/2.425/0.120	3.850/2.520/0.161		
M_{SE} item 3 (alcohol)								−2.805/1.695/0.054		
M_{SE} item 4 (sport)								0.648/0.421/0.088		
M_{SE} item 5 (health)	−0.625/0.518/**0.003**	−0.737/0.515/**0.010**	−0.734/0450/**0.006**	−1.046/0.400/**0.001**	−0.751/0.421/**0.015**	−0.853/0.359/**0.006**	−0.331/0.439/0.156	−0.617/0.418/**0.044**	−0.664/0.438/**0.045**	
M_{SE} item 6 (sleep)			−0.306/0.350/0.230		−0.337/0.359/0.143		−0.210/0.352/0.383		−0.311/0.364/0.307	
M_{SE} item 7 (rq-2)							−0.576/0.549/0.286	−0.348/0.409/0.271		
M_{SE} item 8 (rq-2)										
M_{SE} item 9 (bsss)	−3.249/1.738/**0.030**						−0.935/1.830/0.443			
M_{SE} item 10 (bsss)							−1.086/2.169/0.183	−1.937/2.148/0.087		

(*continued on next page*)

Table 2 *(continued)*

Selected predictors for the RSI (full LASSO model) and the RPI-S on the 4 yellow flag domains—pain experience, distress, social environment, and medical care context (partial LASSO models).

Outcome	M_F full model (RSI)		M_P pain experience (RPI-S_P)		M_S distress (RPI-S_S)		M_{SE} social environment (RPI-S_{SE})		M_{MC} medical care environment (RPI-S_{MC})	
	CPI	DISS	CPI	DISS	CPI	DISS	CPI	DISS	CPI	DISS
Coefficients	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*	Estimation/SD/*P*
M_{SE} item 11 (bsss)							−0.520/2.211/0.210	−3.178/2.326/0.068		
M_{SE} item 12 (bsss)								5.442/1.927/**0.016**		
M_{SE} item 13 (bsss)								0.717/0.862/0.275		
M_{SE} item 14 (bsss)							1.663/0.791/0.080	0.800/0.876/0.157		
M_{SE} item 15 (bsss)							−4.230/1.744/**0.001**	−2.624/1.790/**0.024**		
M_{SE} item 16 (CASMIN)		6.247/2.193/**0.008**					2.809/1.768/0.074	3.691/1.849/0.470		
M_{SE} item 17 (jobl_A)							2.863/1.988/**0.028**			
M_{SE} item 18 (jobl_B)	−3.723/2.016/0.949						−2.084/1.968/0.828	−1.992/1.820/0.339		
M_{SE} item 19 (jobl_k)							13.488/5.142/**0.002**	11.457/5.117/**0.003**		
M_{MC} medical care context										
M_{MC} item 1 (treat01)	−2.118/3.116/0.092								1.710/1.928/0.185	
M_{MC} item 2 (treat03)	3.139/2.259/0.107								3.948/3.471/0.067	9.024/3.386/**0.002**
M_{MC} item 3 (treat04)									3.888/1.618/**0.046**	3.475/1.552/0.062
M_{MC} item 4 (treat06)	4.913/2.877/**0.049**	5.256/1.902/**0.047**								

Selected prognostic predictors for the outcomes pain intensity (CPI) and pain disability (DISS) achieved by applying the LASSO. Presentation of the refit (coefficient/SD/*P* values). Significance is set at $P < 0.05$.

Predictor items of the full model contribute to RSI, predictor items of the partial models contribute to the different RPI-S' (M_P, M_S, M_{SE}, and M_{MC}) (predictors mentioned "**P**" in LASSO) and observation numbers (sample size, mentioned n in LASSO) for each model: M_F (CPI: n = 233, **P** = 205 and DISS: n = 228, **P** = 205), M_P (CPI: n = 383, **P** = 85 and DISS: n = 376, **P** = 85), M_S (CPI: n = 386, **P** = 113 and DISS: n = 379, **P** = 113), M_{SE} (CPI: n = 370, **P** = 38 and DISS: n = 365, **P** = 38), and M_{MC} (CPI: n = 398, **P** = 28 and DISS: n = 391, **P** = 28).

