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Development and internal validation of a multivariable prognostic model for chronification of non-specific neck pain in physiotherapy practice.

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1	Title
2	Development and internal validation of a multivariable prognostic model for chronification of
3	non-specific neck pain in physiotherapy practice.
4	
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4	21	Abstract
6		
7	22	Objective: To develop and internally validate a prognostic model for the chronification of non-
8	22	specific near traumatic neck pain in patients presenting to primary care physiotherapy, with an
9	25	specific, non-tradinatic neck pair in patients presenting to primary care physiotherapy, with an
10	24	emphasis on modifiable psychosocial factors.
12		
13	25	
14	25	Design: A prospective cohort study with a 6-month follow-up between January 2020 and
15	26	March 2023
16	20	
/ 19		
19	27	Setting: 30 primary care physiotherapy.
20		
21	28	Participants: Patients with a new presentation of non-specific, non-traumatic neck pain, with a
22		
23	29	duration lasting no longer than 12 weeks from onset.
24 25		
26	30	Baseline measures: Candidate prognostic variables were collected from participants regarding
27		
28	31	their neck pain symptoms, prior conditions, work-related factors, general factors, psychological
29		
30 21	32	and behavioral factors.
32		
33	33	Outcome measures: Pain intensity at 6 weeks, 3 months, and 6 months on a Numeric Pain
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35	34	Rating Scale (NPRS) after inclusion. A NPRS score of ≥3 at each time point was used to define
36	25	
37	35	chronic neck pain.
39		
40	36	Results: Sixty-two (10%) of the 603 participants developed chronic neck pain. The prognostic
41		
42	37	factors in the final model were sex, pain intensity, reported pain in different body regions,
43	20	headache since and before the neck pain, necture during work, employment status, illness
44 45	20	neadache since and before the neck pain, posture during work, employment status, inness
46	39	beliefs about pain identity and recovery, treatment beliefs, distress, and self-efficacy. The
47	00	
48	40	model demonstrated an optimism-corrected Area Under the Curve (AUC) of 0.83 and a
49		
50 51	41	corrected R ² of 0.24. Calibration was deemed acceptable to good, as indicated by the
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60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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43 model fit.

- *Conclusion:* This model has the potential to obtain a valid prognosis for chronification of a
- 45 (sub)acute non-specific neck pain and included mostly potentially modifiable factors for
- 46 physiotherapy practice. External validation of this model is recommended.
- 47 Key words: neck pain, prognostic model, modifiable factors, chronification

48	Strengths and limitation of this study
49	Novel approach to determine an accurate sample size for prognostic model
50	development, mitigating overfitting.
51	Inclusion of both biomedical and psychosocial prognostic factors which are potentially
52	modifiable by a physiotherapist.
53	Utilization of three follow-up time points for chronic pain outcome assessment.
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55	Introduction
56	Neck pain is a widespread and disabling health condition significantly impacting public
57	health.(1)(2)(3) It is ranked third in terms of years lived with disability in non-fatal diseases,
58	with high costs due to extended work absence and healthcare utilization.(4) Chronic neck pain
59	is particularly costly(5), and the prevalence has increased by 21% from 2005 to 2015, affecting
60	approximately 358 million people worldwide.(6)
61	Physiotherapy is common first-line treatment; unfortunately, the effect is often only
62	moderate.(7)(8)(9) Consequently, identifying prognostic factors for chronification of acute- and
63	subacute neck pain is a top priority for neck pain research and for clinical care.(10)
64	Understanding these factors can aid clinical decision making and potentially prevent the
65	chronification of idiopathic neck pain.
66	The existing literature on prognostic models shows a low performance in predicting
67	chronification of (sub)acute neck pain.(11) Moreover, the external validity of current
68	prognostic models in terms of pain and recovery outcomes have not been proven in patients
69	with (sub)acute neck pain.(12) This may be attributed to the inclusion of heterogeneous groups
70	of patients for the development of these prognostic models, characterized by varying pain
71	duration (acute, subacute and > 3 months), clinical symptoms and prognosis. Additionally,
72	much of the prognostic research has predominantly focused on non-modifiable factors, such as
73	age, pain duration and sex, neglecting potentially modifiable factors.(11) Incorporating
	modifiable factors has the potential to better tailor interventions to individual patients, which
74	
74 75	could enhance the model's applicability and relevance in clinical practice.

It is known that biomedical, psychological, and social factors provide a comprehensive understanding of the neurophysiological changes involved in the chronification of pain.(13) Consequently, there is a compelling need for a biopsychosocial approach that specifically focuses on modifiable prognostic factors for chronification of nonspecific idiopathic, non-traumatic neck pain. This study aimed to (1) identify which modifiable factors are independent prognostic factors of the development of chronic neck pain in patients with acute- or subacute neck pain, and (2) to develop and internally validate a model to predict chronification. Tocct terics only

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83 Methods

- The methods of this study have been extensively described in the study protocol.(14) Briefly
- 85 summarized, the methods were as follows:

86 Study design

- 87 The present study is a prospective longitudinal cohort study that focuses on modifiable
- 88 prognostic factors and follows the guidelines of the PROGRESS framework and TRIPOD
- 89 statement type 1b.(15)(16) This study adheres to the specific statistical recommendations for
- 90 Type 3 prognostic model research.(15) The findings are reported according to the TRIPOD
- 91 statement to ensure transparent reporting of the multivariable prediction model for individual
- 92 prognosis (see Appendix 1).(16)

93 Study setting

- 94 Participants were recruited from 30 Dutch primary care physiotherapy practices by 94
- 95 physiotherapists between January 26, 2020, and August 31, 2022. The study was completed in
- 96 March 2023 (including reminders and time for response).

97 Ethical approval

- 98 The Medical Research Ethics Committee Utrecht declared that the Medical Research Involving
- 99 Human Subjects Act (WMO) does not apply to this study (protocol number 19-766/C).
- 100 Participants who gave informed consent were assigned a unique code to allow anonymous
- 101 data collection, facilitated through the secure Formdesk data transfer system.(17)

102 Participants

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103	Patients were approached if they presented in one of the participating physiotherapy practices
104	with a new episode of (sub)acute nonspecific idiopathic, non-traumatic neck pain. Patients
105	were included if they met the following criteria: age 18 years or older, a new presentation of
106	neck pain no longer than 12 weeks after onset and the patient indicated on the body diagram
107	that he/she experienced regional neck pain. If the patient had a previous episode of neck pain,
108	the patient had to be relatively free from symptoms on the Numerical Pain Rating Scale (NPRS
109	of <3) for at least three months prior to the present episode of neck pain. The exclusion criteria
110	were: neck pain surgery in the past, cervical spine radiculopathy assessed with the Upper Limb
111	Neurodynamic Test 1(18), widespread primary pain (ICD-11) (diffuse musculoskeletal pain in at
112	least 4 of 5 body regions and in at least three or more body quadrants (as defined by upper-
113	lower / left-right side of the body) and axial skeleton (neck, back, chest and abdomen)(19), pain
114	not caused by musculoskeletal origin (not located in the muscles, bones, joints, or
115	tendons)(20), and inability to read or understand the Dutch language.
116	Baseline and follow-up procedure
117	During the first consultation, the physiotherapist informed eligible patients about the study
118	purpose and expectations. Patients who verbally indicated they wanted to participate in the
119	study, signed an informed consent before completing the initial digital questionnaire at
120	baseline (T0). Follow-up questionnaires were sent via email at six weeks (T1), three months
121	(T2), and six months (T3), taking 20-40 minutes to complete. Participants were reminded to
122	complete the questionnaires via email or telephone contact by their treating physiotherapist.

123 *Outcome*

124	The NPRS was used to quantify the presence of chronic pain. If pain was present, defined as an
125	NPRS \geq 3, at all measurement moments (i.e. six weeks, three months, and six months), it was
126	classified as chronic.(21)(14)
127	Candidate Prognostic factors
128	We included candidate prognostic for pain chronification, or non-recovery identified in a
129	previous systematic review and by neck pain experts in a Delphi study with >70% consensus in
130	the first round.(11)(22) Details on candidate prognostic factors and their measurement are
131	provided in our study protocol.(11)
132	- Patient characteristics: sex and age.
133	- Symptoms: pain intensity at baseline measured with the NPRS, duration of the
134	(sub)acute neck pain in weeks, reported pain in different body regions (yes/no),
135	accompanying headache (since the onset of neck pain and headache before the neck
136	pain), and disability measured with the Pain Disability Index, where the sum score was
137	divided by the entered items (PDI).(23)
138	- Work-related factors: happiness at work, job satisfaction, and potential to self-modify
139	posture measured with a self-reported question.
140	- General factors: the lifestyle factors: smoking, alcohol, length and weight (body mass
141	index), sleep quality measured with an adjusted sleep quality question from the Neck
142	Disability Index (NDI)(24)(22), and physical activity measured by meeting the activity
143	level according to the Dutch Healthy Exercise Norm (Yes/No).(25)
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5	144	 Psychological and behavioral factors: illness perceptions regarding recovery and pain
6 7	145	identity, treatment beliefs, catastrophizing, depression and distress, kinesiophobia,
8 9	146	coping, hypervigilance, and self-efficacy. Illness perceptions were assessed using the
10 11	147	Dutch language version of the Brief Illness Perception Questionnaire (IPQ-DLV).(26)
12 13	148	Catastrophizing was measured with the short version of the Pain Catastrophizing Scale
15 16	149	(PCS).(27) To assess depression and distress, the 21-item version of the Depression
17 18	150	Anxiety Stress Scale (DASS-21) was used.(28) Kinesiophobia was measured using the
19 20	151	11-item version of the Tampa Scale for Kinesiophobia (TSK).(29) Coping strategies were
21 22	152	evaluated with the Pain Coping Inventory (PCI).(30)(31) Hypervigilance was assessed
23 24	153	using the Pain Vigilance and Awareness Questionnaire (PVAQ)(32), and self-efficacy in
25 26	154	managing pain was measured with the 2-item version of the Pain Self-Efficacy
27 28	155	Questionnaire.(33)
29 30 31	156	- The remaining factors included, first, the 'therapeutic relationship', assessed through
32 33	157	the self-reported question: 'How much trust do you have in your healthcare
34 35	158	provider/physiotherapist?'. Second, the 'therapist's orientation', which could be either
36 37	159	biomedical or biopsychosocial. The authors categorized this orientation based on open-
38 39	160	ended and multiple-choice questions about neck pain cases.(14)
40 41 42 43	161	Sample size
44 45	162	To ensure a sufficient sample size to reduce the effect of overfitting, the minimum number of
46 47	163	events per candidate prognostic factor was calculated as recommended by Riley et al.
48 49	164	2019.(34) The expected value of the Cox-Snell R-squared of the new model was estimated at
50 51 52 53	165	0.23(35)(36)(22), and the estimated outcome event rate at 45%.(11) The study considered 26 1

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166 candidate prognostic factors, including four non-modifiable and 22 potentially modifiable

- 167 prognostic factors. The a priori sample size calculation suggested a minimum of 598
- 168 participants for the prognostic model.

169 Statistical analysis methods and missing data

- 170 This study followed the Prognosis Research Strategy (PROGRESS) framework type 3
- 171 research.(15) The Statistical software IBM SPSS (version 27) and R (version 4.2.2) were used for
- the statistical analysis.(37)(38) For the analysis, we extensively utilized the following R
- packages: tidyverse, MASS, pROC and Mice.(39)(40)(41)(42) The complete R script used in this
- 174 study can be found on GitHub at https://github.com/uashogeschoolutrecht/painr (see
- 175 Appendix 2 the table of contents).
- We used multiple imputation with fully conditional specification to impute incomplete records,
 assuming data to be at least missing at random (MAR). Predictive mean matching was used to
 impute continuous variables, and logistic regression for categorical variables. After completing
 the data, the outcome variable (chronic pain) was determined for each participant. The factor
 'healthcare provider orientation' exhibited a significant amount of missing data, which could
 not be imputed based on patient-specific information, resulting in the missing's remaining
 available for further analyses.
 - The predictive performance of each candidate prognostic factor of chronic pain was estimated
 using univariable logistic regression analysis. These analyses were not used to decide which
 prognostic factors would be included in the multivariable model.

