

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

**Pain Predict Genetics: Protocol for a prospective observational study of clinical and genetic factors to predict the development of postoperative pain.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-066134
Article Type:	Protocol
Date Submitted by the Author:	28-Jun-2022
Complete List of Authors:	LI, SONG; Radboudumc, Department of Human Genetics van Boekel, Regina L.M.; Radboudumc, Department of Anesthesiology, Pain and Palliative Medicine van den Heuvel, Sandra ; Radboudumc, Department of Anesthesiology, Pain and Palliative Medicine Coenen, Marieke J.H.; Radboudumc, Department of Human Genetics Vissers, Kris ; Radboudumc, Department of Anesthesiology, Pain and Palliative Medicine
Keywords:	PAIN MANAGEMENT, GENETICS, SURGERY, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

1  
2  
3  
4 1 Pain Predict Genetics: Protocol for a prospective observational  
5  
6 2 study of clinical and genetic factors to predict the development  
7  
8 of postoperative pain.  
9  
10 3  
11 4

12  
13 5 Song Li <sup>1</sup>, Regina L.M. van Boekel <sup>2</sup>, Sandra A.S. van den Heuvel <sup>2</sup>, Marieke J.H. Coenen <sup>1</sup>, Kris C.P.  
14 6 Vissers <sup>2</sup>  
15

16 7  
17  
18 8 Authors' Affiliations:  
19

20 9 <sup>1</sup> Department of Human Genetics, Radboud Institute for Health Sciences, Radboud university  
21 10 medical center, Nijmegen, The Netherlands.  
22

23 11 <sup>2</sup> Department of Anesthesiology, Pain and Palliative Medicine, Radboud university medical  
24 12 center, Nijmegen, The Netherlands.  
25

26 13  
27  
28 14 Email:  
29

30 15 Song Li: Song.Li@radboudumc.nl  
31

32 16 Regina (Rianne) van Boekel: Rianne.vanBoekel@radboudumc.nl  
33

34 17 Sandra van den Heuvel Sandra.vandenHeuvel@Radboudumc.nl  
35

36 18 Marieke Coenen: Marieke.Coenen@radboudumc.nl  
37

38 19 Kris C.P. Vissers Kris.Vissers@radboudumc.nl  
39  
40

41 20  
42 21 Corresponding author:  
43

44 22 Regina L.M. van Boekel  
45

46 23 Rianne.vanBoekel@radboudumc.nl  
47

48 24 Radboud University Medical Center,  
49

50 25 Department of Anesthesiology, Pain and Palliative Medicine  
51

52 26 PO Box 9101, intern 549  
53  
54

55 27 6500 HB, Nijmegen, The Netherlands  
56  
57  
58  
59  
60

1  
2  
3 28 Phone: 0031-243668120  
4

5 29 Fax: 0031243613585  
6  
7

8  
9 30

10 31 The number of text pages: 28  
11

12  
13 32 The actual number of figures and tables: 1 Figure, 1 Table, and 1 Supplementary file.  
14

15  
16 33  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## Abstract

**Introduction** Postoperative pain remains a challenging medical condition impacting the quality of life of every patient. Although several predictive factors for postoperative pain have been identified, an adequate prediction of postoperative pain in patients at risk has not been achieved yet.

The primary objective of this study is to identify specific genetic risk factors for the development of acute and chronic postoperative pain to construct a prediction model facilitating a more personalized postoperative pain management for each individual. The secondary objectives are to build a databank enabling researchers to identify other risk factors for postoperative pain, for instance, demographic and clinical outcome indicators; provide insight into (genetic) factors that predict pharmacological pain relief; investigate the relationship between acute and chronic postoperative pain.

**Methods and analysis** In this prospective, observational study, patients who undergo elective surgery will be recruited to a sample size of approximately 10,000 patients. Postoperative acute and chronic pain outcomes will be collected through questionnaires at different time points after surgery in the follow-up of six months. Potential genetic, demographic, and clinical risk factors for prediction model construction will be collected through blood, questionnaires, and electronic health records, respectively.

Genetic factors associated with acute and/or chronic postoperative pain will be identified using a genome-wide association (GWA) analysis. Clinical risk factors as stated in the secondary

1  
2  
3 54 objectives will be assessed by multivariable regression. A clinical easy-to-use prediction model  
4  
5 55 will be created for postoperative pain to allow clinical use for the stratification of patients.  
6  
7

8  
9 56 **Ethics and dissemination** The Institutional Review Board of the Radboud university medical  
10  
11 57 center approved the study (authorization number: 2012/117). The results of this study will be  
12  
13 58 made available through peer-reviewed scientific journals and presentations at relevant  
14  
15 59 conferences, which will finally contribute to personalized postoperative pain management.  
16  
17  
18

19 60 **Trial registration number** NCT02383342  
20  
21

22 61  
23  
24  
25 62 **Keywords:** Postoperative pain, Genome-wide association study (GWAS), Risk factor, Prediction  
26  
27 63 model, Pharmacogenetics  
28  
29  
30

31 64  
32  
33

34 65  
35  
36

37 66  
38  
39

40 67  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Strengths and limitations of this study

- This is a large prospective study to identify genetic and other risk factors for postoperative pain.
- We will build a databank with comprehensive interdisciplinary measurements that assess postoperative pain from multiple perspectives.
- Outcome measurements of pain by patient-reported outcomes, rather than evaluated by professionals.
- The primary goal of this study is to identify genetic variants as biomarkers of postoperative pain, but the collected blood samples enable future research to characterize the multi-omics biomarker signatures of postoperative pain.

## 79 Introduction

80 Pain after surgery remains a challenging medical and societal problem <sup>1</sup>. Pain is one of the most  
81 common postsurgical side effects, with moderate to severe acute postoperative pain occurring  
82 in about 41% of the patients <sup>2-4</sup>. Severe postoperative pain is associated with an increased  
83 incidence of postoperative complications <sup>5</sup>, including prolonged hospital stay, readmissions, and  
84 significant reduction of patient satisfaction and quality of life <sup>6,7</sup>. Besides, acute postoperative  
85 pain is associated with chronic pain development after surgery <sup>8</sup>. A recent position paper from  
86 the International Association for the Study of Pain stated that among the almost 40 million  
87 people undergoing surgery globally each year, one out of ten develops chronic postsurgical pain  
88 (CPSP), and one out of hundred suffers from severe CPSP, which will negatively affect patients'  
89 quality of life <sup>9</sup>. In addition, postoperative pain is a considerable burden on health care service  
90 costs, both directly due to patients' increased consumption of medical care and indirectly due to  
91 absenteeism, reduced productivity, and increased social welfare payments <sup>10-15</sup>.

92 The management of both acute postoperative pain <sup>2,31</sup> and CPSP <sup>2,32</sup> has remained suboptimal.  
93 Despite major investments in clinical protocols and guidelines for structural pain management,  
94 infrastructure, and acute pain services (APS), no significant outcome improvements in the  
95 quality of postoperative pain management for individual patients have been achieved in the last  
96 fifteen years <sup>10,11</sup>.

97 Given the high incidence of postoperative pain, identifying patients at risk for CPSP before the  
98 operation is important to apply more personalized pain prevention strategies. The most  
99 important demographic and clinical risk factors for postoperative pain are younger age, female  
100 sex, smoking, history of depressive symptoms, anxiety symptoms, sleep difficulties, higher body



1  
2  
3 101 mass index, presence of preoperative pain, and use of preoperative analgesics<sup>16</sup>. Based on  
4  
5 102 these factors, models have been developed to predict severe acute postoperative pain<sup>17 18</sup> and  
6  
7  
8 103 CPSP<sup>19 20</sup>. A recent study has evaluated a presurgical risk score for CPSP in a prospective cohort,  
9  
10 104 and it reliably identified about 70% of the patients undergoing surgeries at risk of CPSP<sup>21 22</sup>.  
11  
12  
13 105 As a multifactorial trait, the incidence variation of CPSP in the population can be explained  
14  
15 106 partly by the demographic and clinical risk factors mentioned above, and partly due to the  
16  
17 107 genetic and epigenetic differences among patients<sup>23 24</sup>. To improve the accuracy and power of  
18  
19 108 prediction, efforts have been made to predict CPSP using genetic variants<sup>19 22</sup>. However, no  
20  
21 109 unequivocal genetic predictors have been found yet. In addition, many exploratory studies  
22  
23 110 investigated the possible role of candidate genes in postoperative pain development. In  
24  
25 111 particular, associations have been found between CPSP and the  $\mu$ -opioid receptor (*OPRM1*) and  
26  
27 112 *catechol-O-methyl transferase (COMT)* genes<sup>25 26</sup>. Still, these results have not been confirmed  
28  
29 113 by others. *OPRM1* is also associated with basal pain sensitivity differences<sup>27</sup>, which could be  
30  
31 114 caused by the altered opioid binding potential in the central nervous system<sup>28</sup>. More recently,  
32  
33 115 hypothesis-free methods, such as genome-wide association studies, have been applied for CPSP  
34  
35 116 to identify markers across the genome<sup>29 30</sup>. One of the studies showed that a genetic variant in  
36  
37 117 the *protein-kinase C* gene is linked to neuropathic pain after complete joint replacement. This  
38  
39 118 gene is involved in long-term potentiation, synaptic plasticity, chronic pain, and memory,  
40  
41 119 indicating that this gene may be relevant for neuropathic pain initiation. The disadvantage of  
42  
43 120 this study is that it was small in terms of patient numbers and only focused on one specific  
44  
45 121 surgical procedure.  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 122 besides genetic variants for altered pain sensitivity, also gene variants in drug metabolism can  
4  
5 123 play a role. Understanding the reasons for ineffective treatment can facilitate the early  
6  
7 124 identification of patients at risk and provide more effective and customized postoperative  
8  
9 125 management. Some associated genes with pain treatment outcomes are also involved in pain  
10  
11 126 development, such as *COMT*<sup>33-35</sup>. Genes involved in the action site of active drugs or the drugs'  
12  
13 127 metabolism might play a role in the therapeutic response of this drug. A well-known example is  
14  
15 128 the *cytochrome P450 (CYP)* family investigated for several drugs (e.g., codeine and tramadol)<sup>36</sup>.  
16  
17  
18  
19  
20 129 However, this area has never been charted in a large population<sup>37</sup>.  
21  
22  
23 130 To date, adequate prediction of patients at risk for postoperative pain in clinical practice has not  
24  
25 131 been achieved for several reasons. First, although many demographic, clinical, and lifestyle  
26  
27 132 factors of postoperative pain have been reported<sup>16</sup>, a lack of consensus on the best outcome  
28  
29 133 indicators for postoperative pain management<sup>38 39</sup> hinders choosing the proper outcome  
30  
31 134 variables for prediction model construction. Second, the potential genetic risk factors of  
32  
33 135 postoperative pain prediction remain obscure. The role of genetic factors in postoperative pain  
34  
35 136 have not been investigated sufficiently, making it challenging to select appropriate genetic risk  
36  
37 137 factors to construct a prediction model. Third, when prediction models are updated, external  
38  
39 138 validation (i.e., in a new population) is important before being implemented in a clinical setting  
40  
41 139<sup>40-43</sup>, which is often difficult due to the lack of validation cohorts. For these reasons, we  
42  
43  
44  
45  
46  
47 140 hypothesize that a global structural multicenter diagnostic program of postoperative pain in a  
48  
49 141 surgical patient population will be valuable for better identifying patients at risk of CPSP and  
50  
51 142 ultimately preventing postoperative pain using individualized pharmacological and non-  
52  
53  
54 143 pharmacological interventions.

1  
2  
3 144  
4  
5  
67 145 **Objectives**

9 146 The primary objective of the Pain Predict Genetics (PPG) study is to identify genetic risk factors  
10  
11 147 for acute and chronic postoperative pain development and to construct a prediction model for  
12  
13  
14 148 personalized postoperative pain management.

15  
16  
17 149 The secondary objectives of the PPG study are to 1) identify other risk factors for the  
18  
19 150 development of acute and chronic postoperative pain; 2) provide insights into complications  
20  
21  
22 151 and other clinical outcome indicators after surgery; 3) provide insights into the relationship  
23  
24 152 between acute and chronic postoperative pain; 4) identify (genetic) factors that predict  
25  
26  
27 153 pharmacological pain relief.

28  
29  
30 154 The extensive data collection on (chronic) postoperative pain development of patients  
31  
32 155 undergoing surgery offers many possibilities for additional research questions using  
33  
34  
35 156 conventional statistical methods and artificial intelligence, e.g., machine learning. The cohort  
36  
37 157 could be used to 1) conduct epidemiological studies; 2) investigate other parameters (for  
38  
39  
40 158 example, types of surgery) that are involved in the development of chronic postoperative pain;  
41  
42 159 3) validate new prediction models for (chronic) postoperative pain; 4) identify factors for the  
43  
44  
45 160 postoperative outcome (for example, death, long-term hospitalization, complications); 5)  
46  
47 161 collaborate with other groups to perform large-scale analysis to identify predictors for the  
48  
49  
50 162 development of (chronic) postoperative pain.

## 163 Methods and analyses

### 164 Study design

165 A prospective, observational study of 10,000 patients will undergo elective surgery. This study  
166 will run for at least ten years, during which period it must be possible to include the intended  
167 number of patients. Patient inclusion after CMO (Human Research Committee, in Dutch  
168 Commissie Mensgebonden Onderzoek) approval was started in March 2015, and patient  
169 inclusion was temporarily stopped in 2020 due to COVID restrictions. In the near future, this  
170 study will be continued as a multicenter study; hospitals have already been approached and  
171 indicated that they intend to participate.

### 172 Patient and public involvement

173 During the design of the study the patients aided in the pilot phase of the questionnaires, during  
174 the recruitment the patients are informed concerning the project. In addition, patient reported  
175 outcomes will be used. Patients will be informed about the outcome of the study at several  
176 moments (depending on the obtained results).

### 177 Participants

178 Patients who undergo elective surgery and are eligible for this study will be approached before  
179 their planned surgery during the preoperative consultation. In this way, potential participants  
180 will have sufficient time to consider the study information. If any questions arise, it is possible to  
181 contact the researchers by telephone or ask the questions during the preoperative consultation.  
182 During the preoperative consultation (outpatient clinic or by telephone), the physician  
183 (assistant) will ask the patient if they are interested to participating in the study. If the patient is  
184 willing to participate, the informed consent form will be signed and dated. If patients have an

1  
2  
3 185 online preoperative consultation, this procedure will take place digitally, and patients receive  
4  
5  
6 186 the study forms (signed in advance) at home to return if they consent.  
7  
8  
9 187 Patients are eligible for study inclusion if they 1) are older or equal to 16 years; 2) undergo  
10  
11 188 elective surgery with an incision, including cardiothoracic surgery (e.g., cardiomyotomy), general  
12  
13 189 surgery (e.g., breast resection), neurological surgery (e.g., nerve decompression), oral and  
14  
15  
16 190 maxillofacial surgery (e.g., removal of head and neck benign and malignant tumors),  
17  
18 191 otorhinolaryngology (e.g., tympanoplasty), plastic surgery (e.g., breast reconstruction), trauma  
19  
20  
21 192 and orthopedic surgery (e.g., arthroplasty), urology (e.g., prostatectomy) and vascular surgery  
22  
23 193 (e.g., treatment of varicose veins); 3) can read and understand the patient information; 4) will  
24  
25  
26 194 provide informed consent. Patients will be excluded if they 1) intend to undergo another  
27  
28 195 surgery within six months; 2) do not have enough knowledge of the language in words and  
29  
30  
31 196 understanding to complete questionnaires.  
32  
33

## 34 197 **Measurements**

### 35 198 **Questionnaires**

36  
37  
38 199 After written informed consent, participants will be asked to complete questionnaires before  
39  
40  
41 200 and after their surgery. An overview of the study workflow and data collection time points can  
42  
43 201 be found in **Figure 1** and **Table 1**. All patient data will be stored in an online digital database,  
44  
45  
46 202 Castor<sup>44</sup>. The reliability and validity of all questionnaires for measurement collection have been  
47  
48 203 validated in the corresponding populations.  
49  
50  
51 204

**Table 1: Overview of data collection**

	T0	Day -1	Surgery	Day 1	Day 2	Day 3	Week 1	Week 6	Month 3	Month 6
Informed consent	x									
<b>Questionnaires</b>										
Demographic data		x								
Incision size		x		x						
Pain scores		x		x	x	x	x	x	x	x
Physical activities				x	x	x	x			
Pain disability index		x					x	x	x	x
APAIS		x								
PCS		x								
PSQ		x								
Chronic pain		x							x	x
IDS depression		x								
Brief pain inventory									x	x
<b>Data electronic medical file</b>										
Physical status by ASA										x
Type of surgery										x
Duration of surgery										x
Type of anesthesia										x
Complications										x
Hospital stay										x
Pain medication use										x
Incision size										x
Second surgery within 6 months										x



1  
2  
3 206 The first digital questionnaire must be completed the day before the surgery (no longer than  
4  
5 207 one week before). Before surgery, the following parameters will be collected (**Table 1**,  
6  
7  
8 208 Supplementary File 1): demographic characteristics (such as gender, age, BMI), expected  
9  
10 209 incision size in mm, pain intensity, pain disability, preoperative anxiety and need for  
11  
12 210 information, pain catastrophizing, pain sensitivity, preoperative chronic pain characteristics, and  
13  
14  
15 211 depressive symptoms.

16  
17  
18 212 After surgery, the following parameters will be collected: actual incision size in mm on day 1;  
19  
20 213 pain intensity on day 1, 2, 3, week 1 and 6, and month 3 and 6; physical activities on day 1, 2, 3,  
21  
22 214 week 1; pain disability on week 1 and 6, and month 3 and 6; postoperative chronic pain  
23  
24 215 characteristics on month 3 and 6; characteristics of pain on month 3 and 6.

25  
26  
27  
28 216 Pain intensity will be measured with an 11-point numerical rating scale (NRS) at rest and during  
29  
30 217 a normal patient action at that time<sup>18</sup>. The endpoints represent the extremes of the pain  
31  
32 218 experience: 0 means "no pain at all", and 10 means "worst possible pain".

33  
34  
35  
36 219 Pain disability (disability associated with pain) will be measured by the widely used Pain  
37  
38 220 Disability Index Dutch language version (PDI)<sup>45,46</sup>. The PDI is a 7-item questionnaire to  
39  
40 221 investigate the magnitude of the self-reported disability in different situations such as work,  
41  
42 222 leisure time, daily life activities, and sports. The questionnaire is constructed on an 11-point NRS  
43  
44 223 in which 0 means "no disability" and 10 means "maximum disability".

45  
46  
47  
48 224 Preoperative anxiety and need for information will be evaluated by the Amsterdam  
49  
50 225 Preoperative Anxiety and Information Scale (APAIS)<sup>47</sup>. The APAIS consists of six questions and  
51  
52 226 each score on a 5-point Likert scale from 1 (not at all) to 5 (extremely), with four questions to



1  
2  
3 227 assess the patient's preoperative anxiety score and two questions to assess the patient's need  
4  
5  
6 228 for information regarding the scheduled surgery and anesthesia <sup>18</sup>.  
7  
8  
9 229 Pain catastrophizing is generally described as an absurd negative orientation towards hurtful  
10  
11 230 stimuli and is important in pain coping <sup>48</sup>. It will be measured by the Pain Catastrophizing Scale  
12  
13 231 (PCS), a self-evaluating questionnaire consisting of 13 questions. People are asked to indicate  
14  
15  
16 232 the degree to which they have thoughts and feelings when experiencing pain using the 0 (not at  
17  
18 233 all) to 4 (all the time) scale, and a total score will be yielded (range from 0 to 52).  
19  
20  
21 234 The Pain Sensitivity Questionnaire (PSQ) will measure patients' preoperative pain sensitivity <sup>49</sup>  
22  
23 235 <sup>50</sup>. The PSQ consists of 17 questions that describe daily life situations; respondents score their  
24  
25  
26 236 pain intensity for these situations on an NRS by scoring 0 (not painful) to 10 (severest pain  
27  
28  
29 237 imaginable).  
30  
31  
32 238 Chronic pain characteristics will be measured preoperatively and postoperatively by five  
33  
34 239 questions. The definition of chronic pain is in agreement with IASP terminology of chronic  
35  
36  
37 240 postsurgical pain, i.e., "*chronic pain that develops or increases in intensity after a surgical*  
38  
39 241 *procedure persists beyond the healing process, i.e., at least 3 months after the surgery*" <sup>9</sup>.  
40  
41  
42 242 Patients will be asked to indicate whether they had a recent pain experience, the site of pain  
43  
44 243 and whether it lasted more than three months <sup>51 52</sup>.  
45  
46  
47 244 The severity of overall depressive symptoms will be assessed by the Inventory of Depressive  
48  
49 245 Symptomatology Self Report (IDS-SR) <sup>53 54</sup>. IDS-SR is a 30-item questionnaire, and each item has  
50  
51  
52 246 four statements scored on a four-point scale from 0 to 3. There are two items about either  
53  
54  
55 247 increasing or decreasing appetite and two items about increasing or decreasing weight. Only the  
56  
57  
58  
59  
60

1  
2  
3 248 item with the higher score from both pairs will be chosen. The total score is based on 28 items  
4  
5  
6 249 and ranges from 0 to 84.  
7  
8  
9 250 Physical activities (ability to perform normal activities) will be measured by questions assessing  
10  
11 251 the degree of physical activities interfered by surgery, including bed activities (such as turning),  
12  
13 252 breathing deeply or coughing, sleeping, and activities out of bed. Each item is scored on an 11-  
14  
15  
16 253 point NRS in which 0 means did not interfere and 10 means completely interfered. These  
17  
18 254 questions are derived from the validated International Pain Outcomes questionnaire and are  
19  
20  
21 255 found responsive to asking patients about their ability to perform normal activities directly after  
22  
23 256 surgery<sup>55</sup>.

24  
25  
26 257 Characteristics of pain will be measured by the Brief Pain Inventory – Short Form (BPI-SF), which  
27  
28  
29 258 is a shortened version of the Brief Pain Inventory<sup>56</sup>. BPI-SF evaluates pain severity during the  
30  
31 259 past 24 hours and current level, with 0 representing "no pain" and 10 "the worst pain  
32  
33  
34 260 imaginable". Seven items in BPI-SF assess interference with daily functioning (such as general  
35  
36 261 activity, walking, and work) on an 11-point scale, where 0 represents "no interference" and 10  
37  
38  
39 262 "complete interference".