LASSO, least absolute shrinkage and selection operator; RPI-S, risk prevention index; RSI, risk stratification index.

For example, a RSI <28 would indicate subjects with low CPI (low risk) 12 months later, ie, with low risk. Subjects characterized by a RSI ≥28 and <29 would be at risk of a slightly increased CPI (medium risk) after 12 months. Risk stratification index scores ≥29 and <32 would characterize an increased CPI (high risk) after 12 months. Subjects with RSI ≥32 would be identified and predicted for high CPI (very high risk) after 12 months. The RSI for a 1-year prognosis of increased CPI (high risk) obtained an AUC = 0.81 (95% confidence interval, 0.76–0.86) and AUC = 0.74 (95% confidence interval, 0.63–0.85) for DISS. The results of the 4 RPI-S are listed in **Tables 6 and 7**. The negative LRs for CPI ranged from 0.28 to 0.42 and from 0.22 to 0.47 for DISS, indicating small differences. Positive LRs for CPI ranged from 2.60 to 5.13 and from 1.94 to 8.2 for DISS, indicating moderate differences and substantial aid for clinical decision making (**Table 6**).

4. Discussion

In this study, a screening tool for the 1-year prognosis of persons at high risk of LBP chronification (risk prevention index, RSI), as well as a screening tool to identify persons with treatment-modifiable prognostic indicators from 4 risk factor domains (risk prevention index, RPI-S), were developed and internally validated. The major strengths of the presented screening tool development are the methods, which are in accordance with the Prognosis Research Strategy for clinical outcomes (PROGRESS).[24,42,48] First, the screening tools were derived within the presented 2-year longitudinal study. Then, they were externally validated in 2 further currently conducted randomized exercise treatment studies of 6 and of 12 months (randomized controlled trials reported here[39,57]), where additional domain-specific biopsychosocial education modules (in the 4 RPI-S domains) were developed and combined with exercise treatment.[57] This allowed an evaluation of the treatment response and the effectiveness of the individual treatment allocation because of the RPI-S. These steps: (1) the development of a prognostic model,[48] (2) the defining of modifiable risk factors[42] and their screening, (3) the designing of specific and stratified intervention modules,[24] and (4) the transparent reporting according to the TRIPOD statements[8] (see supplemental digital content, available at http://links.lww.com/PR9/A12), were all completed in high-quality data sets within 1 research network. This procedure enabled the extension of the presented type-3 prognostic study to implement new statistical methods as is required for stratified model research.[5] For LASSO selected predictors p-values were calculated via the LDPE approach,[11,61] which addresses the research gap of statistical inference in high-dimensional data settings. For comparability to other screening tools, we calculated ROC curves to determine cutoff classes.

The RSI provided a precise estimation of the expected individual CPG-DISS and CPI values for persons up to 1 year later with an average prognosis error (RMSE) of 15 points (on a 100-point scale). The brief 5-minute screening tool contained 8 items for pain disability and 17 items for pain intensity. It displayed a performance of AUC = 0.81 for the risk of developing greater CPI and AUC = 0.74 for developing greater DISS. The LRs exhibited substantial improvement in clinical decision making, especially when predicting increased pain. Values above the critical cutoff indicated an 8-fold increase in probability of more severe CPI or DISS after 1 year.

The RPI-S (with 3 up to 16 items, duration time = 15 minutes, for all domains) will assist health care providers when deciding

Table 3

Validity: prognosis error RMSE.