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186	Before multivariable modeling, we computed the variance inflation factor (VIF) to assess
187	multicollinearity. If this factor exceeded 10, the selection of candidate prognostic factors for
188	modeling was guided by the clinical expertise of the authors of this study.
189	All candidate prognostic factors were entered into the multivariable model. To make the model
190	more concise and to identify the most significant prognostic factors, we applied backward
191	elimination.
192	Model performance was quantified as it's discriminative ability, using the Area Under the
193	receiver operating characteristic Curve (AUC), model calibration, using calibration plots and
194	computing the Hosmer and Lemeshow goodness-of-fit test, and as model fit, using
195	Nagelkerke's R ² .
196	Bootstrap resampling with 1000 bootstrap samples was utilized for internal validation to
197	calculate the optimism-corrected AUC and determine the shrinkage factor, thereby adjusting
198	for overfitting by shrinking regression coefficients. After shrinking regression coefficients, we
199	re-estimated the model intercept.
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203 Results

204	A total of 2.567 patients underwent eligibility assessment across 30 physiotherapy practices in
205	the Netherlands. Among these patients, 1.600 were excluded, primarily due to the fact they
206	already had chronic pain (lasting >12 weeks with a NPRS \geq 3), cervical spine radiculopathy, or
207	widespread pain. Additionally, 307 patients refused to participate, citing disinterest, scheduling
208	conflicts, or stress at the time of invitation. Ultimately, 660 potential participants provided
209	informed consent, however, 58 of them did not respond during the baseline measurement
210	phase, resulting in the inclusion of 603 individuals in a period of 2.5 years (Figure 1). Among
211	them, 62 participants (10%) developed chronic pain, while 541 participants experienced
212	recovery from their pain.
213	



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220	For the description of the participants' characteristics, including candidate prognostic factors,
221	and the number of participants with missing data, see Table 1. We included 397 women and
222	206 men. The mean pain intensity at baseline was 5.9 (SD 1.9), and the mean disability was
223	relatively low, with a score of 2.7 (SD 2.1) on a 0-7 scale.
224	There was some loss to follow-up at various follow-up moments. However, only 78 participants
225	did not complete any follow-up measurement. At the 6-weeks measurement, 154 participants
226	failed to submit the required forms. This number increased to 224 at the 3-months follow-up,
227	and to 231 at the 6-month mark.
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	Number (percent)	Mean (SD) Median (IQR)	Missing Count (percent)
Patients characteristics			
Sex			
1 = Male	206 (34.2)		0 (0)
2 = Female	397 (65.8)		- (-)
Age		44,52 (15.7)	1 (.2)
Symptoms		44,0 (31 - 56)	
Pain intensity at baseline (0-10)		5,93 (1.9)	0 (0)
Higher scores indicate a higher degree of pain.		6 (5 - 7)	
Duration of neck pain		4.52 (2.9)	0 (0)
Number of weeks		4 (2 - 6)	
Recurrent pain			1 (.2)
1 = No	198 (32.8)		
2 = Yes	404 (67)		
Reported pain in different body regions			4(7)
$1 = N_0$	210 (34.8)		- (./)
2 - Vos	280 (64 5)		
	505 (04.5)		Γ (Q)
	247 (41)		5 (.8)
	24/ (41)		
2 = Yes	281 (46.6)		
3 = I had headache(s) before the neck pain.	70 (11.6)		
Disability (0-7)		2.73 (2.1)	1 (.2)
Higher scores indicate higher interference of pain with daily		2.3 (1.0 – 4.1)	
activity. The sum score divided by the entered items.			
Work related factors			
Work status			10 (1.7)
1 = Yes	501 (83.1)		
2 = No	92 (15.3)		
Education			16 (2 7)
$\Omega = 1 \text{ ow level of education}$	313 (51.9)		10 (2.7)
1 - High level of education	274 (45 4)		
	2/+(+J.+)		22 (2.0)
παμμιτιεςς at work			25 (5.8)
1 = muppy (IEJ)			
2 = Neutral Of Hol Happy			
3 = INOT WORKING	92 (19)		
Job satisfaction			21 (3.5)
1= Satisfied (ref)	404 (67)		
2 = Neutral or not satisfied	86 (14.3)		
3 = Not working	92 (18.7)		
Potential to self-modify posture			25 (4.2)
1 = Possible (ref)	372 (61.7)		
2 = Neutral or impossible	114 (18.9)		
3 = Not working	92 (19.4)		
General factors			
Physical activity			8 (1 3)
0 - Achieving the Dutch Healthy Evercice Norm	210 (26 2)		0 (1.5)
u - Achieving the Dutch Healthy Evereice Norm	213 (30.3)		
I – NOT ACHIEVING THE DATCH REALTRY EXERCISE NORTH	570 (02.5)		

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Smoking			3 (.5)
1 = No	528 (87.6)		
2 = Yes	72 (11.9)		
Alcohol			5 (.8)
1 = No	129 (21.4)		
2 = Yes	469 (77.8)		
BMI		25.31 (4,3)	
		24.66 (22.5 – 27.7)	
Sleep quality			2 (.3)
0 = No negative experience with sleeping	130 (21.6)		(- <i>y</i>
1 = Negative experience with sleeping	471 (78.1)		
Psychological and behavior factors			
Catastrophizing (0–24)		4.58 (4.6)	3 (.5)
Higher scores indicate more catastrophic thoughts		3 (1 – 7)	
Illness beliefs about recovery (Duration 0-10)		4.13 (2.7)	10 (1.7)
0 a very short time– 10 forever Higher scores indicate a		3 (2 – 6)	
maladaptive illness perception			
Illness beliefs about recovery (Concerned 0-10)		3.96 (2.6)	8 (1.3)
0 Not at all concerned– 10 extremely concerned Higher		4 (2 - 6)	
scores indicate a maladaptive illness perception.			
Treatment beliefs (0–10)	1	7.82 (1.9)	12 (2.0)
0 not at all—10 extremely helpful		8 (7 - 9)	
A lower score indicates a maladaptive illness perception			
Depression (0–21)		2.47 (3.3)	3 (.5)
Higher scores indicate a higher degree of depression		1(0-4)	
Kinesiophobia (11–44)		16.5 (5.2)	3 (.5)
Higher scores indicate a higher degree of kinesiophobia.		15 (12 – 20)	- (-)
Distress (0–21)		4.4 (4.1)	3 (.5)
Higher scores indicate a higher degree of stress.		3(1-7)	- (-)
Coping			5 (.8)
0 = Passive coping	120 (19.9)		
1 = Active coping	478 (79.3)		
Illness beliefs about pain identity (0–10)		6.11 (2.3)	14 (2.3)
0 don't understand at all—10 understand verv clearly. A		6 (5 - 8)	,
lower score indicates a maladaptive illness perception.		(<i>i</i>	
Hypervigilance (0–80)		31.0 (11.4)	3 (.5)
Higher scores indicate a higher degree of vigilance.		31 (23 – 38)	- (/
Self-efficacy (0–12)		10.31 (2.3)	2 (.3)
Higher scores indicate a higher degree of self-efficacy		11(10-12)	_ (,
Remaining factors			
Therapeutic relation (0-10)		8.79 (1.4)	
0 no trust at all– 10 very much confidence.		9 (8 - 10)	10 (1.7)
Health care provider attitude			
1 = Biomedical	134 (22.2)		49 (8.1)*
2 = Biopsychosocial	420 (69.7)		

230 *We missed the attitude measurement for 14 of the 94 physiotherapists, including a total of 49

231 patients.

232 Table 1. Baseline characteristics of the study population

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4	222	University by a management of shares and of shares in a sin
5	233	Univariable prognostic factors of development of chronic pain
7	224	The universable analyses (see Figure 2) revealed significant positive associations between the
8	234	The univariable analyses (see Figure 2) revealed significant positive associations between the
9 10	235	following candidate prognostic factors and chronification of pain: being female, higher pain
11 12	236	intensity at baseline. longer duration of neck pain, experiencing pain in different body regions.
12		
14 15	237	onset of headache since the neck pain began, higher disability scores, unemployment,
16	238	increased scores on catastrophizing, illness beliefs about recovery (concerned and duration),
17 19	220	depression distract and lower treatment beliefs. Some of these factors were identified with
18	239	depression, distress, and lower treatment beliefs. Some of these factors were identified with
20	240	broad confidence intervals (CI). For most factors not showing significant associations, the odds
21	241	ratios (ORs) were close to one, indicating lack of a clinically meaningful association.
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Figure 2. Univariable logistic regression analysis: unadjusted association between each candidate prognostic factor and the outcome chronic pain

Odds Ratio (OR) and corresponding confidence intervals (CI) are presented. BMI denotes Body Mass Index, W represents Weight low. (kg), and H stands for Height (m). P-values are indicated as follows: * for $0.01 , ** for <math>0.001 , and *** for <math>p \le 0.01$, and *** for $p \le 0.01$, and

0.001.

257 Multivariable modeling

258	The inclusion of 'work status' as a category among the work-related prognostic factors resulted
259	in multicollinearity within the following factors: happiness and satisfaction at work, and the
260	ability to change posture during work. To mitigate this issue, we decided to include only the
261	factor 'ability to change posture at work' in our final model. This decision was based on the
262	distinct conceptual domain of this factor, which differs from the psychological construct
263	already well-represented by the other included factors. The candidate prognostic factor 'work
264	status' is thus also referred to the ability to change posture at work in the analysis. Following
265	this adjustment, multicollinearity was no longer observed.
266	Several prognostic factors were identified from the multivariable logistic regression analysis.
267	These included sex (female), higher pain intensity at baseline, reported pain in different body
268	regions, headache since the neck pain, headache(s) prior to neck pain, an inability or neutral
269	score on self-modify posture during work, not working, lower scores pain identity and
270	treatment beliefs, higher scores in beliefs regarding recovery (duration and concerns), and
271	higher scores on distress and self-efficacy. The ORs including 95% confidence intervals are
272	presented and visualized in Figure 3. Of all prognostic factors, not working showed the
273	strongest association (OR: 4.87). The combined prognostic model showed an Area Under the
274	Curve (AUC) of 0.86 (95% Confidence Interval: 0.82 to 0.90) and a Nagelkerke's R^2 of 0.31
275	(Figure 4). The Hosmer-Lemeshow test yielded a p-value of 0.7167, indicating good model fit.
276	The calibration plot (Figure 4) revealed acceptable to good calibration over the range of
277	predicted probabilities. The Brier score was 0.077, indicating solid performance.