### 263 Collection of body material

264 One tube of blood will be collected for DNA isolation. The burden for the patient is minimized  
265 as blood will be taken using the intravenous line in place for surgery. If it is impossible to collect  
266 blood presurgically or postsurgically, we will collect saliva for DNA isolation (Genefix DNA saliva  
267 collectors; GFX-02/50, Isohelix).

## 268 Clinical information

269 The following clinical information will be collected from the electronic patient file six months  
270 after operation (**Table 1**): physical status by The American Society of Anesthesiologists  
271 classification (ASA-status); type of surgery; duration of surgery; type of anesthesia;  
272 postoperative complications within 30 days after surgery, one-time retrospectively, which is  
273 defined as any medical adverse outcome occurring between admission and 30 days after  
274 operation. Complications occurring in the operation room and complications directly related to  
275 anesthesia (e.g., nausea which resolves immediately after medication in the operation room)  
276 will not be included<sup>57</sup>. Furthermore, data on pain medication use, before surgery and after  
277 surgery; actual incision size in mm; second surgery within 6 months; general clinical outcome  
278 indicators, including surgical site infection at 30 days, stroke within 30 days of surgery, death  
279 within 30 days of surgery, admission to the intensive care unit within 14 days of surgery,  
280 readmission to hospital within 30 days of surgery, and length of hospital stay (with or without  
281 in-hospital mortality) will be collected<sup>38</sup>.

## 282 Sample size calculation

283 The power of the genetic study is based on the primary research question investigating which  
284 genetic factors are associated with postoperative pain. Power is calculated using the Genetic  
285 Power Calculator<sup>58</sup>, and the estimated number of patients is based on a GWA approach. For  
286 chronic postoperative pain, we assume a case-control analysis for discrete traits (2df test), a risk  
287 allele frequency of 30%, a linkage disequilibrium ( $D'$ ) of 0.8, a prevalence of chronic  
288 postoperative pain of 15%, and the relative risk of chronic postoperative pain for persons who  
289 are heterozygous of 1.5 and for homozygous persons of 2.25. For a power of 80% with a p-value

1  
2  
3 290 cut off  $5 \times 10^{-8}$  (genome-wide significance threshold), we need 750 patients with chronic  
4  
5 291 postoperative pain and 4,250 people without chronic postoperative pain. For acute pain, the  
6  
7 292 power is even higher. With the same population, we have more than 80% power to detect a  
8  
9 293 relative risk of 1.2 and 1.44 for heterozygous and homozygous patients, respectively. This higher  
10  
11 294 power is due to the higher prevalence of acute (moderate to severe) pain of 55%. Most  
12  
13 295 importantly, results will be replicated in the additional study participants, as the total number of  
14  
15 296 patients included in the study will be 10,000. In addition, we will use cohorts of our  
16  
17 297 collaborators for replication purposes.  
18  
19  
20  
21  
22  
23

## 24 298 **Statistical analysis**

25 299 The key objective is to identify genetic risk factors that can predict development of acute or  
26  
27 300 chronic postoperative pain and validate previously reported SNPs. A GWA approach will be used  
28  
29 301 as the main analysis. Phenotype data and DNA will be used to identify genetic factors. We will  
30  
31 302 use 5,000 patients for the discovery of genetic variants. Samples will be genotyped with the  
32  
33 303 Infinium Global Screening Array (Illumina). Pre-imputation quality control, principal component  
34  
35 304 analyses, and imputation will follow the RICOPILI pipeline<sup>59</sup>. The 1000 Genomes reference panel  
36  
37 305 will be used for imputation, followed by post-imputation quality control in PLINK<sup>60</sup>. Associations  
38  
39 306 between SNPs and the presence of acute or chronic pain will be performed using cutting-edge  
40  
41 307 methods when data collection is finished. Results will be to ensure validity. SNPs that can be  
42  
43 308 validated will be included in the prediction model described below.  
44  
45  
46  
47  
48  
49

50 309 Secondary objectives include identifying other potential risk factors for acute and chronic  
51  
52 310 postoperative pain. Therefore, a univariate association of each potential predictor will be  
53  
54 311 calculated and tested in a multivariable regression model. We will use a least absolute shrinkage  
55  
56  
57  
58  
59  
60

1  
2  
3 312 and selection operator (Lasso) regression. Shrinkage is where data values are shrunk towards a  
4  
5 313 central point, like the mean. Lasso is a regression analysis method that performs both variable  
6  
7  
8 314 selection and regularization to enhance the prediction accuracy and interpretability of the  
9  
10 315 statistical model it produces. After identifying these risk factors, a prediction rule will be created  
11  
12  
13 316 for acute and chronic postoperative pain. Based on this prediction rule, a simple, clinically easy  
14  
15 317 applicable tool will be developed to allow clinical use for the stratification of patients. The  
16  
17  
18 318 predictive performance will be studied in another cohort of patients to test whether the rule is  
19  
20 319 generalizable across time and place. Because it appears from the literature that acute and  
21  
22  
23 320 chronic pain are correlated after surgery, additional correlation analysis will be performed to  
24  
25 321 investigate this correlation in the data.

26  
27  
28 322 Similar approaches will be followed to identify the clinical and genetic factors that predict  
29  
30 323 pharmacological pain relief. For some pain medicines, genes that impact pain relief are already  
31  
32  
33 324 known (e.g., *CYP2D6* and morphine). We will first investigate those genes to see if these variants  
34  
35 325 indeed contribute to pharmacological pain relief differences.

36  
37  
38  
39 326

### 327 **Ethics and dissemination:**

328 The study will be conducted according to the principles of the Declaration of Helsinki version  
329 2013 and in accordance with the Medical Research Involving Human Subjects Act and Good  
330 Clinical Practice. The study was approved by the local ethics committee for human research in  
331 Nijmegen (Medical Review Ethics Committee Region Arnhem-Nijmegen, authorization number:  
332 2012/117). This study was registered on ClinicalTrials.gov (NCT02383342).

1  
2  
3 333 The privacy of the participants is guaranteed by storing encrypted data. Every participant will  
4  
5 334 receive a pseudo-anonymous study number. No identifying data is recorded within the meaning  
6  
7  
8 335 of the law. The key is only accessible to the study team and monitors. Data and material will  
9  
10 336 only be used in coded form within possible collaborations.

11  
12  
13 337 The results of this study will be made available through peer-reviewed scientific journals and  
14  
15 338 presentations at relevant conferences. After a thorough evaluation, decisions will be made  
16  
17 339 regarding including the identified risk factors and constructed prediction models into clinical  
18  
19 340 guidelines, thus facilitating personalized postoperative pain management.  
20  
21  
22  
23

## 24 25 341 Discussion

26  
27 342 This cohort will be a large prospective study to identify risk factors for postoperative pain and to  
28  
29 343 build and evaluate dedicated prediction models for postoperative pain in surgical patients. In  
30  
31 344 addition, the comprehensive information collected in this study will also enable us to answer  
32  
33 345 other research questions regarding postoperative pain, such as the relationships between acute  
34  
35 346 and chronic postoperative pain development. Eventually, these results will be applied in the  
36  
37 347 clinical settings to improve the quality of life for patients who develop postoperative pain.  
38  
39  
40  
41

42 348 The strengths of this study are that we will include all elective major operations rather than  
43  
44 349 limiting to one specific operation as in previous studies<sup>30</sup>, which allows us to investigate the  
45  
46 350 shared genetic background of postoperative pain in different operations. Furthermore, as there  
47  
48 351 are discrepancies in pain intensity scores understanding<sup>61</sup> and pain management decisions<sup>61 62</sup>  
49  
50 352 between patients and caregivers, the patient's perspective should be respected and assessed for  
51  
52 353 pain evaluation and management<sup>63 64</sup>. Therefore, pain assessment will be conducted by patients  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 354 themselves (patient-reported outcomes) rather than professionals in this study, leading to a  
4  
5  
6 355 more comprehensive outcome assessment and interpretation <sup>65</sup>. Moreover, the single-use of  
7  
8 356 NRS might be inadequate for patients' pain experience evaluation and pain management  
9  
10  
11 357 decisions <sup>64 66 67</sup>. Thus, another strength of this cohort is that the experience of pain will be  
12  
13 358 estimated by multidimensional measurements focusing on patients' overall functionality rather  
14  
15 359 than merely a NRS pain score. Besides, the comprehensively collected information for  
16  
17  
18 360 postoperative pain in this cohort also empowers analysis that cannot be performed in large-  
19  
20 361 scale registry data (e.g., UK Biobank) as such phenotype data is not available in those datasets.  
21  
22  
23 362 The data collected in this cohort will also enable additional research using conventional and  
24  
25 363 cutting-edge statistical methods like artificial intelligence.

26  
27  
28 364 The possible limitations of this study are that we will only investigate DNA variants as  
29  
30 365 biomarkers for pain prediction as our primary research goal. However, other epigenetic <sup>67 68</sup>,  
31  
32  
33 366 transcriptomic <sup>68</sup>, proteomics <sup>69</sup>, and metabolic markers <sup>70</sup> are also potentially involved in  
34  
35 367 (postoperative) pain development. For instance, recent studies indicate that methylation  
36  
37  
38 368 patterns might predict opioid treatment outcomes <sup>67 68</sup>. As the DNA sample of patients is  
39  
40 369 accessible, we will be able to investigate additional related research questions, such as the  
41  
42  
43 370 association between epigenetic changes and postoperative pain in the future. In addition, when  
44  
45 371 prediction tools are applied in clinical settings, the sensitivity and specificity of prediction tools  
46  
47  
48 372 are crucial to evaluate their adequacy and usefulness <sup>71</sup>. Although the measurement tools used  
49  
50 373 in prediction models are well-validated and verified (see methods), our findings could still be  
51  
52  
53 374 subject to false positive or negative errors because all measurement tools have limitations.  
54  
55 375 Furthermore, chronic pain assessment is more complex than acute pain <sup>72</sup>, and GWAS findings

1  
2  
3 376 are sometimes incidental<sup>73</sup>. We will consider seeking other available cohorts for validation and  
4  
5 377 applying other statistical methods to validate our findings in future studies, such as polygenic  
6  
7  
8 378 risk scores<sup>74</sup>. Another potential limitation is that loss of follow-up of patients might result in  
9  
10 379 lower patient numbers than expected. Despite this potential concern, we still expect a sufficient  
11  
12  
13 380 sample size as additional centres will start patient inclusion, and the measurements are mainly  
14  
15 381 from patient-reported outcomes via digital follow-up.

16  
17  
18 382 Identifying the genetic background of postoperative pain development may give valuable  
19  
20  
21 383 insights into the mechanisms underlying the relationship between postoperative pain and  
22  
23 384 complications after surgery. This may open the way to identify new targets for treatment and  
24  
25 385 potentially simplify the risk profiling assay for future use, yielding a simpler, more accurate, and  
26  
27  
28 386 cost-efficient assay or product. The contribution of improved prevention and treatment of pain  
29  
30  
31 387 after surgery will benefit many patients undergoing surgery and society by decreasing health  
32  
33 388 care service costs.

34  
35  
36 389

## 390 Trial status

391 Patient recruitment is expected to continue until 2025. Recruitment has already started in  
392 Radboud university medical center, with more than 500 patients recruited as of October 2021.  
393 National and international collaborations will be greatly accepted after careful consideration.

## 394 Author contributions

395 All authors were responsible for the study design. SL drafted the manuscript. All authors  
396 critically reviewed the manuscript.



1  
2  
3  
4 397 **Acknowledgment**

5 398 SL was supported by China Scholarship Council (CSC) Grant number 201908130179.  
6  
7

8  
9 399 **Funding**

10 400 Departmental funding covers the costs of this study [grant number: N/A].  
11  
12  
13

14 401 **Competing interests statement**

15  
16 402 The authors have no relevant financial or non-financial interests to disclose.  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

403 

## References

- 404 1. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012;13(8):715-24. doi:  
405 10.1016/j.jpain.2012.03.009 [published Online First: 2012/05/23]
- 406 2. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence  
407 from published data. *Br J Anaesth* 2002;89(3):409-23.
- 408 3. Sommer M, de Rijke JM, van Kleef M, et al. The prevalence of postoperative pain in a sample of 1490  
409 surgical inpatients. *Eur J Anaesthesiol* 2008;25(4):267-74. doi: 10.1017/S0265021507003031
- 410 4. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res*  
411 2017;10:2287-98. doi: 10.2147/JPR.S144066 [published Online First: 2017/10/14]
- 412 5. van Boekel RLM, Warle MC, Nielen RGC, et al. Relationship Between Postoperative Pain and Overall  
413 30-Day Complications in a Broad Surgical Population: An Observational Study. *Ann Surg*  
414 2019;269(5):856-65. doi: 10.1097/SLA.0000000000002583 [published Online First: 2017/11/15]
- 415 6. Peters CL, Shirley B, Erickson J. The effect of a new multimodal perioperative anesthetic regimen on  
416 postoperative pain, side effects, rehabilitation, and length of hospital stay after total joint  
417 arthroplasty. *The Journal of arthroplasty* 2006;21(6 Suppl 2):132-8. doi:  
418 10.1016/j.arth.2006.04.017
- 419 7. Regenbogen SE, Mullard AJ, Peters N, et al. Hospital Analgesia Practices and Patient-reported Pain  
420 After Colorectal Resection. *Ann Surg* 2016;264(6):1044-50. doi: 10.1097/SLA.0000000000001541
- 421 8. Katz J, Jackson M, Kavanagh BP, et al. Acute pain after thoracic surgery predicts long-term post-  
422 thoracotomy pain. *Clin J Pain* 1996;12(1):50-5. [published Online First: 1996/03/01]
- 423 9. Schug SA, Lavand'homme P, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic  
424 postsurgical or posttraumatic pain. *Pain* 2019;160(1):45-52. doi:  
425 10.1097/j.pain.0000000000001413 [published Online First: 2018/12/27]
- 426 10. Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey  
427 suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003;97(2):534-40,  
428 table of contents.
- 429 11. Meissner W, Coluzzi F, Fletcher D, et al. Improving the management of post-operative acute pain:  
430 priorities for change. *Curr Med Res Opin* 2015;31(11):2131-43. doi:  
431 10.1185/03007995.2015.1092122 [published Online First: 2015/09/12]
- 432 12. Zimberg SE. Reducing pain and costs with innovative postoperative pain management. *Managed care*  
433 *quarterly* 2003;11(1):34-6.
- 434 13. Morrison RS, Magaziner J, McLaughlin MA, et al. The impact of post-operative pain on outcomes  
435 following hip fracture. *Pain* 2003;103(3):303-11.
- 436 14. Zoucas E, Lydrup ML. Hospital costs associated with surgical morbidity after elective colorectal  
437 procedures: a retrospective observational cohort study in 530 patients. *Patient safety in surgery*  
438 2014;8(1):2. doi: 10.1186/1754-9493-8-2
- 439 15. Encinosa WE, Hellinger FJ. The impact of medical errors on ninety-day costs and outcomes: an  
440 examination of surgical patients. *Health services research* 2008;43(6):2067-85. doi:  
441 10.1111/j.1475-6773.2008.00882.x
- 442 16. Yang MMH, Hartley RL, Leung AA, et al. Preoperative predictors of poor acute postoperative pain  
443 control: a systematic review and meta-analysis. *BMJ Open* 2019;9(4):e025091. doi:  
444 10.1136/bmjopen-2018-025091 [published Online First: 2019/04/04]
- 445 17. Kalkman CJ, Visser K, Moen J, et al. Preoperative prediction of severe postoperative pain. *Pain*  
446 2003;105(3):415-23. doi: 10.1016/s0304-3959(03)00252-5 [published Online First: 2003/10/07]

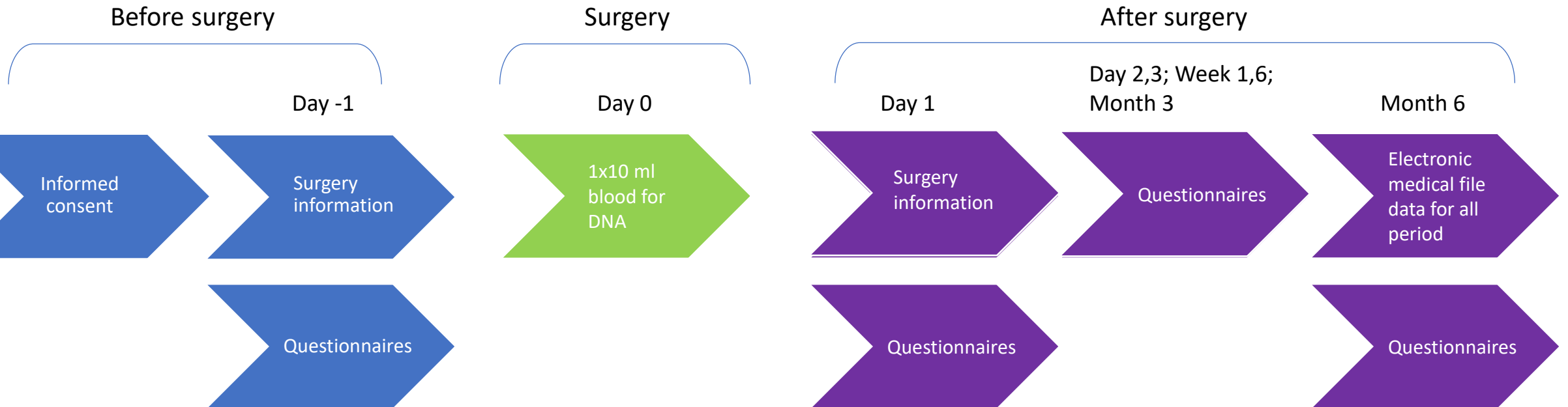
- 1  
2  
3 447 18. Janssen KJ, Kalkman CJ, Grobbee DE, et al. The risk of severe postoperative pain: modification and  
4 448 validation of a clinical prediction rule. *Anesth Analg* 2008;107(4):1330-9. doi:  
5 449 10.1213/ane.0b013e31818227da [published Online First: 2008/09/23]  
6 450 19. Hoofwijk DMN, van Reij RRI, Rutten BPF, et al. Genetic polymorphisms and prediction of chronic  
7 451 post-surgical pain after hysterectomy-a subgroup analysis of a multicenter cohort study. *Acta*  
8 452 *Anaesthesiol Scand* 2019;63(8):1063-73. doi: 10.1111/aas.13413 [published Online First:  
9 453 2019/06/18]  
10 454 20. Althaus A, Hinrichs-Rocker A, Chapman R, et al. Development of a risk index for the prediction of  
11 455 chronic post-surgical pain. *Eur J Pain* 2012;16(6):901-10. doi: 10.1002/j.1532-2149.2011.00090.x  
12 456 21. Montes A, Roca G, Cantillo J, et al. Presurgical risk model for chronic postsurgical pain based on 6  
13 457 clinical predictors: a prospective external validation. *Pain* 2020;161(11):2611-18. doi:  
14 458 10.1097/j.pain.0000000000001945 [published Online First: 2020/06/17]  
15 459 22. Montes A, Roca G, Sabate S, et al. Genetic and Clinical Factors Associated with Chronic Postsurgical  
16 460 Pain after Hernia Repair, Hysterectomy, and Thoracotomy: A Two-year Multicenter Cohort Study.  
17 461 *Anesthesiology* 2015;122(5):1123-41. doi: 10.1097/ALN.0000000000000611 [published Online  
18 462 First: 2015/05/20]  
19 463 23. Mauck M, Van de Ven T, Shaw AD. Epigenetics of chronic pain after thoracic surgery. *Curr Opin*  
20 464 *Anaesthesiol* 2014;27(1):1-5. doi: 10.1097/ACO.0000000000000030 [published Online First:  
21 465 2013/12/05]  
22 466 24. van Reij RRI, Joosten EAJ, van den Hoogen NJ. Dopaminergic neurotransmission and genetic variation  
23 467 in chronification of post-surgical pain. *Br J Anaesth* 2019;123(6):853-64. doi:  
24 468 10.1016/j.bja.2019.07.028 [published Online First: 2019/09/29]  
25 469 25. De Gregori M, Diatchenko L, Belfer I, et al. OPRM1 receptor as new biomarker to help the prediction  
26 470 of post mastectomy pain and recurrence in breast cancer. *Minerva Anesthesiol* 2015;81(8):894-  
27 471 900. [published Online First: 2014/10/11]  
28 472 26. Hoofwijk DM, van Reij RR, Rutten BP, et al. Genetic polymorphisms and their association with the  
29 473 prevalence and severity of chronic postsurgical pain: a systematic review. *Br J Anaesth*  
30 474 2016;117(6):708-19. doi: 10.1093/bja/aew378 [published Online First: 2016/12/14]  
31 475 27. Kim H, Clark D, Dionne RA. Genetic contributions to clinical pain and analgesia: avoiding pitfalls in  
32 476 genetic research. *J Pain* 2009;10(7):663-93. doi: 10.1016/j.jpain.2009.04.001 [published Online  
33 477 First: 2009/06/30]  
34 478 28. Mueller C, Klega A, Buchholz HG, et al. Basal opioid receptor binding is associated with differences in  
35 479 sensory perception in healthy human subjects: a [18F]diprenorphine PET study. *Neuroimage*  
36 480 2010;49(1):731-7. doi: 10.1016/j.neuroimage.2009.08.033 [published Online First: 2009/08/26]  
37 481 29. van Reij RRI, Hoofwijk DMN, Rutten BPF, et al. The association between genome-wide  
38 482 polymorphisms and chronic postoperative pain: a prospective observational study. *Anaesthesia*  
39 483 2020;75 Suppl 1:e111-e20. doi: 10.1111/anae.14832 [published Online First: 2020/01/07]  
40 484 30. Warner SC, van Meurs JB, Schiphof D, et al. Genome-wide association scan of neuropathic pain  
41 485 symptoms post total joint replacement highlights a variant in the protein-kinase C gene. *Eur J*  
42 486 *Hum Genet* 2017;25(4):446-51. doi: 10.1038/ejhg.2016.196 [published Online First: 2017/01/05]  
43 487 31. Sinatra R. Causes and consequences of inadequate management of acute pain. *Pain Med*  
44 488 2010;11(12):1859-71. doi: 10.1111/j.1526-4637.2010.00983.x [published Online First:  
45 489 2010/11/03]  
46 490 32. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet*  
47 491 2019;393(10180):1537-46. doi: 10.1016/S0140-6736(19)30352-6 [published Online First:  
48 492 2019/04/16]  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 493 33. Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid  
4 494 neurotransmitter responses to a pain stressor. *Science* 2003;299(5610):1240-3. doi:  
5 495 10.1126/science.1078546 [published Online First: 2003/02/22]  
6 496 34. Rakvåg TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-  
7 497 methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients.  
8 498 *Pain* 2005;116(1-2):73-8. doi: 10.1016/j.pain.2005.03.032 [published Online First: 2005/06/02]  
9 499 35. Reyes-Gibby CC, Shete S, Rakvåg T, et al. Exploring joint effects of genes and the clinical efficacy of  
10 500 morphine for cancer pain: OPRM1 and COMT gene. *Pain* 2007;130(1-2):25-30. doi:  
11 501 10.1016/j.pain.2006.10.023 [published Online First: 2006/12/13]  
12 502 36. Owusu Obeng A, Hamadeh I, Smith M. Review of Opioid Pharmacogenetics and Considerations for  
13 503 Pain Management. *Pharmacotherapy* 2017;37(9):1105-21. doi: 10.1002/phar.1986 [published  
14 504 Online First: 2017/07/13]  
15 505 37. De Gregori M, Diatchenko L, Ingelmo PM, et al. Human Genetic Variability Contributes to  
16 506 Postoperative Morphine Consumption. *J Pain* 2016;17(5):628-36. doi:  
17 507 10.1016/j.jpain.2016.02.003 [published Online First: 2016/02/24]  
18 508 38. Haller G, Bampoe S, Cook T, et al. Systematic review and consensus definitions for the Standardised  
19 509 Endpoints in Perioperative Medicine initiative: clinical indicators. *Br J Anaesth* 2019;123(2):228-  
20 510 37. doi: 10.1016/j.bja.2019.04.041 [published Online First: 2019/05/28]  
21 511 39. Pogatzki-Zahn E, Schnabel K, Kaiser U. Patient-reported outcome measures for acute and chronic  
22 512 pain: current knowledge and future directions. *Curr Opin Anaesthesiol* 2019;32(5):616-22. doi:  
23 513 10.1097/ACO.0000000000000780 [published Online First: 2019/08/16]  
24 514 40. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern*  
25 515 *Med* 1999;130(6):515-24. doi: 10.7326/0003-4819-130-6-199903160-00016 [published Online  
26 516 First: 1999/03/13]  
27 517 41. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction  
28 518 rules to make decisions. *Ann Intern Med* 2006;144(3):201-9. doi: 10.7326/0003-4819-144-3-  
29 519 200602070-00009 [published Online First: 2006/02/08]  
30 520 42. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med*  
31 521 2000;19(4):453-73. doi: 10.1002/(sici)1097-0258(20000229)19:4<453::aid-sim350>3.0.co;2-5  
32 522 [published Online First: 2000/03/01]  
33 523 43. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models,  
34 524 evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*  
35 525 1996;15(4):361-87. doi: 10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4  
36 526 [published Online First: 1996/02/28]  
37 527 44. Castor EDC. Castor Electronic Data Capture 2019 [27 Aug. 2019]. Available from:  
38 528 <https://castoredc.com> accessed August 28, 2019.  
39 529 45. Soer R, Köke AJ, Vroomen PC, et al. Extensive validation of the pain disability index in 3 groups of  
40 530 patients with musculoskeletal pain. *Spine (Phila Pa 1976)* 2013;38(9):E562-8. doi:  
41 531 10.1097/BRS.0b013e31828af21f [published Online First: 2013/02/08]  
42 532 46. Tait RC, Pollard CA, Margolis RB, et al. The Pain Disability Index: psychometric and validity data. *Arch*  
43 533 *Phys Med Rehabil* 1987;68(7):438-41. [published Online First: 1987/07/01]  
44 534 47. Moerman N, van Dam FS, Muller MJ, et al. The Amsterdam Preoperative Anxiety and Information  
45 535 Scale (APAIS). *Anesth Analg* 1996;82(3):445-51. doi: 10.1097/0000539-199603000-00002  
46 536 [published Online First: 1996/03/01]  
47 537 48. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation.  
48 538 *Psychological Assessment* 1995;7(4):524-32. doi: 10.1037/1040-3590.7.4.524