12-mo follow-up	RMSE	RSI	RPI-S_P	RPI-S_S	RPI-S_{SE}	RPI-S_{MC}
Characteristic pain intensity (CPI)	Model-prediction	16.87	15.44	16.72	17.05	15.81
	Baseline-prediction	18.46	16.26	18.01	19.25	17.73
Subjective pain disability (DISS)	Model-prediction	15.45	15.71	16.20	14.51	13.02
	Baseline-prediction	20.57	19.70	18.80	17.21	22.61

Prognosis error (RMSE) for the 1-year prediction of pain (CPI/DISS) for the screening tools, RSI and RPI-S.
The models with reduced predictors receive lower RMSE than the prediction made using all possible predictors.
RMSE, root-mean-squared error; RPI-S, risk prevention index; RSI, risk stratification index.

whether their patients could benefit from additional biopsychosocial treatment or education within the 4 risk factor domains (pain experience, distress, social environment, and medical care environment). As physical activity was included in its development, the RPI-S may be helpful in identifying patients who would not respond to unimodal exercise treatments but rather to a multimodal with additional psychosocial treatment. Estimation errors (RMSE) of the RPI-S models are similar, suggesting strong influence of baseline pain on dependent variable variation and supporting the chosen follow-up time for screening in secondary prevention.[54]

Both screening tools cover mainly yellow, black, and blue flag factors, as well as demographic and protective factors.[32] For the RSI, these included pain at baseline, unhappiness, social isolation/social support, social status, distress (chronic worries), work dissatisfaction, claims for indemnity, misfortune, pain persistence, sleep problems, and other health care–related topics including medication, insurance status, and physical treatments. In the RPI-S models, pain persistence, avoidance behavior, fatigue, irritability, relationships, and feelings of lack of control over one's own life were also included. The domains stress and pain experience were more strongly associated with future pain disability than pain intensity, whereas social environment affected both. Within the ROC analyses, both instruments achieved better results using pain intensity models, which could be explained by a greater CPI stability in the sample and a better-balanced number of subjects in the CPI subgroups.

In contrast to other instruments, the RSI evolved from 205 predictors and showed a good performance (AUC for CPI = 0.81 and AUC for DISS = 0.74) and economy (reduced from 205 DISS predictors to only 8). The recently published and shortest screening tool for the prediction of pain intensity, PickUP,[52] was extracted from 20 predictors, and the final version contains 5 predictors with a performance of AUC = 0.66. Other tools, such as the StarT Back[22] and the Örebro Musculoskeletal Pain Screening Questionnaire, contain 9 predictors for pain disability (AUC = 0.92) and 24 predictors for disability and return to work, respectively. Most of these screening tools were developed using a different strategy, stepwise regression models,[22,23,30] which prohibits a direct prediction of pain (CPG) and the inclusion of different risk factors because of the risk of over fitting. The lack of these important prognostic indicators in such screening tools is criticized by the authors themselves.[52] When controlling for so many various influencing factors, high-dimensional methods are necessary because they allow for the new approaches presented here that focus on modifiable risk factors.[9,33,59] One benefit of the RPI-S is the identification of individual risk profiles relating to 4 domains avoids "screening out" from 1 treatment and leads to a "screening in" for appropriate treatment.[32] This should enable health care providers to individualize treatment as suggested for future screening developments in personalized medicine.[26]

Table 4

Frequencies of subjects grouped by the CPG scales CPI and DISS.

Risk subgroups	CPI/DISS points	No. of participants	
		CPI (n = 413)	DISS (n = 354)
Low risk	0–29	270	310
Medium risk	29–49	94	31
High risk	50–69	39	9
Very high risk	70–100	10	4

Groups were used for ROC analyses in the development sample. Sample sizes vary due to missing values in the respective outcome measures. Calculations are based on complete cases. CPI/DISS points on a 1 to 100 scale.
CPI, characteristic pain intensity; DISS, subjective pain disability; ROC, receiver operating characteristic.