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278 Internal validation prognostic model chronification neck pain

The bootstrap validation yielded a shrinkage factor of 0.83, which was then used to multiply the regression coefficients by. The resulting model, including re-estimated intercept are in Table 2. The AUC after correction for optimism was 0.83. The optimism-corrected Nagelkerke's R² was 0.24. The intermezzo section highlights a detailed patient profile to clarify the applicability and interpretation of our findings in a practical context. Supplemental figure presents an interactive visualization depicting the varied pain trajectories among participants within our cohort, alongside the linear predictor and the probabilities of chronification derived from our multivariable prognostic model. This visualization illustrates the complexity and variability of pain progression over time. For a comprehensive visualization of all participants, see the web application: https://rstudio-connect.hu.nl/painr-app/. Additionally, an intermezzo Tez oni

	Regression coefficient after shrinkage	Odds Ratio (95% Confidence Interval)	P-value					
Intercept	-5.782							
Sex (female)	0.468	1.76 (0.90 - 3.61)	0.107					
Pain intensity at baseline (0-10)	0.227	1.32 (1.08 - 1.62)	0.008 **	Work status -		•		_
Reported pain in different body regions (no/yes)	0.734	2.43 (1.19 - 5.35)	0.020 *	Pain in different body regions				
No headache(s) <i>(reference)</i> Headache(s) since the neck pain Headache(s) before the neck pain	0.726 -0.070	2.41 (1.21 - 5.03) 0.92 (0.27 - 2.77)	0.015 *	Self-modify work posture	•			
Potential to self-modify posture (reference) Neutral or impossible	0.384 1.311	1.59 (0.71 - 3.43) 4.87 (2.29 - 10.43)	0.247 <0.001 ***	Pain Intensity – Duration beliefs – Self-efficacy –	•			
Not working Illness beliefs about recovery Duration (0–10)	0.184	1.25 (1.11 - 1.42)	<0.001 ***	Concerns Distress				
Illness beliefs about recovery Concerned (0-10)	0.108	1.14 (0.99 - 1.32)	0.075	Headache(s) before the neck pain				
Treatment beliefs (0–10)	-0.204	0.78 (0.67 - 0.92)	0.003 **	Treatment beliefs 🗕 🛛 👴				
Distress (0–21)	0.083	1.11 (1.03 - 1.19)	0.006 **					
Illness beliefs about pain identity (0-10)	-0.142	0.84 (0.73 - 0.97)	0.016 *	0.0	2.5	5.0	7.5	10.0 0
Self-efficacy (0-12)	0.109	1.14 (0.99 - 1.34)	0.086					

Figure 3 Adjusted multivariable logistic regression model

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297 Intermezzo

The patient (participant 110), a male, describes his neck pain intensity as 6 on the Numeric Pain Rating Scale (NPRS) and reports also low back pain. Since the onset of neck pain, he has also developed headaches, which were not present before the neck pain. Despite being employed, he finds it impossible to modify his posture during work. He anticipates the duration of his symptoms to be quite long, assessing it at 9 out of 10. Despite this, his concern for his condition is relatively minimal, with a score of 2 out of 10. His confidence in the therapy is high, rated at 8 on a 0-10 scale. Stress is absent in his case, evidenced by a score of 0 out of 21. While he admits to only a moderate understanding of his pain, scoring a 6 out of 10, he shows a high level of self-efficacy, achieving a full score of 12 on a 0-12 scale.

305 The patient (participant 914), a female, reports experiencing a pain intensity level of 6 on the Numeric Pain Rating Scale 306 (NPRS). She notes pain in other regions of her body as well. Since developing neck pain, she has also begun to experience 307 headaches, which she did not have prior to the neck pain. Cur- rently, she is not employed. She anticipates her symptoms 308 will persist, rating the anticipated duration as 10 on a scale from 0 to 10, indicating a long-term expectation of symptoms. 309 She expresses moderate concern about her neck pain, with a concern level of 5 on a 0-10 scale. Her confidence in the 310 effectiveness of her therapy is also moderate, rated a 5 on a 0-10 scale. She reports experiencing a moderate level of stress, 311 scoring 12 on a 0-21 scale. Her self-reported under- standing of her pain is 6 on a 0-10 scale, and scores a moderate self-312 efficacy, with a score of 6 on a 0-12 scale. 313

314 Linear predictor (LP)

The linear predictor (LP) is given by:

316	LP = -5.782
317	+ (0.468 ×sex[female = 1])
318	+ (0.227 × pain intensity)
319	+ (0.734 × pain in different body regions)
320	+ (0.726 × headache(s) since the neck pain)
321	-(0.070 ×headache(s) before the neck pain)
322	+ (0.384 × potential to self-modify posture at work)
323	+ (1.311 × work status)
324	+ (0.184 ×duration beliefs)
325	+ (0.108 × concerns)
326	-(0.204 ×treatment beliefs)
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5	327	+ (0.083 × distress)
6	328	-(0.142 ×identity beliefs)
7	329	+ (0.109 ×self-efficacy)
7	330	
8	331	
9	332	Probability of chronicity
10	333	Desk-billion of the existence
11	554	
12	335	
13	336	Probability of chronicity = $\frac{1 + e^{LP}}{1 + e^{LP}}$
14	337	
15	220	
16	550	Participant 110
17	339	Linear predictor (LP) calculation for patient X yields $LP = -1.88$, resulting in:
18	240	
19	340 371	$\mathbf{Probability of chronicity} = \frac{1}{1} = 13.2\%$
20	341	$\frac{1}{1 + e^{1.88}}$
21	342	
27	242	
22	343	Participant 914
23	344	Linear predictor (LP) calculation for patient X yields LP = 0.98, resulting in:
24	345	
25	346	Probability of chronicity =
26	347	$1 + e^{-0.98}$
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352 Discussion

353	In this prospective cohort study, we developed and internally validated a prognostic model for
354	predicting the chronification of (sub) acute non-specific neck pain in patients presenting to primary
355	care physiotherapy practices. The internal validated prognostic model demonstrates good prognostic
356	performance, underscored by an optimism-corrected AUC of 0.83. The calibration indicates a solid
357	performance, as indicated by the calibration curve, alongside a commendable Brier score. The
358	Hosmer-Lemeshow test, with a p-value of 0.717, affirms a good model fit. Nonetheless, the model's
359	corrected R ² of 0.24 suggests that the model provides a meaningful but limited explanation of the
360	probability distribution of the outcome. We found several individual significant associations between
361	non- and modifiable factors and the chronification of pain. The model comprising twelve variables,
362	four non-modifiable and eight potentially modifiable by physiotherapists. The non-modifiable factors
363	include sex, reported pain in different body regions, longer existing headache, and employment
364	status (not working). Potentially modifiable factors encompass baseline pain intensity, self-efficacy,
365	headache onset concurrent with the neck pain, the ability to self-modify posture at work, illness
366	beliefs regarding recovery (including concerns and expected duration), and beliefs about neck pain
367	identity and treatment.
367	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several
367 368 369	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several common factors emerge, including age, work status, reported pain in different body regions
367 368 369 370	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several common factors emerge, including age, work status, reported pain in different body regions (headache included), baseline pain identity, and self-efficacy.(43)(44)(45)(46)(47) However, in our
367 368 369 370 371	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several common factors emerge, including age, work status, reported pain in different body regions (headache included), baseline pain identity, and self-efficacy.(43)(44)(45)(46)(47) However, in our study, a higher score on the Pain Self-Efficacy Questionnaire 2-item version was associated with a
367 368 369 370 371 372	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several common factors emerge, including age, work status, reported pain in different body regions (headache included), baseline pain identity, and self-efficacy.(43)(44)(45)(46)(47) However, in our study, a higher score on the Pain Self-Efficacy Questionnaire 2-item version was associated with a higher odds of chronic neck pain. Notably, this association was characterized by a low regression
367 368 369 370 371 372 373	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several common factors emerge, including age, work status, reported pain in different body regions (headache included), baseline pain identity, and self-efficacy.(43)(44)(45)(46)(47) However, in our study, a higher score on the Pain Self-Efficacy Questionnaire 2-item version was associated with a higher odds of chronic neck pain. Notably, this association was characterized by a low regression coefficient and OR, and was also not significant with a small Cl.
 367 368 369 370 371 372 373 374 	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several common factors emerge, including age, work status, reported pain in different body regions (headache included), baseline pain identity, and self-efficacy.(43)(44)(45)(46)(47) However, in our study, a higher score on the Pain Self-Efficacy Questionnaire 2-item version was associated with a higher odds of chronic neck pain. Notably, this association was characterized by a low regression coefficient and OR, and was also not significant with a small CI.
 367 368 369 370 371 372 373 374 375 	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several common factors emerge, including age, work status, reported pain in different body regions (headache included), baseline pain identity, and self-efficacy.(43)(44)(45)(46)(47) However, in our study, a higher score on the Pain Self-Efficacy Questionnaire 2-item version was associated with a higher odds of chronic neck pain. Notably, this association was characterized by a low regression coefficient and OR, and was also not significant with a small Cl. Our model incorporated four illness perception factors: beliefs about recovery (including concerns and duration), identity, and treatment beliefs. Longitudinal studies on low back pain have vielded
 367 368 369 370 371 372 373 374 375 376 	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several common factors emerge, including age, work status, reported pain in different body regions (headache included), baseline pain identity, and self-efficacy.(43)(44)(45)(46)(47) However, in our study, a higher score on the Pain Self-Efficacy Questionnaire 2-item version was associated with a higher odds of chronic neck pain. Notably, this association was characterized by a low regression coefficient and OR, and was also not significant with a small Cl. Our model incorporated four illness perception factors: beliefs about recovery (including concerns and duration), identity, and treatment beliefs. Longitudinal studies on low back pain have yielded similar findings, illustrating individual associations between illness beliefs (e.g., duration and
 367 368 369 370 371 372 373 374 375 376 	identity and treatment. When comparing our model with existing prognostic studies in musculoskeletal pain, several common factors emerge, including age, work status, reported pain in different body regions (headache included), baseline pain identity, and self-efficacy.(43)(44)(45)(46)(47) However, in our study, a higher score on the Pain Self-Efficacy Questionnaire 2-item version was associated with a higher odds of chronic neck pain. Notably, this association was characterized by a low regression coefficient and OR, and was also not significant with a small Cl. Our model incorporated four illness perception factors: beliefs about recovery (including concerns and duration), identity, and treatment beliefs. Longitudinal studies on low back pain have yielded similar findings, illustrating individual associations between illness beliefs (e.g., duration and

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377	treatment beliefs) and negative clinical outcomes over various time periods.(48)(49)(50) In
378	prognostic multivariable models, the added prognostic value of illness perceptions varies.(50)(51)
379	However, models developed and externally validated for neck pain often excluded illness beliefs
380	from their set of candidate prognostic factors.(52)(53)(54)(11) Recent research has shown that
381	modifying illness beliefs related to identity and concerns can mediate outcomes, specifically disability
382	and pain, within primary care physiotherapy practices.(55) Consequently, further research into the
383	modification of illness perception factors and their influence on the development of chronic pain, is
384	imperative. Such studies are crucial to ascertain if physiotherapy interventions can effectively alter
385	patients' outcomes.
386	Furthermore, it is important to note that several psychological factors, such as depression,
387	kinesiophobia, catastrophizing, and poor coping skills, are commonly recognized as associated with
388	and prognostic for chronic pain.(56)(13) These factors did not retain in our final prognostic model.
389	Although these factors showed an association in our univariable analysis, they did not improve the
390	predictive accuracy of our model. Notably, our baseline measurements indicated a distinctly non-

391 normal distribution for these psychological factors, contrasting with studies in chronic pain patients

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392 where these factors are more prevalent. (56) Despite their exclusion from our final model, screening

393 for these factors during the initial pain phase and ongoing monitoring during recovery remain

394 important. This is particularly noteworthy considering the body of evidence indicating that

395 treatments targeting psychological factors, such as catastrophizing, depression, and distress, have

396 shown favorable outcomes when addressed by healthcare providers. However, it is essential to

397 highlight that these studies have primarily focused on patients with chronic musculoskeletal

398 pain.(57)(58)(59)(60)(61) In contrast, it is important to note that the majority of studies involving

- 399 patients with (sub)acute musculoskeletal have primarily focused on pain and disability as outcomes,
- 400 rather than exploring changes in psychological factors as moderators or as outcome

401 variables.(62)(63)(64)