- 1  
2  
3 539 49. Ruscheweyh R, Marziniak M, Stumpfenhorst F, et al. Pain sensitivity can be assessed by self-rating:  
4 540 Development and validation of the Pain Sensitivity Questionnaire. *Pain* 2009;146(1-2):65-74. doi:  
5 541 10.1016/j.pain.2009.06.020 [published Online First: 2009/08/12]  
6 542 50. Van Boekel RLM, Timmerman H, Bronkhorst EM, et al. Translation, Cross-Cultural Adaptation, and  
7 543 Validation of the Pain Sensitivity Questionnaire in Dutch Healthy Volunteers. *Pain Res Manag*  
8 544 2020;2020:1050935. doi: 10.1155/2020/1050935 [published Online First: 2020/08/11]  
9 545 51. Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth* 2008;101(1):77-86. doi:  
10 546 10.1093/bja/aen099 [published Online First: 2008/04/25]  
11 547 52. Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? *Br J*  
12 548 *Anaesth* 2014;113(1):1-4. doi: 10.1093/bja/aeu012 [published Online First: 2014/02/21]  
13 549 53. Rush AJ, Giles DE, Schlessner MA, et al. The Inventory for Depressive Symptomatology (IDS):  
14 550 preliminary findings. *Psychiatry Res* 1986;18(1):65-87. doi: 10.1016/0165-1781(86)90060-0  
15 551 [published Online First: 1986/05/01]  
16 552 54. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS):  
17 553 psychometric properties. *Psychol Med* 1996;26(3):477-86. doi: 10.1017/s0033291700035558  
18 554 [published Online First: 1996/05/01]  
19 555 55. Rothaug J, Zaslansky R, Schwenkglens M, et al. Patients' perception of postoperative pain  
20 556 management: validation of the International Pain Outcomes (IPO) questionnaire. *J Pain*  
21 557 2013;14(11):1361-70. doi: 10.1016/j.jpain.2013.05.016 [published Online First: 2013/09/12]  
22 558 56. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap*  
23 559 1994;23(2):129-38. [published Online First: 1994/03/01]  
24 560 57. Dindo D, Clavien PA. What is a surgical complication? *World J Surg* 2008;32(6):939-41. doi:  
25 561 10.1007/s00268-008-9584-y [published Online First: 2008/04/17]  
26 562 58. Purcell S, Cherny SS, Sham PC. Genetic Power Calculator: design of linkage and association genetic  
27 563 mapping studies of complex traits. *Bioinformatics* 2003;19(1):149-50. doi:  
28 564 10.1093/bioinformatics/19.1.149 [published Online First: 2002/12/25]  
29 565 59. Lam M, Awasthi S, Watson HJ, et al. RICOPILI: Rapid Imputation for COnsortias PIpeLIine.  
30 566 *Bioinformatics* 2020;36(3):930-33. doi: 10.1093/bioinformatics/btz633 [published Online First:  
31 567 2019/08/09]  
32 568 60. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and  
33 569 population-based linkage analyses. *Am J Hum Genet* 2007;81(3):559-75. doi: 10.1086/519795  
34 570 [published Online First: 2007/08/19]  
35 571 61. van Dijk JF, van Wijck AJ, Kappen TH, et al. Postoperative pain assessment based on numeric ratings  
36 572 is not the same for patients and professionals: a cross-sectional study. *Int J Nurs Stud*  
37 573 2012;49(1):65-71. doi: 10.1016/j.ijnurstu.2011.07.009 [published Online First: 2011/08/16]  
38 574 62. Harting B, Johnson T, Abrams R, et al. An exploratory analysis of the correlation of pain scores,  
39 575 patient satisfaction with relief from pain, and a new measure of pain control on the total dose of  
40 576 opioids in pain care. *Qual Manag Health Care* 2013;22(4):322-6. doi:  
41 577 10.1097/qmh.000000000000009 [published Online First: 2013/10/04]  
42 578 63. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain  
43 579 definition of pain: concepts, challenges, and compromises. *Pain* 2020;161(9):1976-82. doi:  
44 580 10.1097/j.pain.0000000000001939 [published Online First: 2020/07/23]  
45 581 64. van Boekel RLM, Vissers KCP, van der Sande R, et al. Moving beyond pain scores: Multidimensional  
46 582 pain assessment is essential for adequate pain management after surgery. *PLoS One*  
47 583 2017;12(5):e0177345. doi: 10.1371/journal.pone.0177345 [published Online First: 2017/05/11]  
48 584 65. Weldring T, Smith SM. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures  
49 585 (PROMs). *Health Serv Insights* 2013;6:61-8. doi: 10.4137/hsi.S11093 [published Online First:  
50 586 2013/01/01]  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 587 66. Sloman R, Wruble AW, Rosen G, et al. Determination of clinically meaningful levels of pain reduction  
4 588 in patients experiencing acute postoperative pain. *Pain Manag Nurs* 2006;7(4):153-8. doi:  
5 589 10.1016/j.pmn.2006.09.001 [published Online First: 2006/12/06]  
6 590 67. Clark CW, Yang JC, Tsui SL, et al. Unidimensional pain rating scales: a multidimensional affect and  
7 591 pain survey (MAPS) analysis of what they really measure. *Pain* 2002;98(3):241-47. doi:  
8 592 10.1016/s0304-3959(01)00474-2 [published Online First: 2002/07/20]  
9 593 68. Dorsey SG, Renn CL, Griffioen M, et al. Whole blood transcriptomic profiles can differentiate  
10 594 vulnerability to chronic low back pain. *PLoS One* 2019;14(5):e0216539. doi:  
11 595 10.1371/journal.pone.0216539 [published Online First: 2019/05/17]  
12 596 69. Van Der Heijden H, Fatou B, Sibai D, et al. Proteomics based markers of clinical pain severity in  
13 597 juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2022;20(1):3. doi: 10.1186/s12969-022-  
14 598 00662-1 [published Online First: 2022/01/17]  
15 599 70. Jha MK, Song GJ, Lee MG, et al. Metabolic Connection of Inflammatory Pain: Pivotal Role of a  
16 600 Pyruvate Dehydrogenase Kinase-Pyruvate Dehydrogenase-Lactic Acid Axis. *J Neurosci*  
17 601 2015;35(42):14353-69. doi: 10.1523/jneurosci.1910-15.2015 [published Online First:  
18 602 2015/10/23]  
19 603 71. Trevethan R. Sensitivity, Specificity, and Predictive Values: Foundations, Plabilities, and Pitfalls in  
20 604 Research and Practice. *Front Public Health* 2017;5:307. doi: 10.3389/fpubh.2017.00307  
21 605 [published Online First: 2017/12/07]  
22 606 72. Fillingim RB, Loeser JD, Baron R, et al. Assessment of Chronic Pain: Domains, Methods, and  
23 607 Mechanisms. *J Pain* 2016;17(9 Suppl):T10-20. doi: 10.1016/j.jpain.2015.08.010 [published Online  
24 608 First: 2016/09/03]  
25 609 73. Ioannidis JP. Non-replication and inconsistency in the genome-wide association setting. *Hum Hered*  
26 610 2007;64(4):203-13. doi: 10.1159/000103512 [published Online First: 2007/06/07]  
27 611 74. van Reij RRI, Voncken JW, Joosten EAJ, et al. Polygenic risk scores indicates genetic overlap between  
28 612 peripheral pain syndromes and chronic postsurgical pain. *Neurogenetics* 2020;21(3):205-15. doi:  
29 613 10.1007/s10048-020-00614-5 [published Online First: 2020/05/08]  
30  
31  
32  
33  
34 614  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure 1: Pain Predict Genetics study design overview.



1  
2  
3 Table of Content  
4  
5  
6

7 Appendix a: General data  
8

9 Appendix b: Pain before and after surgery  
10

11 Appendix c: Physical activities  
12

13 Appendix d: Pain disability index  
14

15 Appendix e: Anxiety and need for information  
16

17 Appendix f: Pain Catastrophizing Scale (PCS)  
18

19 Appendix g: Pain Sensitivity Questionnaire  
20

21 Appendix h: Chronic pain  
22

23 Appendix i: Inventory of depressive symptomatology (self-report) (IDS-SR)  
24

25 Appendix j: Brief Pain Inventory  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## Appendix a: General data

*General data*

- What is your year of birth?
- What is your gender?            male/female
- What is your length ?            \_\_\_\_\_ cm
- What is your weight ?            \_\_\_\_\_ kg
  
- What country were you born in? \_\_\_\_\_
  
- What country(ies) were your parents born in? \_\_\_\_\_
  
- What country(ies) were your grandparents born in? \_\_\_\_\_
  
- What human race are you? (black, white, Asian, etc.) \_\_\_\_\_

*Data of the surgery:*

- *Would you please describe your surgery.*

- How much pain do you expect after surgery (0= no pain, 10=worst pain imaginable)
- Will you stay one or more nights in the hospital after surgery? Yes / No

## Appendix b: Pain before and after surgery

## Pain before and after surgery

Circle how much pain you have, expressed as a number. The pain score means a score between 0 and 10, where 0 means no pain and 10 means the worst pain imaginable. For your pain, consider a figure between 0 and 10. You also tick whether you think the pain is acceptable or not.

Pain while being at rest at this moment (0-10)	No pain 0-1-2-3-4-5-6-7-8-9-10 worst pain imaginable
Pain score at this moment if you perform a normal effort (0-10)	No pain 0-1-2-3-4-5-6-7-8-9-10 worst pain imaginable
Do you think pain is acceptable to you at this moment?	Pain acceptable _  pain not acceptable  _
Only pre-operatively: How much pain do you expect after surgery?	No pain 0-1-2-3-4-5-6-7-8-9-10 worst pain imaginable

## Appendix c: Physical activities

## Physical activities

Circle the one number below that best describes how much, since your surgery, pain interfered with or prevented you from doing physical activities, expressed by figure. The score means a figure between 0 and 10, where 0 means no interference and 10 means complete interference.

1. How much has pain interfered with or prevented you from doing activities in bed such as turning, sitting up, changing position (0= did not interfere, 10= completely interfered)

0-1-2-3-4-5-6-7-8-9-10

2. How much has pain interfered with or prevented you from breathing deeply or coughing (0= did not interfere, 10= completely interfered)

0-1-2-3-4-5-6-7-8-9-10

3. How much has pain interfered with or prevented you from sleeping (0= did not interfere, 10= completely interfered)

0-1-2-3-4-5-6-7-8-9-10

4. Have you been out of bed since your surgery? Yes/no

0-1-2-3-4-5-6-7-8-9-10

5. If yes, how much did pain interfere or prevent you from doing activities out of bed such as walking, sitting in a chair, standing at the sink (0= did not interfere, 10= completely interfered)

0-1-2-3-4-5-6-7-8-9-10

## Appendix d: Pain disability index

## Pain disability index

We would like to know how much pain is preventing you from doing what you would normally do or from doing it as well as you normally would. Respond to each category indicating the overall impact of pain in your life, not just when pain is at its worst.

For each of the 7 categories of life activity listed, please circle the number on the scale that describes the level of disability you typically experience. A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain.

In case of no pain, please circle "0".

<p><b>1. Family/Home Responsibilities</b></p> <p>This category refers to activities of the home or family. It includes chores or duties performed around the house (e.g. yard work) and errands or favors for other family members (e.g. driving the children to school).</p>	<p>No disability    0-1-2-3-4-5-6-7-8-9-10    Worst disability</p>
<p><b>2. Recreation</b></p> <p>This disability includes hobbies, sports, and other similar leisure time activities.</p>	<p>No disability    0-1-2-3-4-5-6-7-8-9-10    Worst disability</p>
<p><b>3. Social activity</b></p> <p>This category refers to activities, which involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out, and other social functions.</p>	<p>No disability    0-1-2-3-4-5-6-7-8-9-10    Worst disability</p>
<p><b>4. Occupation</b></p> <p>This category refers to activities that are part of or directly related to one's job. This includes non-paying jobs as well, such as that of a housewife or volunteer.</p>	<p>No disability    0-1-2-3-4-5-6-7-8-9-10    Worst disability</p>
<p><b>5. Sexual behavior</b></p> <p>This category refers to the frequency and quality of one's sex life.</p>	<p>No disability    0-1-2-3-4-5-6-7-8-9-10    Worst disability</p>
<p><b>6. Self care</b></p>	<p>No disability    0-1-2-3-4-5-6-7-8-9-10    Worst disability</p>

<p>This category includes activities, which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed, etc.)</p>	
<p><b>7. Life-support activities</b></p> <p>This category refers to basic life supporting behaviors such as eating, sleeping and breathing.</p>	<p>No disability 0-1-2-3-4-5-6-7-8-9-10 Worst disability</p>

For peer review only

1  
2  
3 Appendix e: Anxiety and need for information  
4  
5  
6

7 Anxiety and need for information  
8

9 *Please circle the number on the scale that describes your experience:*  
10  
11

<b>The Amsterdam Preoperative Anxiety and Information Scale (APAIS):</b>	Not at all				Extremely
I am worried about the anesthetic	1	2	3	4	5
The anesthetic is on my mind continually	1	2	3	4	5
I am worried about the procedure	1	2	3	4	5
The procedure is on my mind continually	1	2	3	4	5
I would like to know as much as possible about the anesthetic	1	2	3	4	5
I would like to know as much as possible about the procedure	1	2	3	4	5

## Appendix f: Pain Catastrophizing Scale (PCS)

## Pain Catastrophizing Scale (PCS)

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0=not at all    1=to a slight degree    2=to a moderate degree    3=to a great degree    4=all the time

When I'm in pain .....

1.	I worry all the time about whether the pain will end	0	1	2	3	4
2.	I feel I can't go on	0	1	2	3	4
3.	It's terrible and I think that it's never going to get any better	0	1	2	3	4
4.	It's awful and I feel that it overwhelms me	0	1	2	3	4
5.	I feel that I can't stand it any more	0	1	2	3	4
6.	I become afraid that the pain will get worse	0	1	2	3	4
7.	I keep thinking of other painful events	0	1	2	3	4
8.	I anxiously want the pain to go away	0	1	2	3	4
9.	I can't seem to keep it out of my mind	0	1	2	3	4
10.	I keep thinking about how much it hurts	0	1	2	3	4
11.	I keep thinking about how badly I want the pain to stop	0	1	2	3	4
12.	There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
13.	I wonder whether something serious may happen	0	1	2	3	4

## Appendix g: Pain Sensitivity Questionnaire

## Pain Sensitivity Questionnaire

*This questionnaire contains a series of questions in which you should imagine yourself in certain situations. You should then decide if these situations would be painful for you and if yes, how painful they would be.*

**Let 0 stand for no pain; 1 is an only just noticeable pain and 10 the most severe pain that you can imagine or consider possible.**

*Please mark the scale with a cross on the number that is most true for you. Keep in mind that there are no "right" or "wrong" answers; only your personal assessment of the situation counts. Please try as much as possible not to allow your fear or aversion of the imagined situations affect your assessment of painfulness.*

- Imagine you bump your shin badly on a hard edge, for example, on the edge of a glass coffee table. How painful would that be for you?

**0 = not at all painful, 10= most severe pain imaginable**

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine you burn your tongue on a very hot drink.

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine your muscles are slightly sore as the result of physical activity.

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine you trap your finger in a drawer.

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine you take a shower with lukewarm water.

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine you have mild sunburn on your shoulders.



1  
2  
3 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
4  
5  
6

7. Imagine you grazed your knee falling off your bicycle.

8  
9 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
10  
11

- 12 8. Imagine you accidentally bite your tongue or cheek badly while eating.

13  
14 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
15  
16

- 17 9. Imagine walking across a cool tiled floor with bare feet.

18  
19 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
20  
21

- 22 10. Imagine you have a minor cut on your finger and inadvertently get lemon juice in the  
23 wound.

24  
25 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
26  
27

- 28 11. Imagine you prick your fingertip on the thorn of a rose.

29  
30 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
31  
32

- 33 12. Imagine you stick your bare hands in the snow for a couple of minutes or bring your  
34 hands

35 in contact with snow for some time, for example, while making snowballs.

36  
37 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
38  
39

- 40 13. Imagine you shake hands with someone who has a normal grip.

41  
42 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
43  
44

- 45 14. Imagine you shake hands with someone who has a very strong grip.

46  
47 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
48  
49

- 50 15. Imagine you pick up a hot pot by inadvertently grabbing its equally hot handles.

51  
52 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
53  
54

- 55 16. Imagine you are wearing sandals and someone with heavy boots steps on your foot.

56  
57 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
58  
59  
60

1  
2  
3  
4  
5 17. Imagine you bump your elbow on the edge of a table ("funny bone").  
6  
7

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

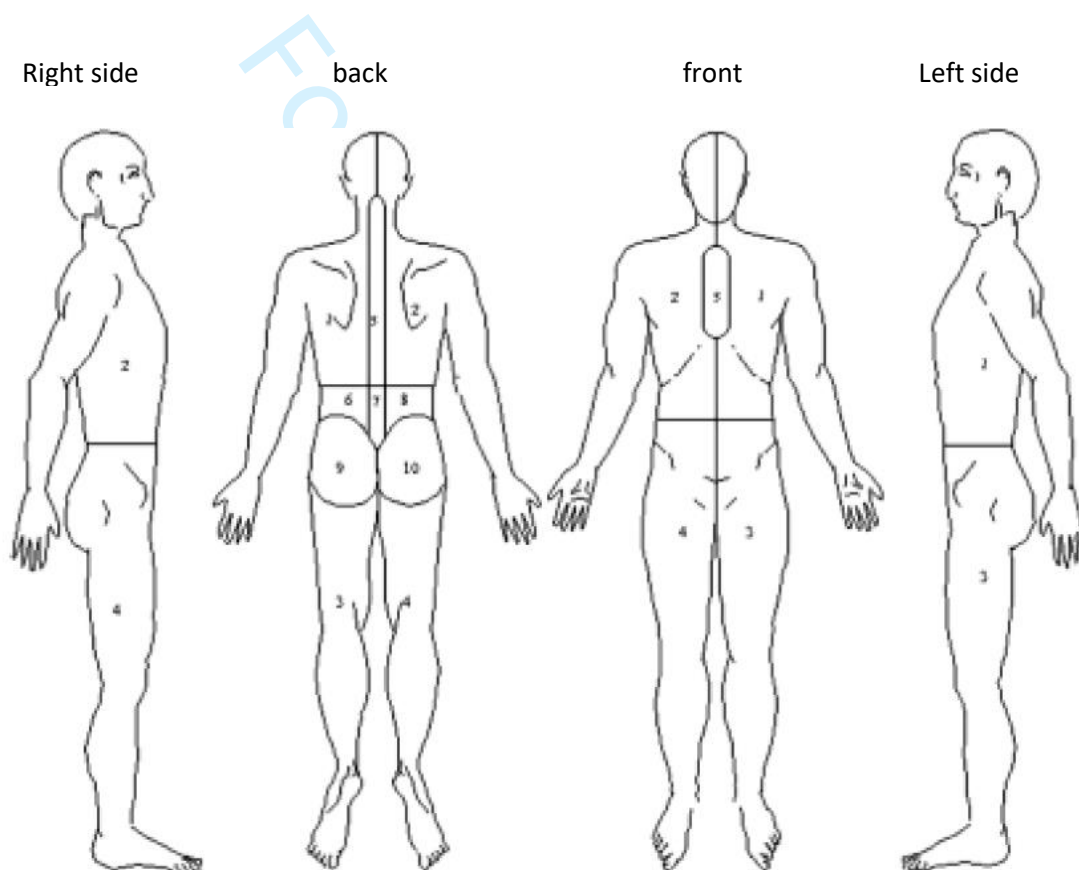
## Appendix h: Chronic pain

## Chronic pain

Did you experience any pain in the last month that lasted for a day or more?