4.1. Limitations

Although our approach produced good validity and generalizability and uses advanced actuarial and clinical methods, there

Table 5

Evaluation of the screening tools' discriminant validity for pain intensity (CPI, n = 413) and disability (DISS, n = 354) calculated for 1-year follow-up.

	Risk subgroups			AUC (95% CI)	
				CPI	DISS
RSI	1	vs.	2/3/4	0.81 (0.77–0.85)	0.79 (0.73–0.85)
	1/2	vs.	3/4	0.81 (0.76–0.86)	0.74 (0.63–0.85)
	1/2/3	vs.	4	0.73 (0.6–0.86)	0.73 (0.53–0.93)
RPI-S_{SE}	1	vs.	2/3/4	0.81 (0.77–0.85)	0.80 (0.74–0.86)
	1/2	vs.	3/4	0.82 (0.77–0.87)	0.79 (0.69–0.89)
	1/2/3	vs.	4	0.73 (0.6–0.86)	0.75 (0.56–0.94)
RPI-S_S	1	vs.	2/3/4	0.81 (0.77–0.85)	0.81 (0.76–0.87)
	1/2	vs.	3/4	0.81 (0.76–0.86)	0.73 (0.61–0.85)
	1/2/3	vs.	4	0.71 (0.57–0.85)	0.69 (0.47–0.91)
RPI-S_P	1	vs.	2/3/4	0.81 (0.77–0.85)	0.79 (0.73–0.85)
	1/2	vs.	3/4	0.81 (0.76–0.86)	0.74 (0.63–0.85)
	1/2/3	vs.	4	0.72 (0.59–0.85)	0.64 (0.40–0.89)
RPI-S_{MC}	1	vs.	2/3/4	0.80 (0.76–0.84)	0.77 (0.71–0.83)
	1/2	vs.	3/4	0.78 (0.72–0.84)	0.71 (0.59–0.83)
	1/2/3	vs.	4	0.72 (0.59–0.85)	0.70 (0.48–0.92)

AUC, area under the curve; CI, confidence interval; CPI, characteristic pain intensity; DISS, subjective pain disability; RPI-S, risk prevention index; RSI, risk stratification index.

Table 6

Sensitivity, specificity, negative and positive likelihood ratios (LR− and LR+), and negative and positive predictive values (NPV and PPV) for each cutoff score, for characteristic pain intensity (CPI) in the development sample.

Cutoff values	Sensitivity (%)	Specificity (%)	LR− (95% CI)	LR+ (95% CI)	NPV (%)	PPV (%)
RSI ≥28	68	80	0.40 (0.31–0.51)	3.39 (2.61–4.42)		
RSI ≥29	80	72	0.29 (0.16–0.50)	2.81 (2.27–3.49)	96.7	25.7
RSI ≥32	70	74	0.28 (0.05–1.52)	2.66 (1.72–4.12)	99.1	5.5
RPI-S_{SE} ≥24	74	73	0.36 (0.27–0.47)	2.74 (2.20–3.41)		
RPI-S_{SE} ≥31	73	80	0.33 (0.21–0.53)	3.61 (2.78–4.71)	96.1	30.6
RPI-S_{SE} ≥37	70	86	0.35 (0.14–0.9)	5.13 (3.19–8.24)	99.3	9.7
RPI-S_S ≥26	70	76	0.39 (0.30–0.51)	2.95 (2.32–3.75)		
RPI-S_S ≥28	78	72	0.31 (0.19–0.53)	2.74 (2.19–3.42)	96.4	25.2
RPI-S_S ≥33	70	80	0.38 (0.15–0.97)	3.48 (2.22–5.46)	99.2	7.0
RPI-S_P ≥26	72	75	0.37 (0.28–0.49)	2.90 (2.30–3.66)		
RPI-S_P ≥28	76	72	0.34 (0.21–0.56)	2.70 (2.14–3.39)	96.1	24.7
RPI-S_P ≥31	70	75	0.40 (0.16–1.03)	2.82 (1.82–4.38)	99.1	5.7
RPI-S_{MC} ≥24	73	70	0.38 (0.29–0.50)	2.45 (1.99–3.01)		
RPI-S_{MC} ≥28	69	73	0.42 (0.27–0.64)	2.60 (2.02–3.35)	95.1	23.6
RPI-S_{MC} ≥31	70	77	0.39 (0.15–1.00)	3.10 (1.99–4.80)	99.2	6.1