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402	Nevertheless, it remains important for primary care physiotherapists to feel competent and capable
403	of effectively addressing these psychological factors and illness beliefs. Unfortunately, the integration
404	of the biopsychosocial model into the primary care physiotherapeutic management of
405	musculoskeletal disorders has to date not been entirely successful.(65)(66)
406	The incidence of chronic pain in our participants 6 months after first presentation at a
407	physiotherapist with (sub)acute non-specific and non-traumatic neck pain differed from our
408	systematic review findings. In our preliminary sample size calculation, a 45% chronicity rate for neck
409	pain was assumed. This rate was calculated by dividing the number of patients by the number of
410	non-recovery of pain cases.(11) This disparity can be attributed to our definition of chronic pain and
411	measurement approach. Unlike the single time point follow-up assessments (e.g. 3, 6, or 12 months)
412	with a specific pain score threshold used in most studies(67), including those in our review(11), our
413	study used a more comprehensive method. We assessed pain intensity at 6 weeks, 3 months, and 6
414	months post-baseline, requiring NPRS score of \geq 3 at each time point to classify them as having
415	chronic pain.(14) This approach provides a more precise representation of chronic pain as a
416	continuous experience. By using this methodology, we excluded the recurrent pain group with pain-
417	free or mild time periods, diverging from the International Classification of Diseased 11 th Revision
418	(ICD-11) broader definition of chronic pain that includes recurrent pain.(19) We hypothesize that
419	differentiating between continuous and recurrent pain will lead to a more effective prognostic
420	model, acknowledging the distinct pain experiences of these groups.
421	The ICD 11 characterizes chronic primary musculoskeletal pain as a disease that is assembly and by
421	significant emotional distance (such as any interview engage (functuation or depressed mood) or functional
422	significant emotional distress (such as anxiety, anger/frustration, or depressed mood) or functional
423	disability, which includes interference with daily life activities and reduced participation in social
424	roles. This delineation underpins the rationale for distinguishing between mild and moderate pain,
425	with a proposed threshold of \geq 3 to define the latter category. This distinction is based on the
426	observation that mild pain typically does not entail marked emotional distress or functional

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427	disability.(68)(69) However, literature indicates that establishing a definitive cut-off point for mild
428	and moderate pain, particularly in terms of pain-related interference with functioning and emotions,
429	is complex.(69)(70)(71)
430	The ICD-11 further recommends the assessment of patient-reported pain using an 11-point scale,
431	focusing on pain intensity and its interference with psychological and physical functioning in daily life
432	for both research purposes and a comprehensive understanding of the patient's pain experience.(19)
433	Nevertheless, for the purposes of comparison and updating various prognostic models, the adoption
434	of a standardized international threshold for chronic pain is recommended.
435	Limitations
436	The calibration curve suggests substantial overestimation of higher risks; this estimation was based
437	on only a few patients, as most had a relatively low estimated risk of chronification. This potential
438	overestimation is, nevertheless, unlikely to remain visible in an external validation with enough
439	participants at high risk.
440	In the initial sample size calculation, we assumed a 45% incidence of chronic pain, based on our
441	systematic review.(11) This calculation allowed for 26 candidate prognostic variables among a cohort
442	of 598 participants.(34) However, this study yielded a lower-than-expected incidence of chronic pain,
443	with only 10% of participants, indicting an underpowered and potentially inadequate sample size.
444	However, the increased risk of overfitting and the potential for overly optimistic model performance
445	seems to be minimal, as suggested by our internal validation analysis which revealed a shrinkage
446	factor close to 1.
447	Clinical application and further research
448	The development of this prognostic model has identified several potential modifiable factors. In
449	clinical practice, a physiotherapist can utilize this model to gain insight an individual patient's
450	probability of experiencing chronic neck pain. Furthermore, it can be beneficial to assess and

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intervene on the modifiable factors in our model. However, we must be aware that although they have been validated for their prognostic value in our 1b prognostic study, it does not mean that modifying these factors will necessarily reduce the risk of developing chronicity. It is highly recommended to evaluate the performance of our model in an external validation study. If the model is found adequate, a prognostic model impact study is required, to quantify the effect on

physiotherapist decision making in patients with NSNP (TRIPOD statement).(16)

Conclusion

This model has the potential to obtain a valid prognosis for chronification of non-specific neck pain and included mostly potential modifiable factors for physiotherapy practice. External validation of

this model is recommended.

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2	160	
3	462	Supplementary information
4	463	
5	464	Acknowledgements
6	465	The authors would like to express their gratitude to all the physiotherapists who facilitated the
/	466	inclusion of patients, and specifically to all the patients who participated in this study.
8	467	
9	468	Contributors
10	469	All authors materially participated in this research. Their main contribution to the manuscript is
11	470	described below:
12	471	Miss Martine Verwoerd: substantial contribution to study conception, study design, data analysis,
13	472	data interpretation, drafting and revising the manuscript, and significant involvement in
14 15	473	conceptualizing the web application and GitHub repository.
15	474	dr. Harriet Wittink: substantial contribution to study conception, study design, data analysis, data
10	475	interpretation, drafting and revising the manuscript;
17	476	dr. Francois Maissan: contribution to study conception, study design, data interpretation and revising
10	477	the manuscript;
20	478	dr. Sander van Kuijk: substantial contribution to the study design, data analysis and data
20	479	interpretation, drafting and revising the manuscript.
21	480	dr. Marc Teunis: substantial contribution to the data analysis and data interpretation, revising the
22	481	manuscript, and key architect of the web application and GitHub repository:
23	482	Prof. dr. Rob J.E.M. Smeets: contribution to study conception, data analysis, data interpretation.
25	483	drafting and revising the manuscript.
25	484	
20	485	Data Availability
28	405	Technical appendix statistical code, and dataset available from the Github repository:
29	480	https://github.com/uashogeschoolutrecht/painr DOI: available upon accentance
30	407	<u>inteps.//github.com/uashogeschooldtreent/pain</u> _DOI. available upon acceptance.
31	400	Tunding
32	489	This work was supported by the Institute of Movement Studies and partly by the Utresht University
33	490	This work was supported by the institute of Movement Studies and party by the Otrecht Oniversity
34	491	Of Applied Sciences research voucher. The funding concerns an internal promotion voucher of the
35	492	University of Applies Sciences. The funders had no role in the study design, data collection, analysis,
36	493	decision to publish, or manuscript preparation.
37	494	
38	495	Competing interests:
39	496	The authors have declared that no competing interests exist.
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721 Appendix 1. TRIPOD Checklist Prediction Model Development and Validation

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Section/Topic	1	Checklist Item	Page
Title and abstract	1		1
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction	1		
		Explain the medical context (including whether diagnostic or prognostic) and	
Background and	За	rationale for developing or validating the multivariable prediction model, including references to existing models.	5-6
objectives	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	5-6
Methods			1
Course of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
Source of data	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7-8
Participants	5b	Describe eligibility criteria for participants.	7-8
	5c	Give details of treatments received, if relevant.	Not applicable
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	Report any actions to blind assessment of the outcome to be predicted.	7-8
Dradictore	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	8-10
Fledictors	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	7-8
Sample size	8	Explain how the study size was arrived at.	10
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	10-11
	10a	Describe how predictors were handled in the analyses.	10-11
Statistical	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	10-11
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	10-11
Risk groups	11	Provide details on how risk groups were created, if done.	Not applicable
Results			
Darticipanto	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	12-16
Farticipants	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	12-16
N a dal	14a	Specify the number of participants and outcome events in each analysis.	13
development	14b	If done, report the unadjusted association between each candidate predictor and outcome.	17-18
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	17-20
	15b	Explain how to the use the prediction model.	23-24
Model performance	16	Report performance measures (with CIs) for the prediction model.	19-22
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	28
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	25-28
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Supplementary

information

Funding

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		l similar technologies.

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6	728	https://github.com/uashogeschoolutrecht/painr
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Interactive Visualization of Patients Pain Trajectories and Chronicity Probability

For the visualization of all participants, see: <u>https://rstudio-connect.hu.nl/painr-app</u>/. In this visualization, "FALSE" indicates no chronic pain (pain < 3 at 6 weeks, 3 months, and 6 months), while "TRUE" denotes chronic pain (pain \ge 3 at all time-points: 6 weeks, 3 months, and 6 months). The X-axis represents the pain score, measured using the Numerical Pain Rating Scale (0-10), and the Y-axis shows the cumulative number of days after the baseline measurement. "Patient_code" is a unique identifier for each patient. "LP" stands for linear predictor, "Prob" represents the probability of chronicity, and "Perc" indicates the percentual probability of chronicity. The bar graph and various values per variable illustrate the regression coefficient, multiplied by the patient data at baseline, across different variables from the prognostic model.

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TRIPOD Checklist Prediction Model Development and Validation

Development and internal validation of a multivariable prognostic model for chronification of nonspecific neck pain in physiotherapy practice.

Section/Topic	<u>ו</u>		Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
		Explain the medical context (including whether diagnostic or prognostic) and	
Background and	3a	rationale for developing or validating the multivariable prediction model, including references to existing models.	5-6
objectives	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	5-6
Methods			I
		Describe the study design or source of data (e.g., randomized trial, cohort, or	_
Source of data	4a	registry data), separately for the development and validation data sets, if applicable.	7
	4b	applicable, end of follow-up.	7
	5a	Specify key elements of the study setting (e.g., primary care, secondary care,	7-8
Participants		general population) including number and location of centres.	
	50	Describe eligibility criteria for participants.	/-8
	5c	Give details of treatments received, if relevant.	Not applica
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	Report any actions to blind assessment of the outcome to be predicted.	7-8
Duodiatous	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	8-10
Predictors	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	7-8
Sample size	8	Explain how the study size was arrived at.	10
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method	10-11
	10a	Describe how predictors were handled in the analyses	10-11
Statistical	10b	Specify type of model, all model-building procedures (including any predictor selection) and method for internal validation	10-11
analysis methods	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models	10-11
Pick groups	11	Provide details on how risk groups were created if done	Not applic
Risk groups	11		
Results		Describe the flow of participants through the study, including the number of	
	13a	participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	12-16
Participants	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome	12-16
	14a	Specify the number of participants and outcome events in each analysis	12
Model development	14b	If done, report the unadjusted association between each candidate predictor and	17-18
Model	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time	17-20
specification	156	point).	22.24
Madal	120		23-24
performance	16	Report performance measures (with CIs) for the prediction model.	19-22
Discussion			1
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	28
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and	25-28
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3	Implications	20	Discuss the potential clinical use of the model and implications for future research.	28-29
4	Other information			
5	Supplementary	21	Provide information about the availability of supplementary resources, such as study	30
6 7	information		protocol, Web calculator, and data sets.	
/ Q	Funding	22	Give the source of funding and the role of the funders for the present study.	30
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BMJ Open

Development and internal validation of a multivariable prognostic model to predict chronic pain after a new episode of non-specific idiopathic, non-traumatic neck pain in physiotherapy primary care practice.