- Yes, next question
- No

Can you indicate in the drawings below where you suffer (have suffered) from pain?



Is this the same spot as the spot you are operated on? Yes/no

Does the pain differ from the pain before surgery? Yes/no

How long have you been affected by the above-mentioned pain?

- Less than three months
- More than three months

## Appendix i: Inventory of depressive symptomatology (self-report) (IDS-SR)

**INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SELF-REPORT)**  
(IDS-SR)

NAME: \_\_\_\_\_ TODAY'S DATE \_\_\_\_\_

Please circle the one response to each item that best describes you for the past seven days.

- |   |   |
|---|---|
| <p>1. <b>Falling Asleep:</b></p> <p>0 I never take longer than 30 minutes to fall asleep.</p> <p>1 I take at least 30 minutes to fall asleep, less than half the time.</p> <p>2 I take at least 30 minutes to fall asleep, more than half the time.</p> <p>3 I take more than 60 minutes to fall asleep, more than half the time.</p> <p>2. <b>Sleep During the Night:</b></p> <p>0 I do not wake up at night.</p> <p>1 I have a restless, light sleep with a few brief awakenings each night.</p> <p>2 I wake up at least once a night, but I go back to sleep easily.</p> <p>3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.</p> <p>3. <b>Waking Up Too Early:</b></p> <p>0 Most of the time, I awaken no more than 30 minutes before I need to get up.</p> <p>1 More than half the time, I awaken more than 30 minutes before I need to get up.</p> <p>2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.</p> <p>3 I awaken at least one hour before I need to, and can't go back to sleep.</p> <p>4. <b>Sleeping Too Much:</b></p> <p>0 I sleep no longer than 7-8 hours/night, without napping during the day.</p> <p>1 I sleep no longer than 10 hours in a 24-hour period including naps.</p> <p>2 I sleep no longer than 12 hours in a 24-hour period including naps.</p> <p>3 I sleep longer than 12 hours in a 24-hour period including naps.</p> <p>5. <b>Feeling Sad:</b></p> <p>0 I do not feel sad</p> <p>1 I feel sad less than half the time.</p> <p>2 I feel sad more than half the time.</p> <p>3 I feel sad nearly all of the time.</p> <p>6. <b>Feeling Irritable:</b></p> <p>0 I do not feel irritable.</p> <p>1 I feel irritable less than half the time.</p> <p>2 I feel irritable more than half the time.</p> <p>3 I feel extremely irritable nearly all of the time.</p> | <p>7. <b>Feeling Anxious or Tense:</b></p> <p>0 I do not feel anxious or tense.</p> <p>1 I feel anxious (tense) less than half the time.</p> <p>2 I feel anxious (tense) more than half the time.</p> <p>3 I feel extremely anxious (tense) nearly all of the time.</p> <p>8. <b>Response of Your Mood to Good or Desired Events:</b></p> <p>0 My mood brightens to a normal level which lasts for several hours when good events occur.</p> <p>1 My mood brightens but I do not feel like my normal self when good events occur.</p> <p>2 My mood brightens only somewhat to a rather limited range of desired events.</p> <p>3 My mood does not brighten at all, even when very good or desired events occur in my life.</p> <p>9. <b>Mood in Relation to the Time of Day:</b></p> <p>0 There is no regular relationship between my mood and the time of day.</p> <p>1 My mood often relates to the time of day because of environmental events (e.g., being alone, working).</p> <p>2 In general, my mood is more related to the time of day than to environmental events.</p> <p>3 My mood is clearly and predictably better or worse at a particular time each day.</p> <p>9A. Is your mood typically worse in the morning, afternoon or night? (circle one)</p> <p>9B. Is your mood variation attributed to the environment? (yes or no) (circle one)</p> <p>10. <b>The Quality of Your Mood:</b></p> <p>0 The mood (internal feelings) that I experience is very much a normal mood.</p> <p>1 My mood is sad, but this sadness is pretty much like the sad mood I would feel if someone close to me died or left.</p> <p>2 My mood is sad, but this sadness has a rather different quality to it than the sadness I would feel if someone close to me died or left.</p> <p>3 My mood is sad, but this sadness is different from the type of sadness associated with grief or loss.</p> |
|---|---|

Please complete either 11 or 12 (not both)

## 11. Decreased Appetite:

- 0 There is no change in my usual appetite.
- 1 I eat somewhat less often or lesser amounts of food than usual.
- 2 I eat much less than usual and only with personal effort.
- 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

## 12. Increased Appetite:

- 0 There is no change from my usual appetite.
- 1 I feel a need to eat more frequently than usual.
- 2 I regularly eat more often and/or greater amounts of food than usual.
- 3 I feel driven to overeat both at mealtime and between meals.

Please complete either 13 or 14 (not both)

## 13. Decreased Weight (Within the Last Two Weeks):

- 0 I have not had a change in my weight.
- 1 I feel as if I've had a slight weight loss.
- 2 I have lost 2 pounds or more.
- 3 I have lost 5 pounds or more.

## 14. Increased Weight (Within the Last Two Weeks):

- 0 I have not had a change in my weight.
- 1 I feel as if I've had a slight weight gain.
- 2 I have gained 2 pounds or more.
- 3 I have gained 5 pounds or more.

## 15. Concentration/Decision Making:

- 0 There is no change in my usual capacity to concentrate or make decisions.
- 1 I occasionally feel indecisive or find that my attention wanders.
- 2 Most of the time, I struggle to focus my attention or to make decisions.
- 3 I cannot concentrate well enough to read or cannot make even minor decisions.

## 16. View of Myself:

- 0 I see myself as equally worthwhile and deserving as other people.
- 1 I am more self-blaming than usual.
- 2 I largely believe that I cause problems for others.
- 3 I think almost constantly about major and minor defects in myself.

## 17. View of My Future:

- 0 I have an optimistic view of my future.
- 1 I am occasionally pessimistic about my future, but for the most part I believe things will get better.
- 2 I'm pretty certain that my immediate future (1-2 months) does not hold much promise of good things for me.
- 3 I see no hope of anything good happening to me anytime in the future.

## 18. Thoughts of Death or Suicide:

- 0 I do not think of suicide or death.
- 1 I feel that life is empty or wonder if it's worth living.
- 2 I think of suicide or death several times a week for several minutes.
- 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

## 19. General Interest:

- 0 There is no change from usual in how interested I am in other people or activities.
- 1 I notice that I am less interested in people or activities.
- 2 I find I have interest in only one or two of my formerly pursued activities.
- 3 I have virtually no interest in formerly pursued activities.

## 20. Energy Level:

- 0 There is no change in my usual level of energy.
- 1 I get tired more easily than usual.
- 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
- 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

## 21. Capacity for Pleasure or Enjoyment (excluding sex):

- 0 I enjoy pleasurable activities just as much as usual.
- 1 I do not feel my usual sense of enjoyment from pleasurable activities.
- 2 I rarely get a feeling of pleasure from any activity.
- 3 I am unable to get any pleasure or enjoyment from anything.

22. Interest in Sex (Please Rate Interest, not Activity):

- 0 I'm just as interested in sex as usual.
- 1 My interest in sex is somewhat less than usual or I do not get the same pleasure from sex as I used to.
- 2 I have little desire for or rarely derive pleasure from sex.
- 3 I have absolutely no interest in or derive no pleasure from sex.

## 23. Feeling slowed down:

- 0 I think, speak, and move at my usual rate of speed.
- 1 I find that my thinking is slowed down or my voice sounds dull or flat.
- 2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
- 3 I am often unable to respond to questions without extreme effort.

## 24. Feeling restless:

- 0 I do not feel restless.
- 1 I'm often fidgety, wring my hands, or need to shift how I am sitting.
- 2 I have impulses to move about and am quite restless.
- 3 At times, I am unable to stay seated and need to pace around.

## 25. Aches and pains:

- 0 I don't have any feeling of heaviness in my arms or legs and don't have any aches or pains.
- 1 Sometimes I get headaches or pains in my stomach, back or joints but these pains are only sometime present and they don't stop me from doing what I need to do.
- 2 I have these sorts of pains most of the time.
- 3 These pains are so bad they force me to stop what I am doing.

## 26. Other bodily symptoms:

- 0 I don't have any of these symptoms: heart pounding fast, blurred vision, sweating, hot and cold flashes, chest pain, heart turning over in my chest, ringing in my ears, or shaking.
- 1 I have some of these symptoms but they are mild and are present only sometimes.
- 2 I have several of these symptoms and they bother me quite a bit.
- 3 I have several of these symptoms and when they occur I have to stop doing whatever I am doing.

Range 0-84    Score: \_\_\_\_\_

## 27. Panic/Phobic symptoms:

- 0 I have no spells of panic or specific fears (phobia) (such as animals or heights).
- 1 I have mild panic episodes or fears that do not usually change my behavior or stop me from functioning.
- 2 I have significant panic episodes or fears that force me to change my behavior but do not stop me from functioning.
- 3 I have panic episodes at least once a week or severe fears that stop me from carrying on my daily activities.

## 28. Constipation/diarrhea:

- 0 There is no change in my usual bowel habits.
- 1 I have intermittent constipation or diarrhea which is mild.
- 2 I have diarrhea or constipation most of the time but it does not interfere with my day-to-day functioning.
- 3 I have constipation or diarrhea for which I take medicine or which interferes with my day-to-day activities.

## 29. Interpersonal Sensitivity:

- 0 I have not felt easily rejected, slighted, criticized or hurt by others at all.
- 1 I have occasionally felt rejected, slighted, criticized or hurt by others.
- 2 I have often felt rejected, slighted, criticized or hurt by others, but these feelings have had only slight effects on my relationships or work.
- 3 I have often felt rejected, slighted, criticized or hurt by others and these feelings have impaired my relationships and work.

## 30. Lethargy/Physical Energy:

- 0 I have not experienced the physical sensation of feeling weighted down and without physical energy.
- 1 I have occasionally experienced periods of feeling physically weighted down and without physical energy, but without a negative effect on work, school, or activity level.
- 2 I feel physically weighted down (without physical energy) more than half the time.
- 3 I feel physically weighted down (without physical energy) most of the time, several hours per day, several days per week.

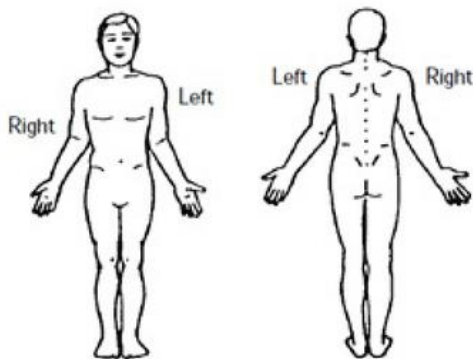
Appendix j: Brief Pain Inventory

Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_ Time: \_\_\_\_\_  
 Name: \_\_\_\_\_  
                     Last                    First                    Middle initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its **worst** in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its **least** in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on **average**.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have **right now**.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

\_\_\_\_\_

\_\_\_\_\_

8) In the past 24 hours, how much **relief** have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10	20	30	40	50	60	70	80	90	100%
No relief										Complete relief

9) Circle the one number that describes how, during the past 24 hours, pain has **interfered** with your:

A. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

# Reporting checklist for genetic association study.

Based on the STREGA guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STREGA reporting guidelines, and cite them as:

Little J, Higgins JP, Ioannidis JP, Moher D, Gagnon F, von Elm E, Khoury MJ, Cohen B, Davey-Smith G, Grimshaw J, Scheet P, Gwinn M, Williamson RE, Zou GY, Hutchings K, Johnson CY, Tait V, Wiens M, Golding J, van Duijn C, McLaughlin J, Paterson A, Wells G, Fortier I, Freedman M, Zecevic M, King R, Infante-Rivard C, Stewart A, Birkett N; STrengthening the REporting of Genetic Association Studies. STrengthening the REporting of Genetic Association Studies (STREGA): An Extension of the STROBE Statement.

Reporting Item

Page Number

### Title and abstract

Title	<a href="#">#1a</a>	Indicate the study's design with a commonly used term in the title or the abstract	1
-------	---------------------	--	---



1	Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and	3
2				
3				
4			balanced summary of what was done and what	
5				
6			was found	
7				
8				
9	<b>Background/rationale</b>			
10				
11				
12		<a href="#">#2</a>	Explain the scientific background and rationale for	6
13				
14			the investigation being reported	
15				
16				
17	<b>Objectives</b>			
18				
19				
20		<a href="#">#3</a>	State specific objectives, including any	9
21				
22			prespecified hypotheses. State if the study is the	
23				
24			first report of a genetic association, a replication	
25				
26			effort, or both.	
27				
28				
29				
30	<b>Study design</b>			
31				
32				
33		<a href="#">#4</a>	Present key elements of study design early in the	10
34				
35			paper	
36				
37				
38				
39	<b>Setting</b>			
40				
41				
42		<a href="#">#5</a>	Describe the setting, locations, and relevant	10
43				
44			dates, including periods of recruitment, exposure,	
45				
46			follow-up, and data collection	
47				
48				
49	<b>Eligibility criteria</b>			
50				
51				
52		<a href="#">#6a</a>	Cohort study – Give the eligibility criteria, and the	11
53				
54			sources and methods of selection of participants.	
55				
56			Describe methods of follow-up. Case-control	
57				
58				
59				
60				

1 study – Give the eligibility criteria, and the sources  
 2 and methods of case ascertainment and control  
 3 selection. Give the rationale for the choice of  
 4 cases and controls. Cross-sectional study – Give  
 5 the eligibility criteria, and the sources and  
 6 methods of selection of participants. Give  
 7 information on the criteria and methods for  
 8 selection of subsets of participants from a larger  
 9 study, when relevant.

10  
 11  
 12  
 13  
 14  
 15  
 16  
 17  
 18  
 19  
 20  
 21  
 22 [#6b](#) Cohort study – For matched studies, give n/a, not matched  
 23 matching criteria and number of exposed and study  
 24 unexposed. Case-control study – For matched  
 25 studies, give matching criteria and the number of  
 26 controls per case.  
 27  
 28  
 29  
 30  
 31  
 32  
 33

## Variables

34  
 35  
 36  
 37 [#7a](#) Clearly define all outcomes, exposures, 11, 14-16  
 38 predictors, potential confounders, and effect  
 39 modifiers. Give diagnostic criteria, if applicable  
 40  
 41  
 42  
 43

44  
 45 [#7b](#) Clearly define genetic exposures (genetic 16  
 46 variants) using a widely-used nomenclature  
 47 system. Identify variables likely to be associated  
 48 with population stratification (confounding by  
 49 ethnic origin).  
 50  
 51  
 52  
 53  
 54  
 55  
 56

## Data

1 **sources/measurement**

2

3

4 [#8a](#) For each variable of interest give sources of data 11, 14-16

5

6 and details of methods of assessment

7

8 (measurement). Describe comparability of

9

10 assessment methods if there is more than one

11

12 group. Give information separately for for exposed

13

14 and unexposed groups if applicable.

15

16

17

18 [#8b](#) Describe laboratory methods, including source 16

19

20 and storage of DNA, genotyping methods and

21

22 platforms (including the allele calling algorithm

23

24 used, and its version), error rates and call rates.

25

26 State the laboratory / centre where genotyping

27

28 was done. Describe comparability of laboratory

29

30 methods if there is more than one group. Specify

31

32 whether genotypes were assigned using all of the

33

34 data from the study simultaneously or in smaller

35

36 batches.

37

38

39

40

41 **Bias**

42

43

44 [#9a](#) Describe any efforts to address potential sources 21

45

46 of bias

47

48

49

50 [#9b](#) Describe any efforts to address potential sources 21

51

52 of bias

53

54

55 **Study size**

1			
2			
3			
4	<b>Quantitative variables</b>		
5			
6			
7			
8	<a href="#">#10</a>	Explain how the study size was arrived at	17
9			
10			
11			
12	<a href="#">#11</a>	Explain how quantitative variables were handled	18
13		in the analyses. If applicable, describe which	
14		groupings were chosen, and why. If applicable,	
15		describe how effects of treatment were dealt with.	
16			
17	<b>Statistical methods</b>		
18			
19			
20	<a href="#">#12a</a>	Describe all statistical methods, including those	18-19
21		used to control for confounding. State software	
22		version used and options (or settings) chosen.	
23			
24			
25			
26			
27			
28	<a href="#">#12b</a>	Describe any methods used to examine	n/a to protocol
29		subgroups and interactions	paper.
30			
31			
32			
33	<a href="#">#12c</a>	Explain how missing data were addressed	n/a to protocol
34			paper.
35			
36			
37			
38			
39	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was	n/a to protocol
40		addressed	paper.
41			
42			
43			
44	<a href="#">#12e</a>	Describe any sensitivity analyses	n/a to protocol
45			paper.
46			
47			
48			
49	<a href="#">#12f</a>	State whether Hardy-Weinberg equilibrium was	18
50		considered and, if so, how.	
51			
52			
53			
54			
55	<a href="#">#12g</a>	Describe any methods used for inferring	18
56		genotypes or haplotypes	
57			
58			
59			
60			

## Participants

1	<a href="#">#12h</a>	Describe any methods used to assess or address	18
2			
3		population stratification.	
4			
5			
6	<a href="#">#12i</a>	Describe any methods used to address multiple	18
7		comparisons or to control risk of false positive	
8		findings.	
9			
10			
11	<a href="#">#12j</a>	Describe any methods used to address and	18
12		correct for relatedness among subjects	
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23	<a href="#">#13a</a>	Report numbers of individuals at each stage of	n/a to protocol
24		study—eg numbers potentially eligible, examined	paper.
25		for eligibility, confirmed eligible, included in the	Participant
26		study, completing follow-up, and analysed. Give	enrollment is not
27		information separately for for exposed and	finished yet
28		unexposed groups if applicable. Report numbers	
29		of individuals in whom genotyping was attempted	
30		and numbers of individuals in whom genotyping	
31		was successful.	
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44	<a href="#">#13b</a>	Give reasons for non-participation at each stage	n/a to protocol
45			paper.
46			Participant
47			enrollment is not
48			finished yet
49			
50			
51			
52			
53			
54			
55			
56	<a href="#">#13c</a>	Consider use of a flow diagram	See figure 1
57			
58			
59			
60			

1 **Descriptive data**  
2  
3

4 [#14a](#) Give characteristics of study participants (eg n/a to protocol  
5 demographic, clinical, social) and information on paper.  
6 exposures and potential confounders. Give Participant  
7 information separately for exposed and enrollment is not  
8 unexposed groups if applicable. Consider giving finished yet  
9 information by genotype  
10  
11  
12  
13  
14  
15  
16  
17

18 [#14b](#) Indicate number of participants with missing data  
19 for each variable of interest  
20  
21  
22  
23

24 [#14c](#) Cohort study – Summarize follow-up time, e.g.  
25 average and total amount.  
26  
27  
28

29 **Outcome data**  
30  
31

32 [#15](#) Cohort study Report numbers of outcome events n/a to protocol  
33 or summary measures over time. Give information paper.  
34 separately for exposed and unexposed groups if Participant  
35 applicable. Report outcomes (phenotypes) for enrollment is not  
36 each genotype category over time Case-control finished yet  
37 study – Report numbers in each exposure  
38 category, or summary measures of exposure. Give  
39 information separately for cases and controls .  
40 Report numbers in each genotype category.  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

unexposed groups if applicable. Report outcomes  
(phenotypes) for each genotype category

## Main results

**#16a** Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

n/a to protocol paper.  
Participant enrollment is not finished yet

**#16b** Report category boundaries when continuous variables were categorized

**#16c** If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

**#16d** Report results of any adjustments for multiple comparisons

## Other analyses

**#17a** Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses

n/a to protocol paper.  
Participant enrollment is not finished yet

**#17b** Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity

1 analyses

2  
3  
4 [#17c](#) Report other analyses done—e.g., analyses of  
5 subgroups and interactions, and sensitivity  
6 analyses  
7  
8  
9

10  
11 **Key results**  
12  
13

14 [#18](#) Summarise key results with reference to study objectives  
15 n/a to protocol  
16 paper.  
17 Participant  
18 enrollment is not  
19 finished yet  
20  
21  
22  
23  
24  
25

26 **Limitations**  
27  
28

29 [#19](#) Discuss limitations of the study, taking into  
30 account sources of potential bias or imprecision. 21  
31  
32 Discuss both direction and magnitude of any  
33 potential bias.  
34  
35  
36  
37  
38

39 **Interpretation**  
40  
41

42 [#20](#) Give a cautious overall interpretation considering 21  
43 objectives, limitations, multiplicity of analyses,  
44 results from similar studies, and other relevant  
45 evidence.  
46  
47  
48  
49  
50  
51

52 **Generalisability**  
53  
54

55 [#21](#) Discuss the generalisability (external validity) of 21  
56 the study results  
57  
58  
59



## Funding

#22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

None The STREGA checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

# BMJ Open

## **Pain Predict Genetics: Protocol for a prospective observational study of clinical and genetic factors to predict the development of postoperative pain.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-066134.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Sep-2022
Complete List of Authors:	LI, SONG; Radboudumc Radboud Institute for Health Sciences, Department of Human Genetics van Boekel, Regina L.M.; Radboudumc, Department of Anesthesiology, Pain and Palliative Medicine van den Heuvel, Sandra ; Radboudumc, Department of Anesthesiology, Pain and Palliative Medicine Coenen, Marieke J.H.; Radboudumc Radboud Institute for Health Sciences, Department of Human Genetics Vissers, Kris ; Radboudumc, Department of Anesthesiology, Pain and Palliative Medicine
<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Epidemiology, Genetics and genomics, Surgery
Keywords:	PAIN MANAGEMENT, GENETICS, SURGERY, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

1  
2  
3  
4 1 Pain Predict Genetics: Protocol for a prospective observational  
5  
6 2 study of clinical and genetic factors to predict the development  
7  
8 of postoperative pain.  
9  
10 3  
11 4

12  
13 5 Song Li <sup>1</sup>, Regina L.M. van Boekel <sup>2</sup>, Sandra A.S. van den Heuvel <sup>2</sup>, Marieke J.H. Coenen <sup>1</sup>, Kris C.P.  
14 6 Vissers <sup>2</sup>  
15

16 7  
17  
18 8 Authors' Affiliations:  
19

20 9 <sup>1</sup> Department of Human Genetics, Radboud Institute for Health Sciences, Radboud university  
21 10 medical center, Nijmegen, The Netherlands.  
22

23 11 <sup>2</sup> Department of Anesthesiology, Pain and Palliative Medicine, Radboud university medical  
24 12 center, Nijmegen, The Netherlands.  
25

26 13  
27  
28 14 Email:  
29

30 15 Song Li: Song.Li@radboudumc.nl  
31

32 16 Regina (Rianne) van Boekel: Rianne.vanBoekel@radboudumc.nl  
33

34 17 Sandra van den Heuvel Sandra.vandenHeuvel@Radboudumc.nl  
35

36 18 Marieke Coenen: Marieke.Coenen@radboudumc.nl  
37

38 19 Kris C.P. Vissers Kris.Vissers@radboudumc.nl  
39  
40

41 20  
42 21 Corresponding author:  
43

44 22 Regina L.M. van Boekel  
45

46 23 Rianne.vanBoekel@radboudumc.nl  
47

48 24 Radboud University Medical Center,  
49

50 25 Department of Anesthesiology, Pain and Palliative Medicine  
51

52 26 PO Box 9101, intern 549  
53  
54

55 27 6500 HB, Nijmegen, The Netherlands  
56  
57  
58  
59  
60

1  
2  
3 28 Phone: 0031-243668120  
4

5 29 Fax: 0031243613585  
6  
7

8  
9 30

10 31 The number of text pages: 28  
11

12  
13 32 The actual number of figures and tables: 1 Figure, 1 Table, and 1 Supplementary file.  
14

15  
16 33  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## Abstract

**Introduction** Postoperative pain remains a challenging medical condition impacting the quality of life of every patient. Although several predictive factors for postoperative pain have been identified, an adequate prediction of postoperative pain in patients at risk has not been achieved yet.