Time frame (baseline and 1-year follow-up). Negative/positive likelihood ratios (LR−/LR+) of 0.2 to 0.5/2 to 5 = small difference, relevant for clinical decision making; 0.1 to 0.2/5 to 10 = moderate difference, substantial in clinical decision making; and <0.1/>10 = clinical important difference, highest test quality. NPV and PPV are provided for the groups at risk of increased CPI and DISS after 1-year since those can be considered as possible patients with pain.

CI, confidence interval; RPI-S, risk prevention index; RSI, risk stratification index.

are some limitations to consider: (1) In prognosis research, a follow-up rate of >80% is desired[31]; this study reached a 1-year follow-up rate of only 65%, which could bias results. (2) Each screening is population dependent, hence trade-offs between sensitivity and specificity depend on the purpose of the screening tool. Therefore, the generalizability to other populations must be evaluated in further studies. (3) In prediction quality, it should be noted that the results could have been influenced by single extreme deviations in the predictors, which may have distorted RMSE. (4) The decrease in discriminant power with increased severity of chronic pain is a result of the small number of subjects in risk subgroups 2, 3, and 4. Thus, results could be affected by outliers. The discriminant validity of both screening tools, as well as the effectiveness of the individual treatment allocation and treatment response, should be evaluated in an external-balanced study population to fix the final screening tools ranges. This was currently conducted in 2 further MiSpEx-exercise randomized

Table 7

Sensitivity, specificity, negative and positive likelihood ratios (LR− and LR+), and negative and positive predictive values (NPV and PPV) for each cutoff score, for pain disability (DISS) in the development sample.

Cutoff values	Sensitivity (%)	Specificity (%)	LR− (95% CI)	LR+ (95% CI)	NPV (%)	PPV (%)
RSI ≥15	75	75	0.33 (0.2–0.56)	2.98 (2.31–3.85)		
RSI ≥22	69	87	0.35 (0.16–0.8)	5.25 (3.33–8.25)	98.5	18.1
RSI ≥25	75	90	0.28 (0.05–1.52)	7.50 (3.93–14.33)	99.6	9.0
RPI-S_{LC} ≥16	73	82	0.33 (0.2–0.54)	4.1 (3.04–5.54)		
RPI-S_{SE} ≥17	80	77	0.29 (0.11–0.78)	3.86 (2.68–5.56)	98.9	12.7
RPI-S_{SE} ≥23	91	75	0.28 (0.05–1.5)	8.2 (4.26–15.79)	99.8	4.6
RPI-S_S ≥13	75	77	0.31 (0.18–0.53)	3.03 (2.36–3.89)		
RPI-S_S ≥15	77	78	0.3 (0.11–0.8)	3.5 (2.44–5.01)	98.8	12.7
RPI-S_S ≥19	75	87	0.29 (0.05–1.57)	5.83 (3.11–10.93)	99.6	7.1
RPI-S_P ≥10	86	64	0.22 (0.1–0.45)	2.37 (1.96–2.86)		
RPI-S_P ≥11	75	61	0.41 (0.07–2.23)	1.94 (1.09–3.48)	99.5	2.5
RPI-S_P ≥16	62	82	0.47 (0.24–0.94)	3.39 (2.08–5.5)	98.1	12.6
RPI-S_{MC} ≥12	70	73	0.41 (0.26–0.65)	2.57 (1.97–3.34)		
RPI-S_{MC} ≥18	62	86	0.45 (0.23–0.89)	4.37 (2.64–7.23)	98.2	15.6
RPI-S_{MC} ≥21	75	90	0.28 (0.05–1.52)	7.5 (3.93–14.33)	99.6	9.0

Time frame (baseline and 1-year follow-up). Negative/positive likelihood ratios (LR−/LR+) of 0.2 to 0.5/2 to 5 = small difference, relevant for clinical decision making; 0.1 to 0.2/5 to 10 = moderate difference, substantial in clinical decision making; and <0.1/>10 = clinical important difference, highest test quality.