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-086683.R1
Article Type:	Original research
Date Submitted by the Author:	11-Jul-2024
Complete List of Authors:	Verwoerd, Martine; HU University of Applied Sciences Utrecht, Institute of Movement Studies Wittink, Harriët ; HU University of Applied Sciences Utrecht Maissan, Francois ; HU University of Applied Sciences Utrecht, Movement studies Teunis, Marc; HU University of Applied Sciences Utrecht van Kuijk, Sander; Maastricht Universitair Medisch Centrum+, Clinical Epidemiology and Medical Technology Assessment Smeets, Rob; Maastricht University, Rehabilitation medicine; CIR, Revalidatie
Primary Subject Heading :	Evidence based practice
Secondary Subject Heading:	Mental health
Keywords:	REHABILITATION MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, PAIN MANAGEMENT, Prognosis

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1	Title
2	Development and internal validation of a multivariable prognostic model to predict chronic
3	pain after a new episode of non-specific idiopathic, non-traumatic neck pain in physiotherapy
4	primary care practice.
5	
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18	*Corresponding author
19	E-mail: <u>martine.verwoerd@hu.nl</u> (MV)
	1

3 4								
5	20	Abstract						
7 8	21	Objective: To develop and internally validate a prognostic model to predict chronic pain after a						
9 10	22	new episode of acute- or subacute nonspecific idiopathic, non-traumatic neck pain in patients						
11 12 13	23	presenting to physiotherapy primary care, emphasizing modifiable biomedical, psychological,						
14 15	24	and social factors.						
16 17 19	25	Design: A prospective cohort study with a 6-month follow-up between January 2020 and						
19 20	26	March 2023.						
21 22 23	27	Setting: 30 physiotherapy primary care practices.						
24 25 26	28	Participants: Patients with a new presentation of nonspecific idiopathic, non-traumatic neck						
27 28	29	pain, with a duration lasting no longer than 12 weeks from onset.						
29 30 31	30	Baseline measures: Candidate prognostic variables collected from participants included age						
32 33	31	and sex, neck pain symptoms, work-related factors, general factors, psychological and						
34 35	32	behavioural factors, and the remaining factors: therapeutic relation and healthcare provider						
36 37 38	33	attitude.						
39 40	34	Outcome measures: Pain intensity at 6 weeks, 3 months, and 6 months on a Numeric Pain						
41 42 43	35	Rating Scale (NPRS) after inclusion. A NPRS score of ≥3 at each time point was used to define						
44 45	36	chronic neck pain.						
46 47 48	37	Results: Sixty-two (10%) of the 603 participants developed chronic neck pain. The prognostic						
49 50	38	factors in the final model were sex, pain intensity, reported pain in different body regions,						
51 52	39	headache since and before the neck pain, posture during work, employment status, illness						
53 54 55 56	40	beliefs about pain identity and recovery, treatment beliefs, distress, and self-efficacy. The 2						
57 58 59								

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41	model demonstrated an optimism-corrected Area Under the Curve (AUC) of 0.83 and a
42	corrected R ² of 0.24. Calibration was deemed acceptable to good, as indicated by the
43	calibration curve. The Hosmer-Lemeshow test yielded a p-value of 0.7167, indicating a good
44	model fit.
45	Conclusion: This model has the potential to obtain a valid prognosis for developing chronic pain
46	after a new episode of acute—and subacute nonspecific idiopathic, non-traumatic neck pain. It
47	includes mostly potentially modifiable factors for physiotherapy practice. External validation of
48	this model is recommended.
49	Key words: neck pain, prognostic model, modifiable factors, chronic pain
	3

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5 4		
5	50	Strengths and limitations of this study
6 7		
7 8	E 1	Novel approach to determine an accurate cample size for prognettic model
9	21	• Nover approach to determine an accurate sample size for prognostic moder
10	52	development, mitigating overfitting.
11		
13	53	 Inclusion of biomedical, psychological, and social prognostic factors which are
14	- 4	
15 16	54	potentially modifiable by a physiotherapist.
17	55	• Utilization of three follow-up time points for chronic pain outcome assessment.
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57 Introduction

Neck pain is a widespread and disabling health condition significantly impacting public health.(1–3) It is ranked third in terms of years lived with disability in non-fatal diseases, with high costs due to extended work absence and healthcare utilization.(4) Chronic neck pain is particularly costly(5), and the prevalence has increased by 21% from 2005 to 2015, affecting approximately 358 million people worldwide.(6) The estimated global number of neck pain cases is projected to be 269 million (219–322) by 2050, an increase of 32.5% (23.9–42.3) from 2020 to 2050.(7)

Physiotherapy is a common first-line treatment; however, its effectiveness in patients with
chronic pain is often only moderate.(8–10) Consequently, identifying prognostic factors to
predict chronic pain is a top priority for neck pain research and for clinical care.(11) By
identifying these prognostic factors, especially modifiable factors, physiotherapists can make
more informed decisions, potentially target modifiable factors, and prevent the development
of chronic idiopathic neck pain.

The existing literature on prognostic models shows a low performance in predicting chronic neck pain.(12) Moreover, the external validity of current prognostic models in terms of pain and recovery outcomes have not been proven in patients with acute- and subacute neck pain.(13) This may be attributed to the inclusion of heterogeneous groups of patients for the development of these prognostic models, characterized by varying pain duration (acute, subacute < 12 weeks and chronic > 3 months), clinical symptoms and prognosis. Furthermore, the varying definitions of the outcome, including persistent and/or recurrent pain groups, contribute to the low performance of these models. Additionally, much of the prognostic

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research has predominantly focused on non-modifiable factors, such as age, pain duration and
sex, neglecting potentially modifiable factors.(12) Incorporating modifiable factors has the
potential to better tailor interventions to individual patients, which could enhance the model's
applicability and relevance in clinical practice.

It is known that biomedical, psychological, and social factors provide a comprehensive understanding of the neurophysiological changes involved in developing chronic pain.(14) Consequently, there is a compelling need for a biopsychosocial approach that specifically focuses on modifiable prognostic factors to predict chronic pain after a new episode of nonspecific idiopathic, non-traumatic neck pain. This study aimed to (1) identify which modifiable factors are independent prognostic factors of the development of chronic neck pain in patients with acute- and subacute neck pain, and (2) to develop and internally validate a model to predict chronic pain.

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91 Methods

92 The methods of this study have been extensively described in the study protocol.(15) Briefly
93 summarized, the methods were as follows:

94 Study design

- 95 The present study is a prospective longitudinal cohort study that focuses on modifiable
- 96 prognostic factors and follows the guidelines of the PROGRESS framework and TRIPOD
- 97 statement type 1b.(16,17) This study adheres to the specific statistical recommendations for
- 98 Type 3 prognostic model research.(16) The findings are reported according to the TRIPOD
- 99 statement to ensure transparent reporting of the multivariable prediction model for individual

100 prognosis (see Appendix 1).(17)

101 Study setting

102 Participants were recruited from 30 Dutch physiotherapy primary care practices by 94

103 physiotherapists between January 26, 2020, and August 31, 2022. The study was completed in

104 March 2023 (including reminders and time for response).

105 Ethical approval

106 The Medical Research Ethics Committee Utrecht declared that the Medical Research Involving

107 Human Subjects Act (WMO) does not apply to this study (protocol number 19-766/C).

- 108 Participants who gave informed consent were assigned a unique code to allow anonymous
- data collection, facilitated through the secure Formdesk data transfer system.(18)

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5	111	Patient and public involvement statement
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8	112	None
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11	113	Participants
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14	114	Patients were approached if they presented in one of the participating physiotherapy practices
15		
16	115	with a new onicode of acute or subacute noncredific idionathic, non-traumatic neck pain
17	112	with a new episode of acute of subacute nonspecific holpatilic, non-tradinatic neck pain.
18		
19	116	Patients were included if they met the following criteria: age 18 years or older, a new
20		
21	117	presentation of neck pain no longer than 12 weeks after onset and the patient indicated on the
22		
23	118	body diagram that he/she experienced regional neck pain. If the patient had a previous episode
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25	119	of neck pain, the patient had to be relatively free from symptoms on the Numerical Pain Rating
20	110	
27	120	Scale (NIDDS of (2) for at least three menths prior to the present episode of pack poin. The
28	120	scale (NPRS of <3) for at least three months prior to the present episode of neck pain. The
29		
50 21	121	exclusion criteria were: neck pain surgery in the past, cervical spine radiculopathy assessed
וכ כי		
52 22	122	with the Upper Limb Neurodynamic Test 1(19), widespread primary pain (ICD-11) (diffuse
27		
25	123	musculoskeletal pain in at least 4 of 5 body regions (e.g. shoulder or upper arm, wrist or hand,
36		
37	124	pelvis, or ankle or food) and in at least three or more body quadrants (as defined by upper-
38	121	perior of unite of foody and in acted to there of more body quadrants (as defined by apper
30	125	lower (left right side of the hady) and avial skaleton (neck back sheet and abdomen)(20) pain
40	125	lower / left-right side of the body) and axial skeleton (neck, back, chest and abdomen)(20), pain
40 41		
47	126	not caused by musculoskeletal origin (not located in the muscles, bones, joints, or
43		
43	127	tendons)(21), and inability to read or understand the Dutch language.
45		
46		
47	128	Baseline and follow-up procedure
48	120	
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50	129	During the first consultation, the physiotherapist informed eligible patients about the study
51		
52	120	nurnose and expectations. Patients who verbally indicated they wanted to participate in the
53	10	purpose and expectations. Fatients who verbany indicated they wanted to participate in the
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4 5 6	131	study, signed an informed consent before completing the initial digital questionnaire at						
7 8	132	baseline (T0). Follow-up questionnaires were sent via email at six weeks (T1), three months						
9 10	133	(T2), and six months (T3), taking 20-40 minutes to complete. Participants were reminded to						
11 12 13	134	complete the questionnaires via email or telephone contact by their treating physiotherapist.						
14 15 16	135	Outcome						
17 18	136	The NPRS was used to quantify the presence of chronic pain. If pain was present, defined as an						
20 21	137	NPRS ≥3, at all measurement moments (i.e. six weeks, three months, and six months), it was						
22 23	138	classified as chronic.(15,22)						
24 25 26	139	Candidate Prognostic factors						
27 28 29	140	We included candidate prognostic factors to predict chronic pain or non-recovery identified in						
30 31	141	a previous systematic review and by neck pain experts in a Delphi study with >70% consensus						
32 33	142	n the first round.(12,23) Details on candidate prognostic factors and their measurement are						
34 35 36 27	143	provided in our study protocol.(12)						
37 38 39	144	- Patient characteristics: sex and age.						
40 41	145	- Symptoms: pain intensity at baseline measured with the NPRS, duration of the acute or						
42 43	146	subacute neck pain in weeks, reported pain in different body regions (yes/no),						
44 45	147	accompanying headache (since the onset of neck pain and headache before the neck						
46 47 48	148	pain), and disability measured with the Pain Disability Index, where the sum score was						
49 50	149	divided by the entered items (PDI).(24)						
51 52	150	- Work-related factors: happiness at work, job satisfaction, and potential to self-modify						
53 54 55 56	151	posture measured with a self-reported question. 9						
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5 6	152	- General factors: the lifestyle factors: smoking, alcohol, length and weight (body mass					
7 8	153	index), sleep quality measured with an adjusted sleep quality question from the Neck					
9 10 11	154	Disability Index (NDI)(23,25), and physical activity measured by meeting the activity					
12 13	155	level according to the Dutch Healthy Exercise Norm (Yes/No).(26)					
14 15	156	- Psychological and behavioral factors: Illness perceptions were assessed using the					
16 17	157	Dutch version of the Brief Illness Perception Questionnaire (IPQ-DLV).(27)					
18 19 20	158	Catastrophizing was measured with the short version of the Pain Catastrophizing Scale					
20 21 22	159	(PCS).(28) Depression and distress were assessed with the 21-item version of the					
23 24	160	Depression Anxiety Stress Scale (DASS-21).(29) Kinesiophobia was measured using the					
25 26	161	11-item version of the Tampa Scale for Kinesiophobia (TSK).(30) Coping strategies were					
27 28	162	evaluated with the Pain Coping Inventory (PCI).(31,32) Hypervigilance was assessed					
29 30 31	163	using the Pain Vigilance and Awareness Questionnaire (PVAQ)(33), and self-efficacy in					
32 33	164	managing pain was measured with the 2-item version of the Pain Self-Efficacy					
34 35	165	Questionnaire.(34)					
36 37	166	- The remaining factors included, first, the 'therapeutic relationship', assessed through					
38 39 40	167	the self-reported question: 'How much trust do you have in your healthcare					
40 41 42	168	provider/physiotherapist?'. Second, the 'therapist's orientation', which could be either					
43 44	169	biomedical or biopsychosocial. The authors categorized this orientation based on open-					
45 46 47	170	ended and multiple-choice questions about neck pain cases.(15)					
48 49 50	171	Sample size					
51 52	172	To ensure a sufficient sample size to reduce the effect of overfitting, the minimum number of					
53 54 55	173	events per candidate prognostic factor was calculated as recommended by Riley et al. 1					
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> 2019.(35) The expected value of the Cox-Snell R-squared of the new model was estimated at 0.23 (23,36,37), and the estimated outcome event rate at 45%.(12) The study considered 26 candidate prognostic factors, including four non-modifiable and 22 potentially modifiable prognostic factors. The a priori sample size calculation suggested a minimum of 598 participants for the prognostic model. Statistical analysis methods and missing data This study followed the Prognosis Research Strategy (PROGRESS) framework type 3 research.(16) The Statistical software IBM SPSS (version 27) and R (version 4.2.2) were used for the statistical analysis. (38,39) For the analysis, we extensively utilized the following R packages: tidyverse, MASS, pROC and Mice.(40–43) The complete R script used in this study can be found on GitHub at https://github.com/uashogeschoolutrecht/painr (see Appendix 2 the table of contents).(44) We used multiple imputation with fully conditional specification to impute incomplete records, assuming data to be at least missing at random (MAR).(45) Predictive mean matching was used to impute continuous variables, and logistic regression for categorical variables. After completing the data, the outcome variable (chronic pain) was determined for each participant. The factor 'healthcare provider orientation' exhibited significant missing data, which could not be imputed based on patient-specific information. As a result, we had to proceed with the available data during the subsequent analysis, even though a significant portion was missing.