The primary objective of this study is to identify specific genetic risk factors for the development of acute and chronic postoperative pain to construct a prediction model facilitating a more personalized postoperative pain management for each individual. The secondary objectives are to build a databank enabling researchers to identify other risk factors for postoperative pain, for instance, demographic and clinical outcome indicators; provide insight into (genetic) factors that predict pharmacological pain relief; investigate the relationship between acute and chronic postoperative pain.

**Methods and analysis** In this prospective, observational study, patients who undergo elective surgery will be recruited to a sample size of approximately 10,000 patients. Postoperative acute and chronic pain outcomes will be collected through questionnaires at different time points after surgery in the follow-up of six months. Potential genetic, demographic, and clinical risk factors for prediction model construction will be collected through blood, questionnaires, and electronic health records, respectively.

Genetic factors associated with acute and/or chronic postoperative pain will be identified using a genome-wide association (GWA) analysis. Clinical risk factors as stated in the secondary

1  
2  
3 54 objectives will be assessed by multivariable regression. A clinical easy-to-use prediction model  
4  
5 55 will be created for postoperative pain to allow clinical use for the stratification of patients.  
6  
7

8  
9 56 **Ethics and dissemination** The Institutional Review Board of the Radboud university medical  
10  
11 57 center approved the study (authorization number: 2012/117). The results of this study will be  
12  
13 58 made available through peer-reviewed scientific journals and presentations at relevant  
14  
15 59 conferences, which will finally contribute to personalized postoperative pain management.  
16  
17  
18

19 60 **Trial registration number** NCT02383342  
20  
21

22 61  
23  
24  
25 62 **Keywords:** Postoperative pain, Genome-wide association study (GWAS), Risk factor, Prediction  
26  
27 63 model, Pharmacogenetics  
28  
29  
30

31 64  
32  
33

34 65  
35  
36

37 66  
38  
39

40 67  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Strengths and limitations of this study

- This is a large prospective study to identify genetic and other risk factors for postoperative pain.
- We will build a databank with comprehensive interdisciplinary measurements that assess postoperative pain from multiple perspectives.
- Outcome measurements of pain by patient-reported outcomes, rather than evaluated by professionals.
- The investigating biomarkers of postoperative pain are limited to genetic variants.

## 77 Introduction

78 Pain after surgery remains a challenging medical and societal problem <sup>1</sup>. Pain is one of the most  
79 common postsurgical side effects, with moderate to severe acute postoperative pain occurring  
80 in about 41% of the patients <sup>2-4</sup>. Severe postoperative pain is associated with an increased  
81 incidence of postoperative complications <sup>5</sup>, including prolonged hospital stay, readmissions, and  
82 significant reduction of patient satisfaction and quality of life <sup>6,7</sup>. Besides, acute postoperative  
83 pain is associated with chronic pain development after surgery <sup>8</sup>. A recent position paper from  
84 the International Association for the Study of Pain stated that among the almost 40 million  
85 people undergoing surgery globally each year, one out of ten develops chronic postsurgical pain  
86 (CPSP), and one out of hundred suffers from severe CPSP, which will negatively affect patients'  
87 quality of life <sup>9</sup>. In addition, postoperative pain is a considerable burden on health care service  
88 costs, both directly due to patients' increased consumption of medical care and indirectly due to  
89 absenteeism, reduced productivity, and increased social welfare payments <sup>10-15</sup>.

90 The management of both acute postoperative pain <sup>2,16</sup> and CPSP <sup>2,17</sup> has remained suboptimal.  
91 Despite major investments in clinical protocols and guidelines for structural pain management,  
92 infrastructure, and acute pain services (APS), no significant outcome improvements in the  
93 quality of postoperative pain management for individual patients have been achieved in the last  
94 fifteen years <sup>10,11</sup>.

95 Given the high incidence of postoperative pain, identifying patients at risk for CPSP before the  
96 operation is important to apply more personalized pain prevention strategies. The most  
97 important demographic and clinical risk factors for postoperative pain are younger age, female  
98 sex, smoking, history of depressive symptoms, anxiety symptoms, sleep difficulties, higher body



1  
2  
3 99 mass index, presence of preoperative pain, and use of preoperative analgesics<sup>18</sup>. Based on  
4  
5  
6 100 these factors, models have been developed to predict severe acute postoperative pain<sup>19 20</sup> and  
7  
8 101 CPSP<sup>21 22</sup>. A recent study has evaluated a presurgical risk score for CPSP in a prospective cohort,  
9  
10 102 and it reliably identified about 70% of the patients undergoing surgeries at risk of CPSP<sup>23 24</sup>.

11  
12  
13 103 As a multifactorial trait, the incidence variation of CPSP in the population can be explained  
14  
15 104 partly by the demographic and clinical risk factors mentioned above, and partly due to the  
16  
17 105 genetic and epigenetic differences among patients<sup>25 26</sup>. To improve the accuracy and power of  
18  
19 106 prediction, efforts have been made to predict CPSP using genetic variants<sup>21 24</sup>. However, no  
20  
21 107 unequivocal genetic predictors have been found yet. In addition, many exploratory studies  
22  
23 108 investigated the possible role of candidate genes in postoperative pain development. In  
24  
25 109 particular, associations have been found between CPSP and the  $\mu$ -opioid receptor (*OPRM1*) and  
26  
27 110 *catechol-O-methyl transferase (COMT)* genes<sup>27 28</sup>. Still, these results have not been confirmed  
28  
29 111 by others. *OPRM1* is also associated with basal pain sensitivity differences<sup>29</sup>, which could be  
30  
31 112 caused by the altered opioid binding potential in the central nervous system<sup>30</sup>. More recently,  
32  
33 113 hypothesis-free methods, such as genome-wide association studies, have been applied for CPSP  
34  
35 114 to identify markers across the genome<sup>31 32</sup>. One of the studies showed that a genetic variant in  
36  
37 115 the *protein-kinase C* gene is linked to neuropathic pain after complete joint replacement. This  
38  
39 116 gene is involved in long-term potentiation, synaptic plasticity, chronic pain, and memory,  
40  
41 117 indicating that this gene may be relevant for neuropathic pain initiation. The disadvantage of  
42  
43 118 this study is that it was small in terms of patient numbers and only focused on one specific  
44  
45 119 surgical procedure.  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 120 besides genetic variants for altered pain sensitivity, also gene variants in drug metabolism can  
4  
5 121 play a role. Understanding the reasons for ineffective treatment can facilitate the early  
6  
7 122 identification of patients at risk and provide more effective and customized postoperative  
8  
9 123 management. Some associated genes with pain treatment outcomes are also involved in pain  
10  
11 124 development, such as *COMT*<sup>33-35</sup>. Genes involved in the action site of active drugs or the drugs'  
12  
13 125 metabolism might play a role in the therapeutic response of this drug. A well-known example is  
14  
15 126 the *cytochrome P450 (CYP)* family investigated for several drugs (e.g., codeine and tramadol)<sup>36</sup>.  
16  
17  
18 127 However, this area has never been charted in a large population<sup>37</sup>.  
19  
20  
21  
22  
23 128 To date, adequate prediction of patients at risk for postoperative pain in clinical practice has not  
24  
25 129 been achieved for several reasons. First, although many demographic, clinical, and lifestyle  
26  
27 130 factors of postoperative pain have been reported<sup>18</sup>, a lack of consensus on the best outcome  
28  
29 131 indicators for postoperative pain management<sup>38 39</sup> hinders choosing the proper outcome  
30  
31 132 variables for prediction model construction. Second, the potential genetic risk factors of  
32  
33 133 postoperative pain prediction remain obscure. The role of genetic factors in postoperative pain  
34  
35 134 have not been investigated sufficiently, making it challenging to select appropriate genetic risk  
36  
37 135 factors to construct a prediction model. Third, when prediction models are updated, external  
38  
39 136 validation (i.e., in a new population) is important before being implemented in a clinical setting  
40  
41 137<sup>40-43</sup>, which is often difficult due to the lack of validation cohorts. For these reasons, we  
42  
43 138 hypothesize that a global structural multicenter diagnostic program of postoperative pain in a  
44  
45 139 surgical patient population will be valuable for better identifying patients at risk of CPSP and  
46  
47 140 ultimately preventing postoperative pain using individualized pharmacological and non-  
48  
49 141 pharmacological interventions.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 142  
4  
5  
67 143 **Objectives**

9 144 The primary objective of the Pain Predict Genetics (PPG) study is to identify genetic risk factors  
10  
11 145 for acute and chronic postoperative pain development and to construct a prediction model for  
12  
13  
14 146 personalized postoperative pain management.

17 147 The secondary objectives of the PPG study are to build a databank enabling researchers to 1)  
18  
19 148 identify other risk factors for the development of acute and chronic postoperative pain; 2)  
20  
21  
22 149 provide insights into complications and other clinical outcome indicators after surgery; 3)  
23  
24 150 provide insights into the relationship between acute and chronic postoperative pain; 4) identify  
25  
26  
27 151 (genetic) factors that predict pharmacological pain relief. The databank will be open to the  
28  
29 152 public with access fees, and reasonable requests will be discussed in the research group before  
30  
31 153 approval.

35 154 The extensive data collection on (chronic) postoperative pain development of patients  
36  
37 155 undergoing surgery offers many possibilities for additional research questions using  
38  
39  
40 156 conventional statistical methods and artificial intelligence, e.g., machine learning. The cohort  
41  
42 157 could be used to 1) conduct epidemiological studies; 2) investigate other parameters (for  
43  
44  
45 158 example, types of surgery) that are involved in the development of chronic postoperative pain;  
46  
47 159 3) validate new prediction models for (chronic) postoperative pain; 4) identify factors for the  
48  
49  
50 160 postoperative outcome (for example, death, long-term hospitalization, complications); 5)  
51  
52 161 collaborate with other groups to perform large-scale analysis to identify predictors for the  
53  
54 162 development of (chronic) postoperative pain.

## 163 Methods and analyses

### 164 Study design

165 A prospective, observational study of 10,000 patients will undergo elective surgery. This study  
166 will run for at least ten years, during which period it must be possible to include the intended  
167 number of patients. Patient inclusion after CMO (Human Research Committee, in Dutch  
168 Commissie Mensgebonden Onderzoek) approval was started in March 2015, and patient  
169 inclusion was temporarily stopped in 2020 due to COVID restrictions. In the near future, this  
170 study will be continued as a multicenter study; hospitals have already been approached and  
171 indicated that they intend to participate.

### 172 Patient and public involvement

173 During the design of the study the patients aided in the pilot phase of the questionnaires, during  
174 the recruitment the patients are informed concerning the project. In addition, patient reported  
175 outcomes will be used. Patients will be informed about the outcome of the study at several  
176 moments (depending on the obtained results).

### 177 Participants

178 Patients who undergo elective surgery and are eligible for this study will be approached before  
179 their planned surgery during the preoperative consultation. In this way, potential participants  
180 will have sufficient time to consider the study information. If any questions arise, it is possible to  
181 contact the researchers by telephone or ask the questions during the preoperative consultation.  
182 During the preoperative consultation (outpatient clinic or by telephone), the physician  
183 (assistant) will ask the patient if they are interested to participating in the study. If the patient is  
184 willing to participate, the informed consent form will be signed and dated. If patients have an

1  
2  
3 185 online preoperative consultation, this procedure will take place digitally, and patients receive  
4  
5 186 the study forms (signed in advance) at home to return if they consent.  
6  
7

8 187 Patients are eligible for study inclusion if they 1) are older or equal to 16 years; 2) undergo  
9  
10 188 elective surgery with an incision, including cardiothoracic surgery (e.g., cardiomyotomy), general  
11  
12 189 surgery (e.g., breast resection), neurological surgery (e.g., nerve decompression), oral and  
13  
14 190 maxillofacial surgery (e.g., removal of head and neck benign and malignant tumors),  
15  
16 191 otorhinolaryngology (e.g., tympanoplasty), plastic surgery (e.g., breast reconstruction), trauma  
17  
18 192 and orthopedic surgery (e.g., arthroplasty), urology (e.g., prostatectomy) and vascular surgery  
19  
20 193 (e.g., treatment of varicose veins); 3) can read and understand the patient information; 4) will  
21  
22 194 provide informed consent. Patients will be excluded if they 1) intend to undergo another  
23  
24 195 surgery within six months; 2) do not have enough knowledge of the language in words and  
25  
26 196 understanding to complete questionnaires.  
27  
28  
29  
30  
31  
32  
33

## 34 197 **Measurements**

### 35 198 **Questionnaires**

36  
37  
38 199 After written informed consent, participants will be asked to complete questionnaires before  
39  
40 200 and after their surgery. An overview of the study workflow and data collection time points can  
41  
42 201 be found in **Figure 1** and **Table 1**. All patient data will be stored in an online digital database,  
43  
44 202 Castor<sup>44</sup>. The reliability and validity of all questionnaires for measurement collection have been  
45  
46 203 validated in the corresponding populations.  
47  
48  
49  
50  
51 204

**Table 1: Overview of data collection**

	T0	Day -1	Surgery	Day 1	Day 2	Day 3	Week 1	Week 6	Month 3	Month 6
Informed consent	x									
<b>Questionnaires</b>										
Demographic data		x								
Incision size		x		x						
Pain scores		x		x	x	x	x	x	x	x
Physical activities				x	x	x	x			
Pain disability index		x					x	x	x	x
APAIS		x								
PCS		x								
PSQ		x								
Chronic pain		x							x	x
IDS depression		x								
Brief pain inventory									x	x
<b>Data electronic medical file</b>										
Physical status by ASA										x
Type of surgery										x
Duration of surgery										x
Type of anesthesia										x
Complications										x
Hospital stay										x
Pain medication use										x
Incision size										x
Second surgery within 6 months										x



1  
2  
3 206 The first digital questionnaire must be completed the day before the surgery (no longer than  
4  
5 207 one week before). Before surgery, the following parameters will be collected (**Table 1**,  
6  
7  
8 208 Supplementary File 1): demographic characteristics (such as gender, age, BMI), expected  
9  
10 209 incision size in mm, pain intensity, pain disability, preoperative anxiety and need for  
11  
12 210 information, pain catastrophizing, pain sensitivity, preoperative chronic pain characteristics, and  
13  
14  
15 211 depressive symptoms.

16  
17  
18 212 After surgery, the following parameters will be collected: actual incision size in mm on day 1;  
19  
20 213 pain intensity on day 1, 2, 3, week 1 and 6, and month 3 and 6; physical activities on day 1, 2, 3,  
21  
22 214 week 1; pain disability on week 1 and 6, and month 3 and 6; postoperative chronic pain  
23  
24 215 characteristics on month 3 and 6; characteristics of pain on month 3 and 6.

25  
26  
27  
28 216 Pain intensity will be measured with an 11-point numerical rating scale (NRS) at rest and during  
29  
30 217 a normal patient action at that time<sup>20</sup>. The endpoints represent the extremes of the pain  
31  
32 218 experience: 0 means "no pain at all", and 10 means "worst possible pain".

33  
34  
35  
36 219 Pain disability (disability associated with pain) will be measured by the widely used Pain  
37  
38 220 Disability Index Dutch language version (PDI)<sup>45,46</sup>. The PDI is a 7-item questionnaire to  
39  
40 221 investigate the magnitude of the self-reported disability in different situations such as work,  
41  
42 222 leisure time, daily life activities, and sports. The questionnaire is constructed on an 11-point NRS  
43  
44 223 in which 0 means "no disability" and 10 means "maximum disability".

45  
46  
47  
48 224 Preoperative anxiety and need for information will be evaluated by the Amsterdam  
49  
50 225 Preoperative Anxiety and Information Scale (APAIS)<sup>47</sup>. The APAIS consists of six questions and  
51  
52 226 each score on a 5-point Likert scale from 1 (not at all) to 5 (extremely), with four questions to



1  
2  
3 227 assess the patient's preoperative anxiety score and two questions to assess the patient's need  
4  
5 228 for information regarding the scheduled surgery and anesthesia <sup>20</sup>.  
6  
7  
8 229 Pain catastrophizing is generally described as an absurd negative orientation towards hurtful  
9  
10 230 stimuli and is important in pain coping <sup>48</sup>. It will be measured by the Pain Catastrophizing Scale  
11  
12 231 (PCS), a self-evaluating questionnaire consisting of 13 questions. People are asked to indicate  
13  
14 232 the degree to which they have thoughts and feelings when experiencing pain using the 0 (not at  
15  
16 233 all) to 4 (all the time) scale, and a total score will be yielded (range from 0 to 52).  
17  
18  
19 234 The Pain Sensitivity Questionnaire (PSQ) will measure patients' preoperative pain sensitivity <sup>49</sup>  
20  
21 235 <sup>50</sup>. The PSQ consists of 17 questions that describe daily life situations; respondents score their  
22  
23 236 pain intensity for these situations on an NRS by scoring 0 (not painful) to 10 (severest pain  
24  
25 237 imaginable).  
26  
27  
28 238 The severity of overall depressive symptoms will be assessed by the Inventory of Depressive  
29  
30 239 Symptomatology Self Report (IDS-SR) <sup>51 52</sup>. IDS-SR is a 30-item questionnaire, and each item has  
31  
32 240 four statements scored on a four-point scale from 0 to 3. There are two items about either  
33  
34 241 increasing or decreasing appetite and two items about increasing or decreasing weight. Only the  
35  
36 242 item with the higher score from both pairs will be chosen. The total score is based on 28 items  
37  
38 243 and ranges from 0 to 84.  
39  
40  
41 244 Physical activities (ability to perform normal activities) will be measured by questions assessing  
42  
43 245 the degree of physical activities interfered by surgery, including bed activities (such as turning),  
44  
45 246 breathing deeply of coughing, sleeping, and activities out of bed. Each item is scored on an 11-  
46  
47 247 point NRS in which 0 means did not interfere and 10 means completely interfered. These

1  
2  
3 248 questions are derived from the validated International Pain Outcomes questionnaire and are  
4  
5  
6 249 found responsive to asking patients about their ability to perform normal activities directly after  
7  
8 250 surgery<sup>53</sup>.

9  
10  
11 251 Characteristics of pain will be measured by the Brief Pain Inventory – Short Form (BPI-SF), which  
12  
13 252 is a shortened version of the Brief Pain Inventory<sup>54</sup>. BPI-SF evaluates pain severity during the  
14  
15  
16 253 past 24 hours and current level, with 0 representing "no pain" and 10 "the worst pain  
17  
18 254 imaginable". Seven items in BPI-SF assess interference with daily functioning (such as general  
19  
20  
21 255 activity, walking, and work) on an 11-point scale, where 0 represents "no interference" and 10  
22  
23 256 "complete interference".

### 27 257 Collection of body material

28 258 One tube of blood will be collected for DNA isolation. The burden for the patient is minimized  
29  
30  
31 259 as blood will be taken using the intravenous line in place for surgery. If it is impossible to collect  
32  
33 260 blood presurgically or postsurgically, we will collect saliva for DNA isolation (Genefix DNA saliva  
34  
35 261 collectors; GFX-02/50, Isohelix).