CI, confidence interval; RPI-S, risk prevention index; RSI, risk stratification index.

controlled trials.[39,57] (5) Finally, the screening instruments still need to be converted into categorized questionnaires with standardized answer formats.

5. Conclusions

This multidimensional approach aimed to develop 2 screening tools for the identification of modifiable psychosocial risk factors that can be applied to upcoming stratified care in secondary prevention, as requested for innovative concepts of prevention.[4,32] The brief RSI (~5 minutes) provides medical practitioners with a quick estimation of prognostic pain and chronicity risk because of psychosocial risk variables in the patients' pain history. A high RSI-profile would indicate the practitioner to investigate if a specific additional psychosocial treatment within the 4 flag domains could be rewarding for the patient, for which the RPI-S can be used. The RPI-S (~15 minutes) identifies patients with specific needs in 4 flag domains, enabling health care providers to better stratify allocation to additional biopsychosocial treatment and education.

Both screening tools were developed in line with modern concepts of secondary prevention and based on a wide range of risk predictors to avoid "screening in" or "screening out" of treatments as well as under and overtreatment of patients. Although the RSI outperforms other screening tools because of its precise estimation of future pain, the RPI-S exceeds other screening tools because of its respect of exercise treatment effect modifiers and its estimation of individual needs allowing for more complex allocations to treatment.

Disclosures

The authors have no conflict of interest to declare.

This study was funded by the German Federal Institute of Sport Science on behalf of the Federal Ministry of the Interior of Germany. It was realized within MiSpEx–the National Research Network for Medicine in Spine Exercise (grant number: 080102A/11-14). All sources of funding for the research reported are declared. The funder did not influence data collection, analysis, interpretation, or writing of the manuscript.

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Final ethical approval was provided on January 25, 2012 from the major institutional ethics review board of the University of Potsdam, Germany (number 36/2011).

Acknowledgments

The authors thank Helmut Küchenhoff, Gerhard Tutz, Sören Matzk, Juliane Müller, Steffen Müller, Jessica Messerschmidt, Daniela Schubert, Hannes Kaplick, Josephine Stoll, Tilmann Engel, Philipp Flössel, Jan Wilke, Andreas Rosenhagen, Tobias Engeroff, Meltem Hacibayramoglu, Martin Handel, Thore Haag, Johanna Vogel, Kristin Kalo, Jonas Newrly, Olga Tjukov, Karsten Dreinhöfer, Monika Hasenbring, Dirk Stengel, Jeronimo Weerts, Jens Kleinert, Michael Kellmann, María Moreno Catalá, Arno Schroll, Ann-Christin Pfeifer, Simone Gantz, and all local principal investigators for their valuable support. They also thank both the technical and medical staff at the study sites for their contributions during the study.

Author contributions: All authors substantially contributed to the conception and realization of the studies. PW and AP wrote the first draft of the manuscript, and all authors critically revised the manuscript for important intellectual content. PW was responsible for methodological design and analysis related to psychosocial factors, and PW, AP, and MS provided all scientific and practical information for the psychosocial content. DD provided the statistical analysis with LASSO and information. CS, WB, HB, HS, AA, and FM provided all scientific information for biomechanical and medical content. FM conceived the study as principal investigator. All authors read and approved the final manuscript.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A12.

Article history:
Received 22 March 2017
Received in revised form 15 August 2017
Accepted 16 August 2017

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