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4	400									
6	193	The predictive performance of each candidate prognostic factor of chronic pain was estimated								
/ 8	194	using univariable logistic regression analysis. These analyses were not used to decide which								
9 10 11 12	195	prognostic factors would be included in the multivariable model.								
13 14	196	Before multivariable modeling, we computed the variance inflation factor (VIF) to assess								
15 16	197	multicollinearity. If this factor exceeded 10, the selection of candidate prognostic factors for								
17 18 19	198	modeling was guided by the clinical expertise of the authors of this study.								
20 21 22	199	All candidate prognostic factors were entered into the multivariable model. To make the model								
23 24	200	more concise and to identify the most significant prognostic factors, we applied backward								
25 26	201	elimination.								
27 28										
29 30	202	Model performance was quantified as it's discriminative ability, using the Area Under the								
31 32	203	receiver operating characteristic Curve (AUC), model calibration, using calibration plots and								
33 34	204	computing the Hosmer and Lemeshow goodness-of-fit test, and as model fit, using								
35 36 37	205	Nagelkerke's R ² .								
38 39	206	Bootstrap resampling with 1000 bootstrap samples was utilized for internal validation to								
40 41	207	calculate the optimism-corrected AUC and determine the shrinkage factor, thereby adjusting								
42 43	208	for overfitting by shrinking regression coefficients. After shrinking regression coefficients, we								
45 46 47	209	re-estimated the model intercept.								
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Results

A total of 2.567 patients underwent eligibility assessment across 30 physiotherapy practices in the Netherlands. Among these patients, 1.600 were excluded, primarily due to the fact they already had chronic pain (lasting >12 weeks with a NPRS \geq 3), cervical spine radiculopathy, or widespread pain. Additionally, 307 patients refused to participate, citing disinterest, scheduling conflicts, or stress at the time of invitation. Ultimately, 660 potential participants provided informed consent, however, 58 of them did not respond during the baseline measurement phase, resulting in the inclusion of 603 individuals in a period of 2.5 years (Figure 1). Among them, 62 participants (10%) developed chronic pain, while 541 participants experienced recovery from their pain.

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For the description of the participants' characteristics, including candidate prognostic factors, and the number of participants with missing data, see Table 1. We included 397 women and 206 men. The mean pain intensity at baseline was 5.9 (SD 1.9), and the mean disability was relatively low, with a score of 2.7 (SD 2.1) on a 0-7 scale. Of our 603 participants, 92 (15.3 %) did not work. We included these participants as not working in all the work-related factors in our multivariable analyses.

There was some loss to follow-up at various follow-up moments. However, only 78 participants
did not complete any follow-up measurement. At the 6-weeks measurement, 154 participants
failed to submit the required forms. This number changed to 224 at the 3-months follow-up,
and to 211 at the 6-month mark. The Little's MCAR test yielded a p-value greater than
0.05, supporting the appropriateness of multiple imputations.(45)
The interventions most frequently applied were (1) joint mobilization, manipulation, traction,
and nerve mobilization techniques, with an application rate of 85.4%, and (2) information and

advice, with an application rate of 86.7%. Exercise and massage were applied to 58.1% and

238 54.7% of the study population. For a detailed overview of the interventions applied across the

239 study population, see Appendix 3.

	Number (percent)	Mean (SD) Median (IQR)	Missing Count (percent)
Patients characteristics			
Sex			
1 = Male	206 (34.2)		0 (0)
2 = Female	397 (65.8)		
Age		44,5 (15.7)	1 (.2)
-		44,0 (31 - 56)	
Symptoms			P
Pain intensity at baseline (0-10)		5,9 (1.9)	0 (0)
Higher scores indicate a higher degree of pain.		6 (5 - 7)	cte
Duration of neck pain		4.5 (2.9)	0 (0)
Number of weeks		4 (2 - 6)	y y
Recurrent pain			1 (.2) 8
1 = No	198 (32.8)		
2 = Yes	404 (67)		rig
Reported pain in different body regions			4(.7)
1 = No	210 (34.8)		5
$2 = Y_{PS}$	389 (64 5)		CL CL
Accompanying headache	565 (61.5)		<u> </u>
$1 = N_0$	247 (41)		1 1 1 1 1 1 1 1 1 1
2 - Ves	281 (46 6)		ð
3 = 1 had headache(s) hefore the neck nain	70 (11 6)		
Disability (0.7)	/0 (11.0)	2 72 (2 1)	
Lisbor scores indicate higher interference of pain with daily		2.75(2.1)	
activity. The sum score divided by the entered items		2.5 (1.0 - 4.1)	ea
Mark related factors			- tec
work related factors			5
Work status			10 (1.7)
1 = Yes	501 (83.1)		
2 = No	92 (15.3)		ind
Education			16 (2.7)
0 = Low level of education	313 (51.9)		ata
1 = High level of eduction	274 (45.4)		3
Happiness at work			23 (3.8)
1 = Happy (ref)	376 (62.4)		ng
2 = Neutral or not happy	112 (18.6)		, >
3 = Not working	92 (19)		
Job satisfaction			21 (3.5)
1= Satisfied (ref)	404 (67)		j (e.e., ji
2 = Neutral or not satisfied	86 (14.3)		ģ
3 = Not working	92 (18.7)		an
Potential to self-modify posture			25 (4.2)
1 = Possible (ref)	372 (61.7)		n
2 = Neutral or impossible	114 (18.9)		lia
3 = Not working	92 (19.4)		
General factors	(echi
Dhusical astivity			0 (1 2)
Physical activity	210 (20 2)		× (1.3) G .
U = Actieving the Dutch Healthy Exercise Norm	219 (30.3)		es.
<i>I</i> = Not achieving the Dutch Healthy Exercise Norm	3/6 (62.3)		

Smoking

1 = No 2 = Yes

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528 (87.6)

72 (11.9)

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Alcohol			5 (.8)	
1 = No	129 (21.4)			
2 = Yes	469 (77.8)			
BMI		25.31 (4.3)		
		24.66 (22.5 – 27.7)		
Sleep quality			2 (.3)	
0 = No negative experience with sleeping	130 (21.6)			
1 = Negative experience with sleeping	471 (78.1)			
Psychological and behavior factors				
Catastrophizing (0–24)		4.58 (4.6)	3 (.5)	
Higher scores indicate more catastrophic thoughts		3(1-7)		j.
Illness beliefs about recovery (Duration 0-10)		4.13 (2.7)	10 (1.7)	
0 a verv short time– 10 forever Hiaher scores indicate a		3(2-6)		3
maladaptive illness perception				
Illness beliefs about recovery (Concerned 0-10)		3.96 (2.6)	8 (1.3)	
0 Not at all concerned– 10 extremely concerned Hiaher		4 (2 – 6)	- ()	:
scores indicate a maladaptive illness perception.		· · · /		
Treatment beliefs (0–10)		7.82 (1.9)	12 (2,0)	
0 not at all—10 extremely helpful		8 (7 - 9)	(,	
A lower score indicates a maladantive illness perception		0(, 3)		
Denression (0–21)		2 47 (3 3)	3 (5)	
Higher scores indicate a higher degree of depression		1(0-4)	5 (.5)	į
Kinesionhobia (11–44)			3 (5)	
Higher scores indicate a higher degree of kinesionhohig		15.5(3.2)	5 (.5)	-
Distross (0-21)		13(12-20)	2 (5)	
Higher scores indicate a higher degree of stress		(4.4(4.1))	5 (.5)	1
Coning		5 (1 - 7)	5 (9)	
0 - Passivo coning	120 (10 0)		5 (.8)	
1 - Active coping	120 (19.9)			
I – Active coping	478 (79.5)	<u>(11/22)</u>	14 (2 2)	;
$\frac{1}{10} \frac{1}{10} \frac$		0.11 (2.3)	14 (2.3)	1
lower seere indicates a maladantive illness percention		0 (5 - 8)		1
lower score malcales a maladaptive niness perception.		21.0 (11.4)	2 (5)	
Hypervigilance (0–80)		31.0 (11.4)	3 (.5)	
Higher scores indicate a higher degree of vignatice.		31 (23 - 38)	2 (2)	ÿ
Self-efficacy (U-12)		10.31 (2.3)	2 (.3)	
Higher scores indicate a higher degree of self-efficacy		11 (10 - 12)		
Remaining factors				
Fherapeutic relation (0-10)		8.79 (1.4)		ġ
0 no trust at all– 10 very much confidence.		9 (8 – 10)	10 (1.7)	
Health care provider attitude				1
1 = Biomedical	134 (22.2)		49 (8.1)*	
2 = Biopsychosocial	420 (69.7)			
We missed the attitude measurement for $1A$ of the	94 nhysiotherani	sts including a total of	49	
we missed the definition medsarement jor 14 0j the	s i priysiotrici upi.			
ationta				

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244 Univariable prognostic factors of development of chronic pain

245 The univariable analyses (see Figure 2) revealed significant positive associations between the 246 following candidate prognostic factors and chronic pain: being female, higher pain intensity at 247 baseline, longer duration of neck pain, experiencing pain in different body regions, onset of 248 headache since the neck pain began, higher disability scores, unemployment, higher scores on 249 catastrophizing, illness beliefs about recovery (concerned and duration), depression, distress, 250 and lower treatment beliefs. Some of these factors were identified with broad confidence 251 intervals (CI). For most factors not showing significant associations, the odds ratios (ORs) were s ,y mean. 252 close to one, indicating lack of a clinically meaningful association.

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25 26 27 28 29 30 31 32 33 34 35 36 37					Enseignement Superieur (<i>/</i> ing for uses related to text and data
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50 51 52 53 54 55 56 57 58 59 60			1		echnologies.

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262 Multivariable modeling

The inclusion of 'work status' as a category among the work-related prognostic factors resulted in multicollinearity within the following factors: happiness and satisfaction at work, and the ability to change posture during work. To mitigate this issue, we decided to include only the factor 'ability to change posture at work' in our final model. This decision was based on the distinct conceptual domain of this factor, which differs from the psychological construct already well-represented by the other included factors. The candidate prognostic factor 'work status' is thus also referred to the ability to change posture at work in the analysis. Following this adjustment, multicollinearity was no longer observed.