### 38 262 Clinical information

39  
40  
41 263 The following clinical information will be collected from the electronic patient file six months  
42  
43 264 after operation (**Table 1**): physical status by The American Society of Anesthesiologists  
44  
45  
46 265 classification (ASA-status); type of surgery; duration of surgery; type of anesthesia;  
47  
48 266 postoperative complications within 30 days after surgery, one-time retrospectively, which is  
49  
50  
51 267 defined as any medical adverse outcome occurring between admission and 30 days after  
52  
53 268 operation. Complications occurring in the operation room and complications directly related to  
54  
55  
56 269 anesthesia (e.g., nausea which resolves immediately after medication in the operation room)

1  
2  
3 270 will not be included<sup>55</sup>. Furthermore, data on pain medication use, before surgery and after  
4  
5 271 surgery; actual incision size in mm; second surgery within 6 months; general clinical outcome  
6  
7 272 indicators, including surgical site infection at 30 days, stroke within 30 days of surgery, death  
8  
9  
10 273 within 30 days of surgery, admission to the intensive care unit within 14 days of surgery,  
11  
12 274 readmission to hospital within 30 days of surgery, and length of hospital stay (with or without  
13  
14  
15 275 in-hospital mortality) will be collected<sup>38</sup>.

### 18 276 Outcome measures

19 277 The outcome measures are acute postoperative pain and chronic postoperative pain. Acute  
20  
21 278 postoperative pain is defined as pain experienced directly after surgery. Thresholds or cut-off  
22  
23 279 points of the pain intensity are set as none to mild (0-3), moderate (4-7), and severe (8-10)<sup>56 57</sup>.  
24  
25 280 The definition of CPSP is in agreement with IASP terminology of chronic postsurgical pain, i.e.,  
26  
27 281 "*chronic pain that develops or increases in intensity after a surgical procedure persists beyond*  
28  
29 282 *the healing process, i.e., at least 3 months after the surgery*"<sup>9</sup>. CPSP will be measured by a  
30  
31 283 chronic pain characteristics questionnaire postoperatively at three and six months. Patients will  
32  
33 284 be asked to indicate whether they had a recent pain experience, the site of pain, and whether it  
34  
35 285 lasted more than three months<sup>58 59</sup>. The intensity of CPSP will also be characterized by the pain  
36  
37 286 scores questionnaire using the same threshold as acute postoperative pain. The influence of  
38  
39 287 pain on functional and mood changes will be measured by the PDI and the BPI-SF.

### 47 288 Sample size calculation

48 289 The power of the genetic study is based on the primary research question investigating which  
49  
50 290 genetic factors are associated with postoperative pain. Power is calculated using the Genetic  
51  
52 291 Power Calculator<sup>60</sup>, and the estimated number of patients is based on a GWA approach. For  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 292 chronic postoperative pain, we assume a case-control analysis for discrete traits (2df test), a risk  
4  
5 293 allele frequency of 30%, a linkage disequilibrium (D') of 0.8, a prevalence of chronic  
6  
7  
8 294 postoperative pain of 15%, and the relative risk of chronic postoperative pain for persons who  
9  
10 295 are heterozygous of 1.5 and for homozygous persons of 2.25. For a power of 80% with a p-value  
11  
12 296 cut off  $5 \times 10^{-8}$  (genome-wide significance threshold), we need 750 patients with chronic  
13  
14  
15 297 postoperative pain and 4,250 people without chronic postoperative pain. For acute pain, the  
16  
17  
18 298 power is even higher. With the same population, we have more than 80% power to detect a  
19  
20 299 relative risk of 1.2 and 1.44 for heterozygous and homozygous patients, respectively. This higher  
21  
22  
23 300 power is due to the higher prevalence of acute (moderate to severe) pain of 55%. Most  
24  
25 301 importantly, results will be replicated in the additional study participants, as the total number of  
26  
27  
28 302 patients included in the study will be 10,000. In addition, we will use cohorts of our  
29  
30 303 collaborators for replication purposes.

### 304 Statistical analysis

305 The key objective is to identify genetic risk factors that can predict development of acute or  
36  
37 306 chronic postoperative pain and validate previously reported SNPs. A GWA approach will be used  
38  
39  
40 307 as the main analysis. Phenotype data and DNA will be used to identify genetic factors. We will  
41  
42  
43 308 use 5,000 patients for the discovery of genetic variants. Samples will be genotyped with the  
44  
45 309 Infinium Global Screening Array (Illumina). Pre-imputation quality control, principal component  
46  
47 310 analyses, and imputation will follow the RICOPILI pipeline <sup>61</sup>. Potential confounding by ethnic  
48  
49  
50 311 origin will be corrected by principal component analyses. The 1000 Genomes reference panel  
51  
52 312 will be used for imputation, followed by post-imputation quality control in PLINK <sup>62</sup>. Associations  
53  
54  
55 313 between SNPs and the presence of acute or chronic pain will be performed using cutting-edge

1  
2  
3 314 methods when data collection is finished. Results will be to ensure validity. SNPs that can be  
4  
5  
6 315 validated will be included in the prediction model described below.  
7  
8  
9 316 Secondary objectives include identifying other potential risk factors for acute and chronic  
10  
11 317 postoperative pain. Therefore, a univariate association of each potential predictor will be  
12  
13 318 calculated and tested in a multivariable regression model. We will use a least absolute shrinkage  
14  
15  
16 319 and selection operator (Lasso) regression. Shrinkage is where data values are shrunk towards a  
17  
18 320 central point, like the mean. Lasso is a regression analysis method that performs both variable  
19  
20  
21 321 selection and regularization to enhance the prediction accuracy and interpretability of the  
22  
23 322 statistical model it produces. After identifying these risk factors, a prediction rule will be created  
24  
25  
26 323 for (moderate to severe) acute and chronic postoperative pain. Based on this prediction rule, a  
27  
28 324 simple, clinically easy applicable tool will be developed to allow clinical use for the stratification  
29  
30  
31 325 of patients. The predictive performance will be studied in another cohort of patients to test  
32  
33 326 whether the rule is generalizable across time and place. Because it appears from the literature  
34  
35  
36 327 that acute and chronic pain are correlated after surgery, additional correlation analysis will be  
37  
38 328 performed to investigate this correlation in the data.

39  
40  
41 329 Similar approaches will be followed to identify the clinical and genetic factors that predict  
42  
43  
44 330 pharmacological pain relief. For some pain medicines, genes that impact pain relief are already  
45  
46 331 known (e.g., *CYP2D6* and morphine). We will first investigate those genes to see if these variants  
47  
48 332 indeed contribute to pharmacological pain relief differences.  
49

50  
51 333  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 334 Ethics and dissemination:

335 The study will be conducted according to the principles of the Declaration of Helsinki version  
336 2013 and in accordance with the Medical Research Involving Human Subjects Act and Good  
337 Clinical Practice. The study was approved by the local ethics committee for human research in  
338 Nijmegen (Medical Review Ethics Committee Region Arnhem-Nijmegen, authorization number:  
339 2012/117). This study was registered on ClinicalTrials.gov (NCT02383342).

340 The privacy of the participants is guaranteed by storing encrypted data. Every participant will  
341 receive a pseudo-anonymous study number. No identifying data is recorded within the meaning  
342 of the law. The key is only accessible to the study team and monitors. Data and material will  
343 only be used in coded form within possible collaborations.

344 The results of this study will be made available through peer-reviewed scientific journals and  
345 presentations at relevant conferences. After a thorough evaluation, decisions will be made  
346 regarding including the identified risk factors and constructed prediction models into clinical  
347 guidelines, thus facilitating personalized postoperative pain management.

## 348 Discussion

349 This cohort will be a large prospective study to identify risk factors for postoperative pain and to  
350 build and evaluate dedicated prediction models for postoperative pain in surgical patients. In  
351 addition, the comprehensive information collected in this study will also enable us to answer  
352 other research questions regarding postoperative pain, such as the relationships between acute  
353 and chronic postoperative pain development. Eventually, these results will be applied in the  
354 clinical settings to improve the quality of life for patients who develop postoperative pain.

1  
2  
3 355 The strengths of this study are that we will include all elective major operations rather than  
4  
5  
6 356 limiting to one specific operation as in previous studies <sup>32</sup>, which allows us to investigate the  
7  
8 357 shared genetic background of postoperative pain in different operations. Furthermore, as there  
9  
10 358 are discrepancies in pain intensity scores understanding <sup>63</sup> and pain management decisions <sup>63 64</sup>  
11  
12  
13 359 between patients and caregivers, the patient's perspective should be respected and assessed for  
14  
15 360 pain evaluation and management <sup>65 66</sup>. Therefore, pain assessment will be conducted by patients  
16  
17 361 themselves (patient-reported outcomes) rather than professionals in this study, leading to a  
18  
19  
20 362 more comprehensive outcome assessment and interpretation <sup>67</sup>. Moreover, the single-use of  
21  
22  
23 363 NRS might be inadequate for patients' pain experience evaluation and pain management  
24  
25 364 decisions <sup>66 68 69</sup>. Thus, another strength of this cohort is that the experience of pain will be  
26  
27  
28 365 estimated by multidimensional measurements focusing on patients' overall functionality rather  
29  
30 366 than merely a NRS pain score. Besides, the comprehensively collected information for  
31  
32  
33 367 postoperative pain in this cohort also empowers analysis that cannot be performed in large-  
34  
35 368 scale registry data (e.g., UK Biobank) as such phenotype data is not available in those datasets.  
36  
37 369 The data collected in this cohort will also enable additional research using conventional and  
38  
39  
40 370 cutting-edge statistical methods like artificial intelligence.  
41  
42  
43 371 The possible limitations of this study are that we will only investigate DNA variants as  
44  
45 372 biomarkers for pain prediction as our primary research goal. However, other epigenetic <sup>69 70</sup>,  
46  
47  
48 373 transcriptomic <sup>70</sup>, proteomics <sup>71</sup>, and metabolic markers <sup>72</sup> are also potentially involved in  
49  
50 374 (postoperative) pain development. For instance, recent studies indicate that methylation  
51  
52  
53 375 patterns might predict opioid treatment outcomes <sup>69 70</sup>. As the DNA sample of patients is  
54  
55 376 accessible, we will be able to characterize the multi-omics biomarker signatures of  
56  
57  
58  
59  
60

1  
2  
3 377 postoperative pain in future researchs, such as investigating the association between epigenetic  
4  
5  
6 378 changes and postoperative pain. In addition, when prediction tools are applied in clinical  
7  
8 379 settings, the sensitivity and specificity of prediction tools are crucial to evaluate their adequacy  
9  
10 380 and usefulness<sup>73</sup>. Although the measurement tools used in prediction models are well-validated  
11  
12 381 and verified (see methods), our findings could still be subject to false positive or negative errors  
13  
14  
15 382 because all measurement tools have limitations. Furthermore, chronic pain assessment is more  
16  
17 383 complex than acute pain<sup>74</sup>, and GWAS findings are sometimes incidental<sup>75</sup>. We will consider  
18  
19  
20 384 seeking other available cohorts for validation and applying other statistical methods to validate  
21  
22 385 our findings in future studies, such as polygenic risk scores<sup>76</sup>. Another potential limitation is that  
23  
24  
25 386 loss of follow-up of patients might result in lower patient numbers than expected. Despite this  
26  
27 387 potential concern, we still expect a sufficient sample size as additional centres will start patient  
28  
29  
30 388 inclusion, and the measurements are mainly from patient-reported outcomes via digital follow-  
31  
32 389 up.

33  
34  
35 390 Identifying the genetic background of postoperative pain development may give valuable  
36  
37 391 insights into the mechanisms underlying the relationship between postoperative pain and  
38  
39 392 complications after surgery. This may open the way to identify new targets for treatment and  
40  
41 393 potentially simplify the risk profiling assay for future use, yielding a simpler, more accurate, and  
42  
43 394 cost-efficient assay or product. The contribution of improved prevention and treatment of pain  
44  
45 395 after surgery will benefit many patients undergoing surgery and society by decreasing health  
46  
47 396 care service costs.

48  
49  
50  
51  
52  
53 397



## 398 Trial status

399 Patient recruitment is expected to continue until 2025. Recruitment has already started in  
400 Radboud university medical center, with more than 500 patients recruited as of October 2021.  
401 National and international collaborations will be greatly accepted after careful consideration.

## 402 Author contributions

403 RvB, MC and KV are responsible for overall planning and execution, formulation and evolution of  
404 overarching research goals and aims, development and design of the methodology. RvB, MC,  
405 and SvdH will be responsible for project management and coordination responsibility. Analyses  
406 and data visualization will be conducted by SL, RvB, and MC. SL prepared the draft of the  
407 manuscript, and all authors critically revised the manuscript.

## 408 Acknowledgment

409 SL was supported by China Scholarship Council (CSC) Grant number 201908130179.

## 410 Funding

411 Departmental funding covers the costs of this study [grant number: N/A]. We aim to apply for  
412 extra grants to cover the potential cost of including more patients and the cost of databank  
413 maintenance.

## 414 Competing interests statement

415 The authors have no relevant financial or non-financial interests to disclose.

416 

## References

- 417 1. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012;13(8):715-24. doi:  
418 10.1016/j.jpain.2012.03.009 [published Online First: 2012/05/23]
- 419 2. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence  
420 from published data. *Br J Anaesth* 2002;89(3):409-23.
- 421 3. Sommer M, de Rijke JM, van Kleef M, et al. The prevalence of postoperative pain in a sample of 1490  
422 surgical inpatients. *Eur J Anaesthesiol* 2008;25(4):267-74. doi: 10.1017/S0265021507003031
- 423 4. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res*  
424 2017;10:2287-98. doi: 10.2147/JPR.S144066 [published Online First: 2017/10/14]
- 425 5. van Boekel RLM, Warle MC, Nielen RGC, et al. Relationship Between Postoperative Pain and Overall  
426 30-Day Complications in a Broad Surgical Population: An Observational Study. *Ann Surg*  
427 2019;269(5):856-65. doi: 10.1097/SLA.0000000000002583 [published Online First: 2017/11/15]
- 428 6. Peters CL, Shirley B, Erickson J. The effect of a new multimodal perioperative anesthetic regimen on  
429 postoperative pain, side effects, rehabilitation, and length of hospital stay after total joint  
430 arthroplasty. *The Journal of arthroplasty* 2006;21(6 Suppl 2):132-8. doi:  
431 10.1016/j.arth.2006.04.017
- 432 7. Regenbogen SE, Mullard AJ, Peters N, et al. Hospital Analgesia Practices and Patient-reported Pain  
433 After Colorectal Resection. *Ann Surg* 2016;264(6):1044-50. doi: 10.1097/SLA.0000000000001541
- 434 8. Katz J, Jackson M, Kavanagh BP, et al. Acute pain after thoracic surgery predicts long-term post-  
435 thoracotomy pain. *Clin J Pain* 1996;12(1):50-5. [published Online First: 1996/03/01]
- 436 9. Schug SA, Lavand'homme P, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic  
437 postsurgical or posttraumatic pain. *Pain* 2019;160(1):45-52. doi:  
438 10.1097/j.pain.0000000000001413 [published Online First: 2018/12/27]
- 439 10. Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey  
440 suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003;97(2):534-40,  
441 table of contents.
- 442 11. Meissner W, Coluzzi F, Fletcher D, et al. Improving the management of post-operative acute pain:  
443 priorities for change. *Curr Med Res Opin* 2015;31(11):2131-43. doi:  
444 10.1185/03007995.2015.1092122 [published Online First: 2015/09/12]
- 445 12. Zimberg SE. Reducing pain and costs with innovative postoperative pain management. *Managed care*  
446 *quarterly* 2003;11(1):34-6.
- 447 13. Morrison RS, Magaziner J, McLaughlin MA, et al. The impact of post-operative pain on outcomes  
448 following hip fracture. *Pain* 2003;103(3):303-11.
- 449 14. Zoucas E, Lydrup ML. Hospital costs associated with surgical morbidity after elective colorectal  
450 procedures: a retrospective observational cohort study in 530 patients. *Patient safety in surgery*  
451 2014;8(1):2. doi: 10.1186/1754-9493-8-2
- 452 15. Encinosa WE, Hellinger FJ. The impact of medical errors on ninety-day costs and outcomes: an  
453 examination of surgical patients. *Health services research* 2008;43(6):2067-85. doi:  
454 10.1111/j.1475-6773.2008.00882.x
- 455 16. Sinatra R. Causes and consequences of inadequate management of acute pain. *Pain Med*  
456 2010;11(12):1859-71. doi: 10.1111/j.1526-4637.2010.00983.x [published Online First:  
457 2010/11/03]
- 458 17. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet*  
459 2019;393(10180):1537-46. doi: 10.1016/S0140-6736(19)30352-6 [published Online First:  
460 2019/04/16]

- 1  
2  
3 461 18. Yang MMH, Hartley RL, Leung AA, et al. Preoperative predictors of poor acute postoperative pain  
4 462 control: a systematic review and meta-analysis. *BMJ Open* 2019;9(4):e025091. doi:  
5 463 10.1136/bmjopen-2018-025091 [published Online First: 2019/04/04]  
6 464 19. Kalkman CJ, Visser K, Moen J, et al. Preoperative prediction of severe postoperative pain. *Pain*  
7 465 2003;105(3):415-23. doi: 10.1016/s0304-3959(03)00252-5 [published Online First: 2003/10/07]  
8 466 20. Janssen KJ, Kalkman CJ, Grobbee DE, et al. The risk of severe postoperative pain: modification and  
9 467 validation of a clinical prediction rule. *Anesth Analg* 2008;107(4):1330-9. doi:  
10 468 10.1213/ane.0b013e31818227da [published Online First: 2008/09/23]  
11 469 21. Hoofwijk DMN, van Reij RRI, Rutten BPF, et al. Genetic polymorphisms and prediction of chronic  
12 470 post-surgical pain after hysterectomy-a subgroup analysis of a multicenter cohort study. *Acta*  
13 471 *Anaesthesiol Scand* 2019;63(8):1063-73. doi: 10.1111/aas.13413 [published Online First:  
14 472 2019/06/18]  
15 473 22. Althaus A, Hinrichs-Rocker A, Chapman R, et al. Development of a risk index for the prediction of  
16 474 chronic post-surgical pain. *Eur J Pain* 2012;16(6):901-10. doi: 10.1002/j.1532-2149.2011.00090.x  
17 475 23. Montes A, Roca G, Cantillo J, et al. Presurgical risk model for chronic postsurgical pain based on 6  
18 476 clinical predictors: a prospective external validation. *Pain* 2020;161(11):2611-18. doi:  
19 477 10.1097/j.pain.0000000000001945 [published Online First: 2020/06/17]  
20 478 24. Montes A, Roca G, Sabate S, et al. Genetic and Clinical Factors Associated with Chronic Postsurgical  
21 479 Pain after Hernia Repair, Hysterectomy, and Thoracotomy: A Two-year Multicenter Cohort Study.  
22 480 *Anesthesiology* 2015;122(5):1123-41. doi: 10.1097/ALN.0000000000000611 [published Online  
23 481 First: 2015/05/20]  
24 482 25. Mauck M, Van de Ven T, Shaw AD. Epigenetics of chronic pain after thoracic surgery. *Curr Opin*  
25 483 *Anaesthesiol* 2014;27(1):1-5. doi: 10.1097/ACO.0000000000000030 [published Online First:  
26 484 2013/12/05]  
27 485 26. van Reij RRI, Joosten EAJ, van den Hoogen NJ. Dopaminergic neurotransmission and genetic variation  
28 486 in chronification of post-surgical pain. *Br J Anaesth* 2019;123(6):853-64. doi:  
29 487 10.1016/j.bja.2019.07.028 [published Online First: 2019/09/29]  
30 488 27. De Gregori M, Diatchenko L, Belfer I, et al. OPRM1 receptor as new biomarker to help the prediction  
31 489 of post mastectomy pain and recurrence in breast cancer. *Minerva Anesthesiol* 2015;81(8):894-  
32 490 900. [published Online First: 2014/10/11]  
33 491 28. Hoofwijk DM, van Reij RR, Rutten BP, et al. Genetic polymorphisms and their association with the  
34 492 prevalence and severity of chronic postsurgical pain: a systematic review. *Br J Anaesth*  
35 493 2016;117(6):708-19. doi: 10.1093/bja/aew378 [published Online First: 2016/12/14]  
36 494 29. Kim H, Clark D, Dionne RA. Genetic contributions to clinical pain and analgesia: avoiding pitfalls in  
37 495 genetic research. *J Pain* 2009;10(7):663-93. doi: 10.1016/j.jpain.2009.04.001 [published Online  
38 496 First: 2009/06/30]  
39 497 30. Mueller C, Klega A, Buchholz HG, et al. Basal opioid receptor binding is associated with differences in  
40 498 sensory perception in healthy human subjects: a [18F]diprenorphine PET study. *Neuroimage*  
41 499 2010;49(1):731-7. doi: 10.1016/j.neuroimage.2009.08.033 [published Online First: 2009/08/26]  
42 500 31. van Reij RRI, Hoofwijk DMN, Rutten BPF, et al. The association between genome-wide  
43 501 polymorphisms and chronic postoperative pain: a prospective observational study. *Anaesthesia*  
44 502 2020;75 Suppl 1:e111-e20. doi: 10.1111/anae.14832 [published Online First: 2020/01/07]  
45 503 32. Warner SC, van Meurs JB, Schiphof D, et al. Genome-wide association scan of neuropathic pain  
46 504 symptoms post total joint replacement highlights a variant in the protein-kinase C gene. *Eur J*  
47 505 *Hum Genet* 2017;25(4):446-51. doi: 10.1038/ejhg.2016.196 [published Online First: 2017/01/05]  
48 506 33. Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid  
49 507 neurotransmitter responses to a pain stressor. *Science* 2003;299(5610):1240-3. doi:  
50 508 10.1126/science.1078546 [published Online First: 2003/02/22]  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 509 34. Rakvåg TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-  
4 510 methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients.  
5 511 *Pain* 2005;116(1-2):73-8. doi: 10.1016/j.pain.2005.03.032 [published Online First: 2005/06/02]  
6 512 35. Reyes-Gibby CC, Shete S, Rakvåg T, et al. Exploring joint effects of genes and the clinical efficacy of  
7 513 morphine for cancer pain: OPRM1 and COMT gene. *Pain* 2007;130(1-2):25-30. doi:  
8 514 10.1016/j.pain.2006.10.023 [published Online First: 2006/12/13]  
9 515 36. Owusu Obeng A, Hamadeh I, Smith M. Review of Opioid Pharmacogenetics and Considerations for  
10 516 Pain Management. *Pharmacotherapy* 2017;37(9):1105-21. doi: 10.1002/phar.1986 [published  
11 517 Online First: 2017/07/13]  
12 518 37. De Gregori M, Diatchenko L, Ingelmo PM, et al. Human Genetic Variability Contributes to  
13 519 Postoperative Morphine Consumption. *J Pain* 2016;17(5):628-36. doi:  
14 520 10.1016/j.jpain.2016.02.003 [published Online First: 2016/02/24]  
15 521 38. Haller G, Bampoe S, Cook T, et al. Systematic review and consensus definitions for the Standardised  
16 522 Endpoints in Perioperative Medicine initiative: clinical indicators. *Br J Anaesth* 2019;123(2):228-  
17 523 37. doi: 10.1016/j.bja.2019.04.041 [published Online First: 2019/05/28]  
18 524 39. Pogatzki-Zahn E, Schnabel K, Kaiser U. Patient-reported outcome measures for acute and chronic  
19 525 pain: current knowledge and future directions. *Curr Opin Anaesthesiol* 2019;32(5):616-22. doi:  
20 526 10.1097/ACO.0000000000000780 [published Online First: 2019/08/16]  
21 527 40. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern*  
22 528 *Med* 1999;130(6):515-24. doi: 10.7326/0003-4819-130-6-199903160-00016 [published Online  
23 529 First: 1999/03/13]  
24 530 41. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction  
25 531 rules to make decisions. *Ann Intern Med* 2006;144(3):201-9. doi: 10.7326/0003-4819-144-3-  
26 532 200602070-00009 [published Online First: 2006/02/08]  
27 533 42. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med*  
28 534 2000;19(4):453-73. doi: 10.1002/(sici)1097-0258(20000229)19:4<453::aid-sim350>3.0.co;2-5  
29 535 [published Online First: 2000/03/01]  
30 536 43. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models,  
31 537 evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*  
32 538 1996;15(4):361-87. doi: 10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4  
33 539 [published Online First: 1996/02/28]  
34 540 44. Castor EDC. Castor Electronic Data Capture 2019 [27 Aug. 2019]. Available from:  
35 541 <https://castoredc.com> accessed August 28, 2019.  
36 542 45. Soer R, Köke AJ, Vroomen PC, et al. Extensive validation of the pain disability index in 3 groups of  
37 543 patients with musculoskeletal pain. *Spine (Phila Pa 1976)* 2013;38(9):E562-8. doi:  
38 544 10.1097/BRS.0b013e31828af21f [published Online First: 2013/02/08]  
39 545 46. Tait RC, Pollard CA, Margolis RB, et al. The Pain Disability Index: psychometric and validity data. *Arch*  
40 546 *Phys Med Rehabil* 1987;68(7):438-41. [published Online First: 1987/07/01]  
41 547 47. Moerman N, van Dam FS, Muller MJ, et al. The Amsterdam Preoperative Anxiety and Information  
42 548 Scale (APAIS). *Anesth Analg* 1996;82(3):445-51. doi: 10.1097/0000539-199603000-00002  
43 549 [published Online First: 1996/03/01]  
44 550 48. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation.  
45 551 *Psychological Assessment* 1995;7(4):524-32. doi: 10.1037/1040-3590.7.4.524  
46 552 49. Ruscheweyh R, Marziniak M, Stumpfenhorst F, et al. Pain sensitivity can be assessed by self-rating:  
47 553 Development and validation of the Pain Sensitivity Questionnaire. *Pain* 2009;146(1-2):65-74. doi:  
48 554 10.1016/j.pain.2009.06.020 [published Online First: 2009/08/12]