Several prognostic factors were identified from the multivariable logistic regression analysis. These included sex (female), higher pain intensity at baseline, reported pain in different body regions, headache since the onset of neck pain, headache(s) before the neck pain, an inability or neutral score on self-modify posture during work, not working, lower scores pain identity and treatment beliefs, higher scores in beliefs regarding recovery (duration and concerns), and higher scores on distress and self-efficacy. The ORs including 95% confidence intervals are presented and visualized in Figure 3. Of all prognostic factors, not working showed the strongest association (OR: 4.87). The combined prognostic model showed an Area Under the Curve (AUC) of 0.86 (95% Confidence Interval: 0.82 to 0.90) and a Nagelkerke's R² of 0.31 (Figure 4). The Hosmer-Lemeshow test yielded a p-value of 0.7167, indicating good model fit. The calibration plot (Figure 4) revealed acceptable to good calibration over the range of predicted probabilities. The Brier score was 0.077, indicating solid performance.

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5 6 7	283	Internal validation prognostic model
8 9	284	The bootstrap validation yielded a shrinkage factor of 0.83, which was then used to multiply
10 11 12	285	the regression coefficients by. The resulting model, including re-estimated intercept are in
12 13 14	286	Figure 3. The AUC after correction for optimism was 0.83. The optimism-corrected Nagelkerke's
15 16	287	R ² was 0.24.
17 18 19	288	The intermezzo section highlights a detailed patient profile to clarify the applicability and
20 21	289	interpretation of our findings in a practical context. Supplemental figure presents an interactive
22 23 24	290	visualization depicting the varied pain trajectories among participants within our cohort,
24 25 26	291	alongside the linear predictor and the probabilities of chronic pain derived from our
27 28	292	multivariable prognostic model. This visualization illustrates the complexity and variability of
29 30 21	293	pain progression over time. For a comprehensive visualization of all participants, see the web
32 33	294	application: <u>https://rstudio-connect.hu.nl/painr-app/</u> .
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Intermezzo

The patient (participant 110), a male, describes his neck pain intensity as 6 on the Numeric Pain Rating Scale (NPRS) and reports also low back pain. Since the onset of neck pain, he has also developed headaches, which were not present before the neck pain. Despite being employed, he finds it impossible to modify his posture during work. He anticipates the duration of his symptoms to be quite long, assessing it at 9 out of 10. Despite this, his concern for his condition is relatively minimal, with a score of 2 out of 10. His confidence in the therapy is high, rated at 8 on a 0-10 scale. Stress is absent in his case, evidenced by a score of 0 out of 21. While he admits to only a moderate understanding of his pain, scoring a 6 out of 10, he shows a high level of self-efficacy, achieving a full score of 12 on a 0-12 scale.

The patient (participant 914), a female, reports experiencing a pain intensity level of 6 on the Numeric Pain Rating Scale (NPRS). She notes pain in other regions of her body as well. Since developing neck pain, she has also begun to experience headaches, which she did not have prior to the neck pain. Currently, she is not employed. She anticipates her symptoms will persist, rating the anticipated duration as 10 on a scale from 0 to 10, indicating a long-term expectation of symptoms. She expresses moderate concern about her neck pain, with a concern level of 5 on a 0-10 scale. Her confidence in the effectiveness of her therapy is also moderate, rated a 5 on a 0-10 scale. She reports experiencing a moderate level of stress, scoring 12 on a 0-21 scale. Her self-reported understanding of her pain is 6 on a 0-10 scale, and scores a moderate self-efficacy, with a score of 6 on a 0-12 scale.

Linear predictor (LP) The linear predictor (LP) is given by: LP = -5.782+ (0.468 × sex[female = 1]) + (0.227 × pain intensity) + (0.734 × pain in different body regions) + (0.726 × headache(s) since the neck pain) -(0.070 × headache(s) before the neck pain) + (0.384 × potential to self-modify posture at work) + (1.311 × work status) + (0.184 × duration beliefs) + (0.108 × concerns) -(0.204 ×treatment beliefs) + (0.083 × distress) -(0.142 ×identity beliefs) + (0.109 ×self-efficacy) Probability of chronicity Probability of chronicity Probability of chronicity = $1 + e^{-\overline{LP}}$ Participant 110 Linear predictor (LP) calculation for patient X yields LP = -1.88, resulting in: = 13.2%Probability of chronicity = $\frac{1 + e^{1.88}}{1 + e^{1.88}}$ Participant 914

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4 5	343	Linear predictor (LP) calculation for patient X yields $LP = 0.98$, resulting in:
6 7	344	1 = 72.7%
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351 Discussion

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In this prospective cohort study, we (1) identified which (modifiable factors) are independent 352 353 prognostic factors of the development of chronic neck pain, and we (2) developed and internally 354 validated a prognostic model for predicting chronic pain after a new episode of acute- or subacute 355 nonspecific idiopathic, non-traumatic neck pain. We found several significant associations between 356 non- and modifiable factors and chronic pain: being female, higher pain intensity at baseline, longer 357 duration of neck pain, experiencing pain in different body regions, the onset of headache since the 358 neck pain began, higher disability scores, unemployment, higher scores on catastrophizing, illness 359 beliefs about recovery (concerned and duration), depression, distress, and lower treatment beliefs. The internally validated prognostic model demonstrates good prognostic performance, underscored 360 361 by an optimism-corrected AUC of 0.83. The calibration indicates a solid performance, as indicated by 362 the calibration curve, alongside a commendable Brier score. The Hosmer-Lemeshow test, with a p-363 value of 0.717, affirms a good model fit. Nonetheless, the model's corrected R² of 0.24 suggests that 364 the model provides a meaningful but limited explanation of the probability distribution of the 365 outcome of chronic pain. The model comprises twelve variables, four non-modifiable and eight

potentially modifiable by physiotherapists. The non-modifiable factors include sex, reported pain in
different body regions, longer existing headaches, and employment status (not working). Potentially
modifiable factors encompass baseline pain intensity, self-efficacy, headache onset concurrent with
neck pain, the ability to self-modify posture at work, illness beliefs regarding recovery (including
concerns and expected duration), and beliefs about neck pain identity and treatment.

When comparing our individual prognostic factors and those included in our prognostic model with
existing prognostic studies in musculoskeletal pain, several common factors emerge, including age,
work status, reported pain in different body regions (including headache), baseline pain identity, and
self-efficacy.(46–50) In our study, not working showed a high OR in both univariable and
multivariable analyses. A physiotherapist cannot directly modify this factor; however, attention could
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be given to potentially modifiable factors associated with unemployment, such as physical disability and mental health.(51,52) In addition, in our study, a higher score on the Pain Self-Efficacy Questionnaire 2-item version was associated with higher odds of chronic neck pain. Notably, this association was characterized by a low regression coefficient and OR and was insignificant with a small CI. Moreover, this outcome may be biased using this short questionnaire, where the largest group of our population scored above 10 on a 0-12 point scale for self-efficacy, exhibiting a known ceiling effect.(53) This notable outcome might, therefore, be questioned.

Our model incorporated four illness perception factors: beliefs about recovery (including concerns and duration), identity, and treatment beliefs. Longitudinal studies on low back pain have yielded similar findings, illustrating individual associations between illness beliefs (e.g., duration and treatment beliefs) and negative clinical outcomes over various time periods.(54-56) However, in prognostic multivariable models, the contribution of illness perceptions to the robustness of a prognostic model varies. (56,57) Notably, illness beliefs are often excluded from the candidate prognostic factors in models developed and externally validated for neck pain models.(12,58–60) Recent research has shown that modifying illness beliefs related to identity and concerns can mediate outcomes, specifically disability and pain, within physiotherapy primary care practices.(61) Consequently, further research into the modification of illness perception factors and their influence on the development of chronic pain, is imperative. Such studies are crucial to ascertain if physiotherapy interventions can effectively alter patients' outcomes. Furthermore, it is important to note that several psychological factors, such as depression, kinesiophobia, catastrophizing, and poor coping skills, are commonly recognized as associated with and prognostic for chronic pain.(14,62) These factors were not retained in our final prognostic model. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Although these factors showed an association in our univariable analysis, they did not improve the

predictive accuracy of our model. Notably, our baseline measurements indicated a distinctly non-

normal distribution for these psychological factors, contrasting with studies in chronic pain patients

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401 where these factors are more prevalent.(63) Despite their exclusion from our final model, screening 402 for these factors during the initial pain phase and ongoing monitoring during recovery remain 403 important. This is particularly noteworthy considering the body of evidence indicating that 404 treatments targeting psychological factors, such as catastrophizing, depression, and distress, have 405 shown favorable outcomes when addressed by healthcare providers. However, it is essential to 406 highlight that these studies have primarily focused on patients with chronic musculoskeletal 407 pain.(50,63–65) In contrast, it is important to note that most studies involving patients with acute-408 and subacute musculoskeletal pain have mainly focused on pain and disability as outcomes. 409 However, these studies, which investigate the effectiveness of treating physiological factors, should 410 also examine whether identified changes in these psychological factors contribute to the reduction in 411 pain intensity or disability observed in their study population. (50,66,67) 412 The incidence of chronic pain in our participants differed from our systematic review findings. Our 413 preliminary sample size calculation assumed a 45% chronicity rate for neck pain, which divided the 414 number of patients by the non-recovery cases.(12) This disparity can be attributed to our definition of chronic pain and the definition of the measurement approach. Unlike most studies that use single 415 416 time point assessment (e.g. 3, 6, or 12 months) with specific pain score threshold(68), including those 417 in our review(12), our study used a more comprehensive approach. This approach provides a precise representation of chronic pain as a continuous experience. Using this methodology, we excluded the 418 419 recurrent pain group, which includes pain-free or mild time periods, diverging from the International 420 Classification of Diseased 11th Revision (ICD-11) broader definition of chronic pain.(20) We 421 hypothesize that distinguishing between continuous and recurrent pain will lead to a more effective 422 prognostic model, acknowledging the distinct pain experiences of these groups. 423 Limitations 424 The calibration curve suggests a substantial overestimation of higher risks; this estimation was based

425 on only a few patients, as most had a relatively low estimated risk of chronic pain.

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In the initial sample size calculation, we assumed a 45% incidence of chronic pain, based on our
systematic review.(12) This calculation allowed for 26 candidate prognostic variables among a cohort
of 598 participants.(35) However, this study yielded a lower-than-expected incidence of chronic pain,
with only 10% of participants, indicating an underpowered and potentially inadequate sample size.
However, the increased risk of overfitting and the potential for overly optimistic model performance
seems to be minimal, as suggested by our internal validation analysis, which revealed a shrinkage
factor close to one.

433 Chronic primary pain, as described by the ICD-11, is accompanied by significant emotional distress or
434 functional disability. We used a threshold of ≥3 to define chronic pain based on the observation that
435 mild pain typically does not entail marked emotional distress or functional disability.(69,70)
436 However, the literature indicates that establishing a definitive cut-off point for mild and moderate
437 pain, especially regarding pain-related interference with functioning and emotions, is complex.(70–
438 72) Therefore, choosing a threshold of 3 is debatable, and selecting a different threshold could yield
439 different study results.

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Furthermore, in our study's protocol discussion, we noted that our study did not influence the therapies participants received; however, these therapies could potentially affect both the outcomes and the accuracy and generalizability of the developed model. Participants were treated according to the Dutch Physiotherapy Guideline for neck pain, which might modify our candidate prognostic factors and potentially reduce chronicity risks. Given the diversity of factors, the variety of modalities used by physiotherapists, and the therapists' varied backgrounds, we considered the impact of these therapies on our study results minimal. Ideally, these therapies would either not be applied or should have been analyzed within the multivariable prognostic model to assess their impact; however, this was not feasible due to sample size constraints.

449 Our final prognostic model retained the factor 'self-modifying posture during work'. This factor was
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 450 measured subjectively using a non-validated question, which poses a limitation as it may not

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distinguish between perceived and actual behavior during work. The limitation of this subjective
measurement lies in its inability to clearly distinguish whether individuals perceive that they can
change positions during work or are changing their positions. Additionally, this type of questioning
prevents us from confirming the accuracy of reports, such as whether a patient who claims they
cannot change positions is indeed unable to do so. Establishing the validity and discriminative ability
of the different concepts being tested is important to investigate.

⁷ 457 Clinical a

Clinical application and further research

The development of this prognostic model has identified several potential modifiable factors. In clinical practice, a physiotherapist can utilize this model to gain insight into a patient's probability of experiencing chronic neck pain. Furthermore, assessing and intervening on the modifiable factors in our model can be beneficial. However, we must be aware that although they have been validated for their prognostic value in our 1b prognostic study, it does not mean that modifying these factors will necessarily reduce the risk of developing chronicity. It is highly recommended to evaluate the performance of our model in an external validation study. If the model is found adequate, a prognostic model impact study is required, to quantify the effect on physiotherapist decision making in patients with acute- or subacute nonspecific idiopathic, non-traumatic neck pain (TRIPOD statement).(17)

³ 468 **Conclusion**

469 This model has the potential to obtain a valid prognosis for developing chronic pain after a new
 470 episode of acute—or subacute nonspecific idiopathic, non-traumatic neck pain. It includes mostly
 471 potential modifiable factors for physiotherapy practice. External validation of this model is
 472 recommended.

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10	480	Contributors
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13	483	Miss Martine Verwoerd is the guarantor, substantial contribution to study conception, study design,
14	484	data analysis, data interpretation, drafting and revising the manuscript, and significant involvement
15	485	in conceptualizing the web application and GitHub repository.
16	486	dr. Harriet Wittink: substantial contribution to study conception, study design, data analysis, data
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23	492	dr. Marc Teunis: substantial contribution to the data analysis and data interpretation, revising the
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25	494	Prof. dr. Rob LEM. Smeets: contribution to study concention, data analysis, data interpretation.
26	495	drafting and revising the manuscript
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30	497	Technical annendix, statistical code, and dataset available from the Github repository:
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32	500	<u>inteps.//github.com/dashogeschooldtreent/pam</u> _bol. available upon acceptance.
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40 41	507	Competing interests:
42	508	The authors have declared that no competing interests exist.
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Figure 2. Univariable logistic regression analysis: unadjusted association between each candidate prognostic factor and the outcome of chronic pain

The first figure displays the continuous variables, while the second illustrates the categorical and dichotomous variables. and Odds Ratio (OR) and corresponding confidence intervals (CI) are presented. BMI denotes Body Mass Index, W represents Weight (kg), and H stands for Height (m). P-values are indicated as follows: * for $0.01 , ** for <math>0.001 , and *** for <math>p \le 0.001$.

Regression coefficient after shrinkage Odds Ratio (95% Confidence Interval) P-value Intercept -5.782 - Sex (female) 0.468 1.76 (0.90 - 3.61) 0.107 Pain intensity at baseline (0-10) 0.227 1.32 (1.08 - 1.62) 0.008 ** Reported pain in different body regions (no/yes) 0.734 2.43 (1.19 - 5.35) 0.020 * No headache(s) (reference) 0.726 2.41 (1.21 - 5.03) 0.015 * Headache(s) since the neck pain 0.726 2.41 (1.21 - 5.03) 0.015 * Potential to self-modify posture (reference) 0.384 1.59 (0.71 - 3.43) 0.247 Neutral or impossible 1.311 4.87 (2.29 - 10.43) 0.001 *** Illness beliefs about recovery Duration (0-10) 0.184 1.25 (1.11 - 1.42) <0.001 *** Illness beliefs about recovery Concerned 0.108 1.14 (0.99 - 1.32) 0.075 0.075	Regression coefficient after shrinkage Odds Ratio (95% Confidence Interval) P-value -5.782 - 0.468 1.76 (0.90 - 3.61) 0.107 eline (0-10) 0.227 1.32 (1.08 - 1.62) 0.008 ** ferent body regions 0.734 2.43 (1.19 - 5.35) 0.020 * the neck pain 0.726 2.41 (1.21 - 5.03) 0.015 * 0.92 (0.27 - 2.77) 0.885 9ain in different body regions lify posture 0.384 1.59 (0.71 - 3.43) 0.247 le 1.311 4.87 (2.29 - 10.43) 0.001 *** recovery Duration 0.184 1.25 (1.11 - 1.42) <0.001 *** -10) -0.204 0.78 (0.67 - 0.92) 0.003 **	Regression coefficient after shrinkage Odds Ratio (95% Confidence Interval) P-value tercept -5.782					
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Figure 3 Adjusted multivariable logistic regression model

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Self-efficacy (0–12)

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and similar technologies.

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Figure 4. Area under the receiver operating characteristic and Calibration curve

The tick marks at the bottom of the Calibration curve represent the distribution of predicted probabilities. Each tick mark indicated a predicted probability for an individual observation. A dense cluster of tick marks indicated more observations with that specific predicted probability. This distribution occurs within the dataset.

1 Supplementary Information

2 Interactive Visualization of Patients Pain Trajectories and Chronicity Probability

For the visualization of all participants, see: https://rstudio-connect.hu.nl/painr-app/. In this visualization, "FALSE" indicates no chronic pain (pain < 3 at 6 weeks, 3 months, and 6 months), while "TRUE" denotes chronic pain (pain ≥ 3 at all time-points: 6 weeks, 3 months, and 6 months). The X-axis represents the pain score, measured using the Numerical Pain Rating Scale (0-10), and the Y-axis shows the cumulative number of days after the baseline measurement. "Patient_code" is a unique identifier for each patient. "LP" stands for linear predictor, "Prob" represents the probability of chronicity, and "Perc" indicates the percentual probability of chronicity. The bar graph and various values per variable illustrate the regression coefficient, multiplied by the patient data at baseline, across different variables from the prognostic model.



13 Supplementary Information

14 Appendix 1. TRIPOD Checklist Prediction Model Development and Validation

15			_
Section/Topic	1	Checklist Item	Page
Title and abstract			
TitleIIdentify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.			1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size,	2
Introduction	l	predictors, outcome, statistical analysis, results, and conclusions.	
Introduction	1	Explain the medical context (including whether diagnostic or prognostic) and	
Background and	За	rationale for developing or validating the multivariable prediction model, including references to existing models.	5-6
objectives	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	5-6
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
Source of data	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7-8
Participants	5b	Describe eligibility criteria for participants.	7-8
	5c	Give details of treatments received, if relevant.	Not applicable
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	Report any actions to blind assessment of the outcome to be predicted.	7-8
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	8-10
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	7-8
Sample size	size 8 Explain how the study size was arrived at.		10
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	10-11
	10a	Describe how predictors were handled in the analyses.	10-11
Statistical analysis	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	10-11
methods	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	10-11
Risk groups 11 Provide details on how risk groups were created, if done.		Not applicable	
Results			
Dortioinonto	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	12-16
Farticipants	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	12-16
M 1 1	14a	Specify the number of participants and outcome events in each analysis.	13
Model development	14b	If done, report the unadjusted association between each candidate predictor and outcome.	17-18
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	17-20
	15b	Explain how to the use the prediction model.	23-24
Model performance	16	Report performance measures (with CIs) for the prediction model.	19-22
Discussion			
Limitations 18 Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).		28	
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	25-28

2				
3	Implications	20	Discuss the potential clinical use of the model and implications for future research.	28-29
4	Other information			
5	Supplementary	21	Provide information about the availability of supplementary resources, such as study	20
6	information	21	protocol, Web calculator, and data sets.	30
7	Funding	22	Give the source of funding and the role of the funders for the present study.	30
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3 4 5	120 121	5.22 Formally testing the Goodness-of-fit using the Hosmer and Lemeshow 5.23 Intermezzo – linear predictors
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³ 123 Supplementary Information ⁴ 124 Appendix 3 Overview Applied

124 Appendix 3 Overview Applied interventions study population

Table Intervention included patients (N = 596)

Interve	entions	Number of patients	Applied (%)	Number of patients	Not applied (%)	
1.	Workplace, ergonomic and working time advice	99	16,6	497	83,4	
2.	Medical devices, collar or cervical pillow	1	0,2	595	98.2	
3.	Joint mobilizations, manipulation, traction, nerve mobilization techniques	509	85,4	86	14,6	
4.	Exercise therapy	346	58,1	250	41,9	
5.	Electrotherapy, laser, ultrasound, shockwave or heat therapy	0	0	596	100	
6.	Dry needling	492	17,4	104	82,6	
7.	Information and advice 🦯 🕖	79	86,7	517	13,3	
8.	Kinesiotaping	16	2,7	580	97,3	
9.	Massage	326	54,7	270	45,3	



127 Figure: Applied therapy included patients (N = 596)

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TRIPOD Checklist Prediction Model Development and Validation

Development and internal validation of a multivariable prognostic model for chronification of nonspecific neck pain in physiotherapy practice.

Section/Topic			Page	
Title and abstract				
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the	1	
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size,	2	
	<u> </u>	predictors, outcome, statistical analysis, results, and conclusions.		
Introduction	1		1	
		Explain the medical context (including whether diagnostic or prognostic) and		
Background and	3a	rationale for developing or validating the multivariable prediction model, including references to existing models.	5-6	
objectives	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	5-6	
Methods				
		Describe the study design or source of data (e.g., randomized trial, cohort, or		
Source of data	4a	registry data), separately for the development and validation data sets, if applicable.	7	
Source of data	4b	applicable, end of follow-up.	7	
	50	Specify key elements of the study setting (e.g., primary care, secondary care,	70	
Deutisiaeate	Dd	general population) including number and location of centres.	7-8	
Participants	5b	Describe eligibility criteria for participants.	7-8	
	5c	Give details of treatments received, if relevant.	Not applica	
	Ge	Clearly define the outcome that is predicted by the prediction model, including how		
Outcome	6a	and when assessed.	8	
	6b	Report any actions to blind assessment of the outcome to be predicted.	7-8	
	1_	Clearly define all predictors used in developing or validating the multivariable		
- U.	7a	prediction model, including how and when they were measured.	8-10	
Predictors	7b	Report any actions to blind assessment of predictors for the outcome and other predictors	7-8	
Sample size	8	Explain how the study size was arrived at	10	
Missing data 9		Describe how missing data were handled (e.g., complete-case analysis, single	10-11	
Ū.		imputation, multiple imputation) with details of any imputation method.		
	10a	Describe how predictors were handled in the analyses.	10-11	
Statistical	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	10-11	
analysis methods	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	10-11	
Risk groups	11	Provide details on how risk groups were created, if done.	Not applica	
Results				
		Describe the flow of participants through the study, including the number of		
	13a	participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful	12-16	
Participants	13b	Describe the characteristics of the participants (basic demographics, clinical	12-16	
		features, available predictors), including the number of participants with missing		
		data for predictors and outcome.		
	14a	Specify the number of participants and outcome events in each analysis.	13	
development	14b	If done, report the unadjusted association between each candidate predictor and outcome	17-18	
		Present the full prediction model to allow predictions for individuals (i.e., all		
Model	15a	regression coefficients, and model intercept or baseline survival at a given time	17-20	
specification		point).		
15		Explain how to the use the prediction model.	23-24	
Model				
performance	16	Report performance measures (with CIs) for the prediction model.	19-22	
Discussion	1		l	
		Discuss any limitations of the study (such as poprepresentative sample, few events per		
Limitations	18	nredictor missing data)	28	
		Give an overall interpretation of the results considering objectives limitations and		
Interpretation	19b	results from similar studies, and other relevant evidence	25-28	
	1			

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2				
3	Implications	20	Discuss the potential clinical use of the model and implications for future research.	28-29
4	Other information			
5	Supplementary	21	Provide information about the availability of supplementary resources, such as study	30
0 7	Eupling	22	protocol, Web calculator, and data sets.	20
, 8	Funding	22	Give the source of funding and the fole of the funders for the present study.	30
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