- 1  
2  
3 555 50. Van Boekel RLM, Timmerman H, Bronkhorst EM, et al. Translation, Cross-Cultural Adaptation, and  
4 556 Validation of the Pain Sensitivity Questionnaire in Dutch Healthy Volunteers. *Pain Res Manag*  
5 557 2020;2020:1050935. doi: 10.1155/2020/1050935 [published Online First: 2020/08/11]  
6 558 51. Rush AJ, Giles DE, Schlessler MA, et al. The Inventory for Depressive Symptomatology (IDS):  
7 559 preliminary findings. *Psychiatry Res* 1986;18(1):65-87. doi: 10.1016/0165-1781(86)90060-0  
8 560 [published Online First: 1986/05/01]  
9 561 52. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS):  
10 562 psychometric properties. *Psychol Med* 1996;26(3):477-86. doi: 10.1017/s0033291700035558  
11 563 [published Online First: 1996/05/01]  
12 564 53. Rothaug J, Zaslansky R, Schwenkglens M, et al. Patients' perception of postoperative pain  
13 565 management: validation of the International Pain Outcomes (IPO) questionnaire. *J Pain*  
14 566 2013;14(11):1361-70. doi: 10.1016/j.jpain.2013.05.016 [published Online First: 2013/09/12]  
15 567 54. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap*  
16 568 1994;23(2):129-38. [published Online First: 1994/03/01]  
17 569 55. Dindo D, Clavien PA. What is a surgical complication? *World J Surg* 2008;32(6):939-41. doi:  
18 570 10.1007/s00268-008-9584-y [published Online First: 2008/04/17]  
19 571 56. Gerbershagen HJ, Rothaug J, Kalkman CJ, et al. Determination of moderate-to-severe postoperative  
20 572 pain on the numeric rating scale: a cut-off point analysis applying four different methods. *Br J*  
21 573 *Anaesth* 2011;107(4):619-26. doi: 10.1093/bja/aer195 [published Online First: 20110630]  
22 574 57. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of  
23 575 Chronic Pain for the International Classification of Diseases (ICD-11). *Pain* 2019;160(1):19-27.  
24 576 doi: 10.1097/j.pain.0000000000001384  
25 577 58. Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth* 2008;101(1):77-86. doi:  
26 578 10.1093/bja/aen099 [published Online First: 2008/04/25]  
27 579 59. Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? *Br J*  
28 580 *Anaesth* 2014;113(1):1-4. doi: 10.1093/bja/aeu012 [published Online First: 2014/02/21]  
29 581 60. Purcell S, Cherny SS, Sham PC. Genetic Power Calculator: design of linkage and association genetic  
30 582 mapping studies of complex traits. *Bioinformatics* 2003;19(1):149-50. doi:  
31 583 10.1093/bioinformatics/19.1.149 [published Online First: 2002/12/25]  
32 584 61. Lam M, Awasthi S, Watson HJ, et al. RICOPIII: Rapid Imputation for COnsortias PIpeLIine.  
33 585 *Bioinformatics* 2020;36(3):930-33. doi: 10.1093/bioinformatics/btz633 [published Online First:  
34 586 2019/08/09]  
35 587 62. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and  
36 588 population-based linkage analyses. *Am J Hum Genet* 2007;81(3):559-75. doi: 10.1086/519795  
37 589 [published Online First: 2007/08/19]  
38 590 63. van Dijk JF, van Wijck AJ, Kappen TH, et al. Postoperative pain assessment based on numeric ratings  
39 591 is not the same for patients and professionals: a cross-sectional study. *Int J Nurs Stud*  
40 592 2012;49(1):65-71. doi: 10.1016/j.ijnurstu.2011.07.009 [published Online First: 2011/08/16]  
41 593 64. Harting B, Johnson T, Abrams R, et al. An exploratory analysis of the correlation of pain scores,  
42 594 patient satisfaction with relief from pain, and a new measure of pain control on the total dose of  
43 595 opioids in pain care. *Qual Manag Health Care* 2013;22(4):322-6. doi:  
44 596 10.1097/qmh.000000000000009 [published Online First: 2013/10/04]  
45 597 65. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain  
46 598 definition of pain: concepts, challenges, and compromises. *Pain* 2020;161(9):1976-82. doi:  
47 599 10.1097/j.pain.0000000000001939 [published Online First: 2020/07/23]  
50 600 66. van Boekel RLM, Vissers KCP, van der Sande R, et al. Moving beyond pain scores: Multidimensional  
51 601 pain assessment is essential for adequate pain management after surgery. *PLoS One*  
52 602 2017;12(5):e0177345. doi: 10.1371/journal.pone.0177345 [published Online First: 2017/05/11]

- 1  
2  
3 603 67. Weldring T, Smith SM. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures  
4 604 (PROMs). *Health Serv Insights* 2013;6:61-8. doi: 10.4137/hsi.S11093 [published Online First:  
5 605 2013/01/01]
- 6 606 68. Sloman R, Wruble AW, Rosen G, et al. Determination of clinically meaningful levels of pain reduction  
7 607 in patients experiencing acute postoperative pain. *Pain Manag Nurs* 2006;7(4):153-8. doi:  
8 608 10.1016/j.pmn.2006.09.001 [published Online First: 2006/12/06]
- 9 609 69. Clark CW, Yang JC, Tsui SL, et al. Unidimensional pain rating scales: a multidimensional affect and  
10 610 pain survey (MAPS) analysis of what they really measure. *Pain* 2002;98(3):241-47. doi:  
11 611 10.1016/s0304-3959(01)00474-2 [published Online First: 2002/07/20]
- 12 612 70. Dorsey SG, Renn CL, Griffioen M, et al. Whole blood transcriptomic profiles can differentiate  
13 613 vulnerability to chronic low back pain. *PLoS One* 2019;14(5):e0216539. doi:  
14 614 10.1371/journal.pone.0216539 [published Online First: 2019/05/17]
- 15 615 71. Van Der Heijden H, Fatou B, Sibai D, et al. Proteomics based markers of clinical pain severity in  
16 616 juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2022;20(1):3. doi: 10.1186/s12969-022-  
17 617 00662-1 [published Online First: 2022/01/17]
- 18 618 72. Jha MK, Song GJ, Lee MG, et al. Metabolic Connection of Inflammatory Pain: Pivotal Role of a  
19 619 Pyruvate Dehydrogenase Kinase-Pyruvate Dehydrogenase-Lactic Acid Axis. *J Neurosci*  
20 620 2015;35(42):14353-69. doi: 10.1523/jneurosci.1910-15.2015 [published Online First:  
21 621 2015/10/23]
- 22 622 73. Trevethan R. Sensitivity, Specificity, and Predictive Values: Foundations, Plabilities, and Pitfalls in  
23 623 Research and Practice. *Front Public Health* 2017;5:307. doi: 10.3389/fpubh.2017.00307  
24 624 [published Online First: 2017/12/07]
- 25 625 74. Fillingim RB, Loeser JD, Baron R, et al. Assessment of Chronic Pain: Domains, Methods, and  
26 626 Mechanisms. *J Pain* 2016;17(9 Suppl):T10-20. doi: 10.1016/j.jpain.2015.08.010 [published Online  
27 627 First: 2016/09/03]
- 28 628 75. Ioannidis JP. Non-replication and inconsistency in the genome-wide association setting. *Hum Hered*  
29 629 2007;64(4):203-13. doi: 10.1159/000103512 [published Online First: 2007/06/07]
- 30 630 76. van Reij RRI, Voncken JW, Joosten EAJ, et al. Polygenic risk scores indicates genetic overlap between  
31 631 peripheral pain syndromes and chronic postsurgical pain. *Neurogenetics* 2020;21(3):205-15. doi:  
32 632 10.1007/s10048-020-00614-5 [published Online First: 2020/05/08]

633

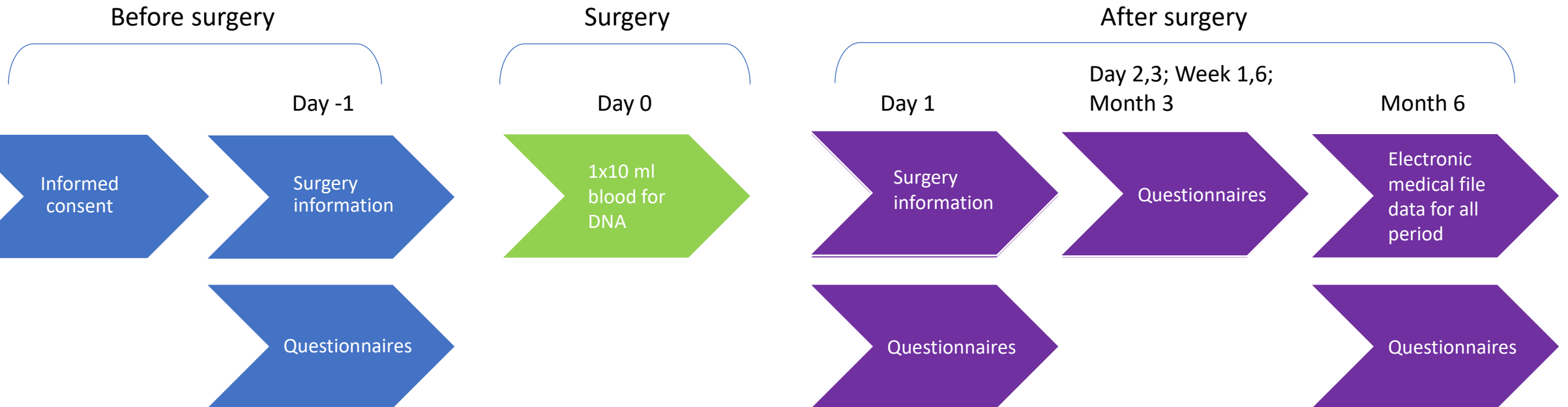
634

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

635 Figure 1: Pain Predict Genetics study design overview. After written informed consent, participants will  
636 be asked to complete questionnaires before and after their surgery. One tube of blood will be collected  
637 for DNA isolation using the intravenous line in place for surgery. Clinical information will be collected  
638 from the electronic patient file after the operation.

For peer review only

Figure 1: Pain Predict Genetics study design overview.





1  
2  
3 Table of Content  
4  
5  
6

7 Appendix a: General data  
8

9 Appendix b: Pain before and after surgery  
10

11 Appendix c: Physical activities  
12

13 Appendix d: Pain disability index  
14

15 Appendix e: Anxiety and need for information  
16

17 Appendix f: Pain Catastrophizing Scale (PCS)  
18

19 Appendix g: Pain Sensitivity Questionnaire  
20

21 Appendix h: Chronic pain  
22

23 Appendix i: Inventory of depressive symptomatology (self-report) (IDS-SR)  
24

25 Appendix j: Brief Pain Inventory  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Appendix a: General data

*General data*

- What is your year of birth?
- What is your gender?            male/female
- What is your length ?            \_\_\_\_\_ cm
- What is your weight ?            \_\_\_\_\_ kg
  
- What country were you born in? \_\_\_\_\_
  
- What country(ies) were your parents born in? \_\_\_\_\_
  
- What country(ies) were your grandparents born in? \_\_\_\_\_
  
- What human race are you? (black, white, Asian, etc.) \_\_\_\_\_

*Data of the surgery:*

- *Would you please describe your surgery.*

- How much pain do you expect after surgery (0= no pain, 10=worst pain imaginable)
- Will you stay one or more nights in the hospital after surgery? Yes / No

## Appendix b: Pain before and after surgery

## Pain before and after surgery

Circle how much pain you have, expressed as a number. The pain score means a score between 0 and 10, where 0 means no pain and 10 means the worst pain imaginable. For your pain, consider a figure between 0 and 10. You also tick whether you think the pain is acceptable or not.

Pain while being at rest at this moment (0-10)	No pain 0-1-2-3-4-5-6-7-8-9-10 worst pain imaginable
Pain score at this moment if you perform a normal effort (0-10)	No pain 0-1-2-3-4-5-6-7-8-9-10 worst pain imaginable
Do you think pain is acceptable to you at this moment?	Pain acceptable _  pain not acceptable  _
Only pre-operatively: How much pain do you expect after surgery?	No pain 0-1-2-3-4-5-6-7-8-9-10 worst pain imaginable

1  
2  
3 Appendix c: Physical activities  
4  
5  
6

7 Physical activities

8  
9 Circle the one number below that best describes how much, since your surgery, pain interfered  
10 with or prevented you from doing physical activities, expressed by figure. The score means a  
11 figure between 0 and 10, where 0 means no interference and 10 means complete interference.  
12

13 1. How much has pain interfered with or prevented you from doing activities in bed such as  
14 turning, sitting up, changing position (0= did not interfere, 10= completely interfered)  
15

16 0-1-2-3-4-5-6-7-8-9-10  
17

18 2. How much has pain interfered with or prevented you from breathing deeply or coughing (0=  
19 did not interfere, 10= completely interfered)  
20

21 0-1-2-3-4-5-6-7-8-9-10  
22

23 3. How much has pain interfered with or prevented you from sleeping (0= did not interfere, 10=  
24 completely interfered)  
25

26 0-1-2-3-4-5-6-7-8-9-10  
27

28 4. Have you been out of bed since your surgery?  
29

30 Yes/no  
31

32  
33 5. If yes, how much did pain interfere or prevent you from doing activities out of bed such as  
34 walking, sitting in a chair, standing at the sink (0= did not interfere, 10= completely interfered)  
35

36 0-1-2-3-4-5-6-7-8-9-10  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Appendix d: Pain disability index

## Pain disability index

*We would like to know how much pain is preventing you from doing what you would normally do or from doing it as well as you normally would. Respond to each category indicating the overall impact of pain in your life, not just when pain is at its worst.*

*For each of the 7 categories of life activity listed, please circle the number on the scale that describes the level of disability you typically experience. A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain.*

*In case of no pain, please circle "0".*

<p><b>1. Family/Home Responsibilities</b></p> <p>This category refers to activities of the home or family. It includes chores or duties performed around the house (e.g. yard work) and errands or favors for other family members (e.g. driving the children to school).</p>	<p>No disability 0-1-2-3-4-5-6-7-8-9-10 Worst disability</p>
<p><b>2. Recreation</b></p> <p>This disability includes hobbies, sports, and other similar leisure time activities.</p>	<p>No disability 0-1-2-3-4-5-6-7-8-9-10 Worst disability</p>
<p><b>3. Social activity</b></p> <p>This category refers to activities, which involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out, and other social functions.</p>	<p>No disability 0-1-2-3-4-5-6-7-8-9-10 Worst disability</p>
<p><b>4. Occupation</b></p> <p>This category refers to activities that are part of or directly related to one's job. This includes non-paying jobs as well, such as that of a housewife or volunteer.</p>	<p>No disability 0-1-2-3-4-5-6-7-8-9-10 Worst disability</p>
<p><b>5. Sexual behavior</b></p> <p>This category refers to the frequency and quality of one's sex life.</p>	<p>No disability 0-1-2-3-4-5-6-7-8-9-10 Worst disability</p>
<p><b>6. Self care</b></p>	<p>No disability 0-1-2-3-4-5-6-7-8-9-10 Worst disability</p>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

<p>This category includes activities, which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed, etc.)</p>	
<p><b>7. Life-support activities</b></p> <p>This category refers to basic life supporting behaviors such as eating, sleeping and breathing.</p>	<p>No disability 0-1-2-3-4-5-6-7-8-9-10 Worst disability</p>

For peer review only

## Appendix e: Anxiety and need for information

## Anxiety and need for information

*Please circle the number on the scale that describes your experience:*

<b>The Amsterdam Preoperative Anxiety and Information Scale (APAIS):</b>	Not at all				Extremely
I am worried about the anesthetic	1	2	3	4	5
The anesthetic is on my mind continually	1	2	3	4	5
I am worried about the procedure	1	2	3	4	5
The procedure is on my mind continually	1	2	3	4	5
I would like to know as much as possible about the anesthetic	1	2	3	4	5
I would like to know as much as possible about the procedure	1	2	3	4	5

1  
2  
3 Appendix f: Pain Catastrophizing Scale (PCS)  
4  
5  
6

7 Pain Catastrophizing Scale (PCS)  
8

9 We are interested in the types of thoughts and feelings that you have when you are in pain.  
10 Listed below are thirteen statements describing different thoughts and feelings that may be  
11 associated with pain. Using the following scale, please indicate the degree to which you have  
12 these thoughts and feelings when you are experiencing pain.  
13

14  
15 0=not at all 1=to a slight degree 2=to a moderate degree 3=to a great degree 4=all the time  
16

17  
18  
19 When I'm in pain .....

20	21	1. I worry all the time about whether the pain will end	0	1	2	3	4
22	23	2. I feel I can't go on	0	1	2	3	4
24	25	3. It's terrible and I think that it's never going to get any better	0	1	2	3	4
26	27	4. It's awful and I feel that it overwhelms me	0	1	2	3	4
28	29	5. I feel that I can't stand it any more	0	1	2	3	4
30	31	6. I become afraid that the pain will get worse	0	1	2	3	4
32	33	7. I keep thinking of other painful events	0	1	2	3	4
34	35	8. I anxiously want the pain to go away	0	1	2	3	4
36	37	9. I can't seem to keep it out of my mind	0	1	2	3	4
38	39	10. I keep thinking about how much it hurts	0	1	2	3	4
40	41	11. I keep thinking about how badly I want the pain to stop	0	1	2	3	4
42	43	12. There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
44	45	13. I wonder whether something serious may happen	0	1	2	3	4
46	47						
48	49						
50	51						
52	53						
54	55						
56	57						
58	59						
60							



## Appendix g: Pain Sensitivity Questionnaire

## Pain Sensitivity Questionnaire

*This questionnaire contains a series of questions in which you should imagine yourself in certain situations. You should then decide if these situations would be painful for you and if yes, how painful they would be.*

**Let 0 stand for no pain; 1 is an only just noticeable pain and 10 the most severe pain that you can imagine or consider possible.**

*Please mark the scale with a cross on the number that is most true for you. Keep in mind that there are no "right" or "wrong" answers; only your personal assessment of the situation counts. Please try as much as possible not to allow your fear or aversion of the imagined situations affect your assessment of painfulness.*

- Imagine you bump your shin badly on a hard edge, for example, on the edge of a glass coffee table. How painful would that be for you?

**0 = not at all painful, 10= most severe pain imaginable**

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine you burn your tongue on a very hot drink.

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine your muscles are slightly sore as the result of physical activity.

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine you trap your finger in a drawer.

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine you take a shower with lukewarm water.

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

- Imagine you have mild sunburn on your shoulders.

1  
2  
3 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
4  
5

- 6  
7 7. Imagine you grazed your knee falling off your bicycle.

8  
9 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
10

- 11  
12 8. Imagine you accidentally bite your tongue or cheek badly while eating.

13  
14 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
15  
16

- 17  
18 9. Imagine walking across a cool tiled floor with bare feet.

19  
20 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
21  
22

- 23 10. Imagine you have a minor cut on your finger and inadvertently get lemon juice in the  
24 wound.

25  
26 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
27  
28

- 29 11. Imagine you prick your fingertip on the thorn of a rose.

30  
31 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
32  
33

- 34 12. Imagine you stick your bare hands in the snow for a couple of minutes or bring your  
35 hands

36  
37 in contact with snow for some time, for example, while making snowballs.

38  
39 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
40  
41

- 42 13. Imagine you shake hands with someone who has a normal grip.

43  
44 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
45  
46

- 47 14. Imagine you shake hands with someone who has a very strong grip.

48  
49 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
50  
51

- 52 15. Imagine you pick up a hot pot by inadvertently grabbing its equally hot handles.

53  
54 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
55  
56

- 57 16. Imagine you are wearing sandals and someone with heavy boots steps on your foot.

58  
59 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
60

1  
2  
3  
4  
5 17. Imagine you bump your elbow on the edge of a table ("funny bone").  
6

7 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

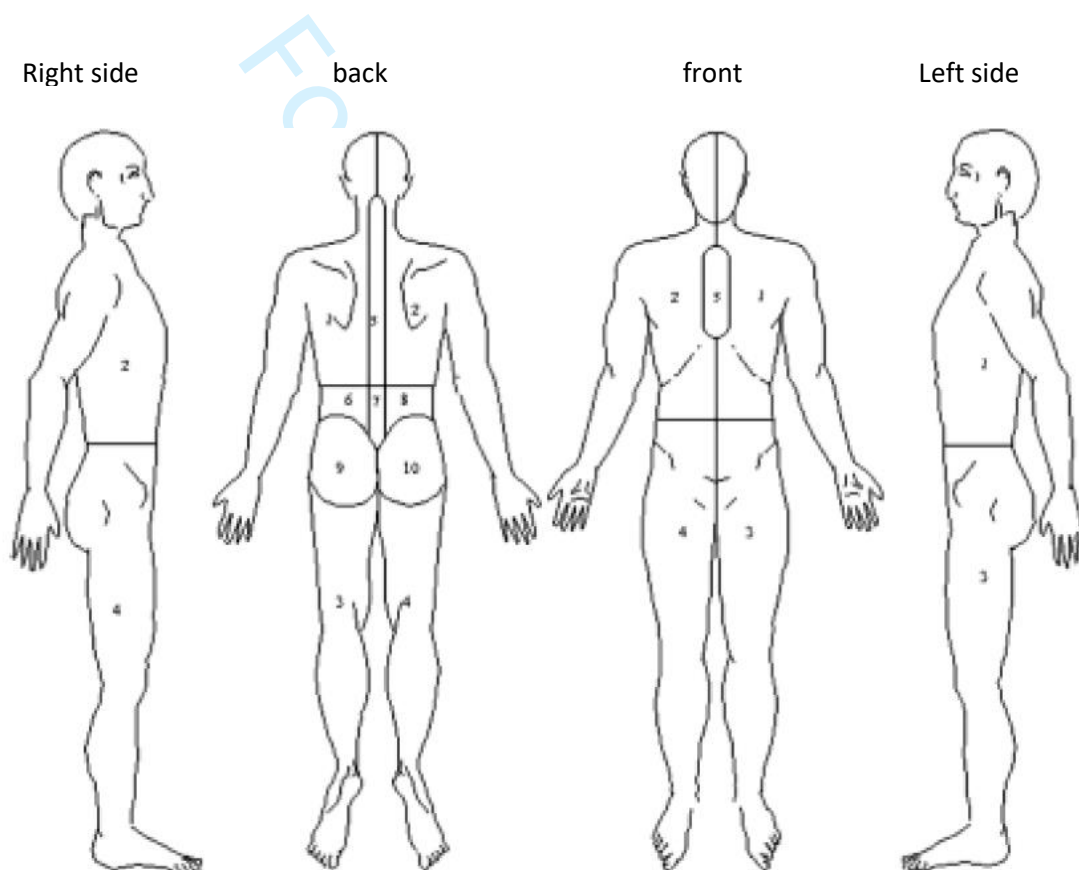
## Appendix h: Chronic pain

## Chronic pain

Did you experience any pain in the last month that lasted for a day or more?

- Yes, next question
- No

Can you indicate in the drawings below where you suffer (have suffered) from pain?



Is this the same spot as the spot you are operated on? Yes/no

Does the pain differ from the pain before surgery? Yes/no

How long have you been affected by the above-mentioned pain?

- Less than three months
- More than three months

## Appendix i: Inventory of depressive symptomatology (self-report) (IDS-SR)

**INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SELF-REPORT)**  
(IDS-SR)

NAME: \_\_\_\_\_ TODAY'S DATE \_\_\_\_\_

Please circle the one response to each item that best describes you for the past seven days.

- |   |   |
|---|---|
| <p>1. <b>Falling Asleep:</b></p> <p>0 I never take longer than 30 minutes to fall asleep.</p> <p>1 I take at least 30 minutes to fall asleep, less than half the time.</p> <p>2 I take at least 30 minutes to fall asleep, more than half the time.</p> <p>3 I take more than 60 minutes to fall asleep, more than half the time.</p> <p>2. <b>Sleep During the Night:</b></p> <p>0 I do not wake up at night.</p> <p>1 I have a restless, light sleep with a few brief awakenings each night.</p> <p>2 I wake up at least once a night, but I go back to sleep easily.</p> <p>3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.</p> <p>3. <b>Waking Up Too Early:</b></p> <p>0 Most of the time, I awaken no more than 30 minutes before I need to get up.</p> <p>1 More than half the time, I awaken more than 30 minutes before I need to get up.</p> <p>2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.</p> <p>3 I awaken at least one hour before I need to, and can't go back to sleep.</p> <p>4. <b>Sleeping Too Much:</b></p> <p>0 I sleep no longer than 7-8 hours/night, without napping during the day.</p> <p>1 I sleep no longer than 10 hours in a 24-hour period including naps.</p> <p>2 I sleep no longer than 12 hours in a 24-hour period including naps.</p> <p>3 I sleep longer than 12 hours in a 24-hour period including naps.</p> <p>5. <b>Feeling Sad:</b></p> <p>0 I do not feel sad</p> <p>1 I feel sad less than half the time.</p> <p>2 I feel sad more than half the time.</p> <p>3 I feel sad nearly all of the time.</p> <p>6. <b>Feeling Irritable:</b></p> <p>0 I do not feel irritable.</p> <p>1 I feel irritable less than half the time.</p> <p>2 I feel irritable more than half the time.</p> <p>3 I feel extremely irritable nearly all of the time.</p> | <p>7. <b>Feeling Anxious or Tense:</b></p> <p>0 I do not feel anxious or tense.</p> <p>1 I feel anxious (tense) less than half the time.</p> <p>2 I feel anxious (tense) more than half the time.</p> <p>3 I feel extremely anxious (tense) nearly all of the time.</p> <p>8. <b>Response of Your Mood to Good or Desired Events:</b></p> <p>0 My mood brightens to a normal level which lasts for several hours when good events occur.</p> <p>1 My mood brightens but I do not feel like my normal self when good events occur.</p> <p>2 My mood brightens only somewhat to a rather limited range of desired events.</p> <p>3 My mood does not brighten at all, even when very good or desired events occur in my life.</p> <p>9. <b>Mood in Relation to the Time of Day:</b></p> <p>0 There is no regular relationship between my mood and the time of day.</p> <p>1 My mood often relates to the time of day because of environmental events (e.g., being alone, working).</p> <p>2 In general, my mood is more related to the time of day than to environmental events.</p> <p>3 My mood is clearly and predictably better or worse at a particular time each day.</p> <p>9A. Is your mood typically worse in the morning, afternoon or night? (circle one)</p> <p>9B. Is your mood variation attributed to the environment? (yes or no) (circle one)</p> <p>10. <b>The Quality of Your Mood:</b></p> <p>0 The mood (internal feelings) that I experience is very much a normal mood.</p> <p>1 My mood is sad, but this sadness is pretty much like the sad mood I would feel if someone close to me died or left.</p> <p>2 My mood is sad, but this sadness has a rather different quality to it than the sadness I would feel if someone close to me died or left.</p> <p>3 My mood is sad, but this sadness is different from the type of sadness associated with grief or loss.</p> |
|---|---|

Please complete either 11 or 12 (not both)

## 11. Decreased Appetite:

- 0 There is no change in my usual appetite.
- 1 I eat somewhat less often or lesser amounts of food than usual.
- 2 I eat much less than usual and only with personal effort.
- 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

## 12. Increased Appetite:

- 0 There is no change from my usual appetite.
- 1 I feel a need to eat more frequently than usual.
- 2 I regularly eat more often and/or greater amounts of food than usual.
- 3 I feel driven to overeat both at mealtime and between meals.

Please complete either 13 or 14 (not both)

## 13. Decreased Weight (Within the Last Two Weeks):

- 0 I have not had a change in my weight.
- 1 I feel as if I've had a slight weight loss.
- 2 I have lost 2 pounds or more.
- 3 I have lost 5 pounds or more.

## 14. Increased Weight (Within the Last Two Weeks):

- 0 I have not had a change in my weight.
- 1 I feel as if I've had a slight weight gain.
- 2 I have gained 2 pounds or more.
- 3 I have gained 5 pounds or more.

## 15. Concentration/Decision Making:

- 0 There is no change in my usual capacity to concentrate or make decisions.
- 1 I occasionally feel indecisive or find that my attention wanders.
- 2 Most of the time, I struggle to focus my attention or to make decisions.
- 3 I cannot concentrate well enough to read or cannot make even minor decisions.

## 16. View of Myself:

- 0 I see myself as equally worthwhile and deserving as other people.
- 1 I am more self-blaming than usual.
- 2 I largely believe that I cause problems for others.
- 3 I think almost constantly about major and minor defects in myself.

## 17. View of My Future:

- 0 I have an optimistic view of my future.
- 1 I am occasionally pessimistic about my future, but for the most part I believe things will get better.
- 2 I'm pretty certain that my immediate future (1-2 months) does not hold much promise of good things for me.
- 3 I see no hope of anything good happening to me anytime in the future.

## 18. Thoughts of Death or Suicide:

- 0 I do not think of suicide or death.
- 1 I feel that life is empty or wonder if it's worth living.
- 2 I think of suicide or death several times a week for several minutes.
- 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

## 19. General Interest:

- 0 There is no change from usual in how interested I am in other people or activities.
- 1 I notice that I am less interested in people or activities.
- 2 I find I have interest in only one or two of my formerly pursued activities.
- 3 I have virtually no interest in formerly pursued activities.

## 20. Energy Level:

- 0 There is no change in my usual level of energy.
- 1 I get tired more easily than usual.
- 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
- 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

## 21. Capacity for Pleasure or Enjoyment (excluding sex):

- 0 I enjoy pleasurable activities just as much as usual.
- 1 I do not feel my usual sense of enjoyment from pleasurable activities.
- 2 I rarely get a feeling of pleasure from any activity.
- 3 I am unable to get any pleasure or enjoyment from anything.

22. Interest in Sex (Please Rate Interest, not Activity):

- 0 I'm just as interested in sex as usual.
- 1 My interest in sex is somewhat less than usual or I do not get the same pleasure from sex as I used to.
- 2 I have little desire for or rarely derive pleasure from sex.
- 3 I have absolutely no interest in or derive no pleasure from sex.

## 23. Feeling slowed down:

- 0 I think, speak, and move at my usual rate of speed.
- 1 I find that my thinking is slowed down or my voice sounds dull or flat.
- 2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
- 3 I am often unable to respond to questions without extreme effort.

## 24. Feeling restless:

- 0 I do not feel restless.
- 1 I'm often fidgety, wring my hands, or need to shift how I am sitting.
- 2 I have impulses to move about and am quite restless.
- 3 At times, I am unable to stay seated and need to pace around.

## 25. Aches and pains:

- 0 I don't have any feeling of heaviness in my arms or legs and don't have any aches or pains.
- 1 Sometimes I get headaches or pains in my stomach, back or joints but these pains are only sometime present and they don't stop me from doing what I need to do.
- 2 I have these sorts of pains most of the time.
- 3 These pains are so bad they force me to stop what I am doing.

## 26. Other bodily symptoms:

- 0 I don't have any of these symptoms: heart pounding fast, blurred vision, sweating, hot and cold flashes, chest pain, heart turning over in my chest, ringing in my ears, or shaking.
- 1 I have some of these symptoms but they are mild and are present only sometimes.
- 2 I have several of these symptoms and they bother me quite a bit.
- 3 I have several of these symptoms and when they occur I have to stop doing whatever I am doing.

Range 0-84 Score: \_\_\_\_\_

## 27. Panic/Phobic symptoms:

- 0 I have no spells of panic or specific fears (phobia) (such as animals or heights).
- 1 I have mild panic episodes or fears that do not usually change my behavior or stop me from functioning.
- 2 I have significant panic episodes or fears that force me to change my behavior but do not stop me from functioning.
- 3 I have panic episodes at least once a week or severe fears that stop me from carrying on my daily activities.

## 28. Constipation/diarrhea:

- 0 There is no change in my usual bowel habits.
- 1 I have intermittent constipation or diarrhea which is mild.
- 2 I have diarrhea or constipation most of the time but it does not interfere with my day-to-day functioning.
- 3 I have constipation or diarrhea for which I take medicine or which interferes with my day-to-day activities.

## 29. Interpersonal Sensitivity:

- 0 I have not felt easily rejected, slighted, criticized or hurt by others at all.
- 1 I have occasionally felt rejected, slighted, criticized or hurt by others.
- 2 I have often felt rejected, slighted, criticized or hurt by others, but these feelings have had only slight effects on my relationships or work.
- 3 I have often felt rejected, slighted, criticized or hurt by others and these feelings have impaired my relationships and work.

## 30. Lethargy/Physical Energy:

- 0 I have not experienced the physical sensation of feeling weighted down and without physical energy.
- 1 I have occasionally experienced periods of feeling physically weighted down and without physical energy, but without a negative effect on work, school, or activity level.
- 2 I feel physically weighted down (without physical energy) more than half the time.
- 3 I feel physically weighted down (without physical energy) most of the time, several hours per day, several days per week.





# Reporting checklist for genetic association study.

Based on the STREGA guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STREGA reporting guidelines, and cite them as:

Little J, Higgins JP, Ioannidis JP, Moher D, Gagnon F, von Elm E, Khoury MJ, Cohen B, Davey-Smith G, Grimshaw J, Scheet P, Gwinn M, Williamson RE, Zou GY, Hutchings K, Johnson CY, Tait V, Wiens M, Golding J, van Duijn C, McLaughlin J, Paterson A, Wells G, Fortier I, Freedman M, Zecevic M, King R, Infante-Rivard C, Stewart A, Birkett N; STrengthening the REporting of Genetic Association Studies. STrengthening the REporting of Genetic Association Studies (STREGA): An Extension of the STROBE Statement.

	Reporting Item	Page Number
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	1

1	Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and	3
2				
3				
4			balanced summary of what was done and what	
5				
6			was found	
7				
8				
9	<b>Background/rationale</b>			
10				
11				
12		<a href="#">#2</a>	Explain the scientific background and rationale for	6
13				
14			the investigation being reported	
15				
16				
17	<b>Objectives</b>			
18				
19				
20		<a href="#">#3</a>	State specific objectives, including any	9
21				
22			prespecified hypotheses. State if the study is the	
23				
24			first report of a genetic association, a replication	
25				
26			effort, or both.	
27				
28				
29				
30	<b>Study design</b>			
31				
32				
33		<a href="#">#4</a>	Present key elements of study design early in the	10
34				
35			paper	
36				
37				
38				
39	<b>Setting</b>			
40				
41				
42		<a href="#">#5</a>	Describe the setting, locations, and relevant	10
43				
44			dates, including periods of recruitment, exposure,	
45				
46			follow-up, and data collection	
47				
48				
49	<b>Eligibility criteria</b>			
50				
51				
52		<a href="#">#6a</a>	Cohort study – Give the eligibility criteria, and the	11
53				
54			sources and methods of selection of participants.	
55				
56			Describe methods of follow-up. Case-control	
57				
58				
59				
60				

1 study – Give the eligibility criteria, and the sources  
 2 and methods of case ascertainment and control  
 3 selection. Give the rationale for the choice of  
 4 cases and controls. Cross-sectional study – Give  
 5 the eligibility criteria, and the sources and  
 6 methods of selection of participants. Give  
 7 information on the criteria and methods for  
 8 selection of subsets of participants from a larger  
 9 study, when relevant.

10  
 11  
 12  
 13  
 14  
 15  
 16  
 17  
 18  
 19  
 20  
 21  
 22 #6b Cohort study – For matched studies, give n/a, not matched  
 23 matching criteria and number of exposed and study  
 24 unexposed. Case-control study – For matched  
 25 studies, give matching criteria and the number of  
 26 controls per case.  
 27  
 28  
 29  
 30  
 31  
 32  
 33

## Variables

34  
 35  
 36  
 37 #7a Clearly define all outcomes, exposures, 11, 14-17  
 38 predictors, potential confounders, and effect  
 39 modifiers. Give diagnostic criteria, if applicable  
 40  
 41  
 42  
 43

44  
 45 #7b Clearly define genetic exposures (genetic 18  
 46 variants) using a widely-used nomenclature  
 47 system. Identify variables likely to be associated  
 48 with population stratification (confounding by  
 49 ethnic origin).  
 50  
 51  
 52  
 53  
 54  
 55  
 56

## Data

1 **sources/measurement**

2

3

4 [#8a](#) For each variable of interest give sources of data 11, 14-16

5

6 and details of methods of assessment

7

8 (measurement). Describe comparability of

9

10 assessment methods if there is more than one

11

12 group. Give information separately for for exposed

13

14 and unexposed groups if applicable.

15

16

17

18 [#8b](#) Describe laboratory methods, including source 16

19

20 and storage of DNA, genotyping methods and

21

22 platforms (including the allele calling algorithm

23

24 used, and its version), error rates and call rates.

25

26 State the laboratory / centre where genotyping

27

28 was done. Describe comparability of laboratory

29

30 methods if there is more than one group. Specify

31

32 whether genotypes were assigned using all of the

33

34 data from the study simultaneously or in smaller

35

36 batches.

37

38

39

40

41 **Bias**

42

43

44 [#9a](#) Describe any efforts to address potential sources 22

45

46 of bias

47

48

49

50 [#9b](#) Describe any efforts to address potential sources 22

51

52 of bias

53

54

55 **Study size**

56

57

58

59

60

1			
2			
3			
4	<b>Quantitative variables</b>		
5			
6			
7			
8	<a href="#">#10</a>	Explain how the study size was arrived at	17
9			
10			
11			
12			
13			
14			
15			
16			
17	<b>Statistical methods</b>		
18			
19			
20			
21	<a href="#">#12a</a>	Describe all statistical methods, including those	18-19
22		used to control for confounding. State software	
23		version used and options (or settings) chosen.	
24			
25			
26			
27			
28	<a href="#">#12b</a>	Describe any methods used to examine	n/a to protocol
29		subgroups and interactions	paper.
30			
31			
32			
33	<a href="#">#12c</a>	Explain how missing data were addressed	n/a to protocol
34			paper.
35			
36			
37			
38			
39	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was	n/a to protocol
40		addressed	paper.
41			
42			
43			
44	<a href="#">#12e</a>	Describe any sensitivity analyses	n/a to protocol
45			paper.
46			
47			
48			
49	<a href="#">#12f</a>	State whether Hardy-Weinberg equilibrium was	18
50		considered and, if so, how.	
51			
52			
53			
54			
55	<a href="#">#12g</a>	Describe any methods used for inferring	18
56		genotypes or haplotypes	
57			
58			
59			
60			

## Participants

1	<a href="#">#12h</a>	Describe any methods used to assess or address	18
2		population stratification.	
3			
4			
5			
6	<a href="#">#12i</a>	Describe any methods used to address multiple	18
7		comparisons or to control risk of false positive	
8		findings.	
9			
10			
11			
12			
13			
14	<a href="#">#12j</a>	Describe any methods used to address and	18
15		correct for relatedness among subjects	
16			
17			
18			
19			
20			
21			
22			
23	<a href="#">#13a</a>	Report numbers of individuals at each stage of	n/a to protocol
24		study—eg numbers potentially eligible, examined	paper.
25		for eligibility, confirmed eligible, included in the	Participant
26		study, completing follow-up, and analysed. Give	enrollment is not
27		information separately for for exposed and	finished yet
28		unexposed groups if applicable. Report numbers	
29		of individuals in whom genotyping was attempted	
30		and numbers of individuals in whom genotyping	
31		was successful.	
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44	<a href="#">#13b</a>	Give reasons for non-participation at each stage	n/a to protocol
45			paper.
46			Participant
47			enrollment is not
48			finished yet
49			
50			
51			
52			
53			
54			
55			
56	<a href="#">#13c</a>	Consider use of a flow diagram	See figure 1
57			
58			
59			
60			

1 **Descriptive data**  
2  
3

4 [#14a](#) Give characteristics of study participants (eg n/a to protocol  
5 demographic, clinical, social) and information on paper.  
6 exposures and potential confounders. Give Participant  
7 information separately for exposed and enrollment is not  
8 unexposed groups if applicable. Consider giving finished yet  
9 information by genotype  
10  
11  
12  
13  
14  
15  
16  
17

18 [#14b](#) Indicate number of participants with missing data  
19 for each variable of interest  
20  
21  
22  
23

24 [#14c](#) Cohort study – Summarize follow-up time, e.g.  
25 average and total amount.  
26  
27  
28

29 **Outcome data**  
30  
31

32 [#15](#) Cohort study Report numbers of outcome events n/a to protocol  
33 or summary measures over time. Give information paper.  
34 separately for exposed and unexposed groups if Participant  
35 applicable. Report outcomes (phenotypes) for enrollment is not  
36 each genotype category over time Case-control finished yet  
37 study – Report numbers in each exposure  
38 category, or summary measures of exposure. Give  
39 information separately for cases and controls .  
40 Report numbers in each genotype category.  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

unexposed groups if applicable. Report outcomes  
(phenotypes) for each genotype category

## Main results

**#16a** Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

n/a to protocol paper.  
Participant enrollment is not finished yet

**#16b** Report category boundaries when continuous variables were categorized

**#16c** If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

**#16d** Report results of any adjustments for multiple comparisons

## Other analyses

**#17a** Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses

n/a to protocol paper.  
Participant enrollment is not finished yet

**#17b** Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity



1 analyses

2  
3  
4 [#17c](#) Report other analyses done—e.g., analyses of  
5 subgroups and interactions, and sensitivity  
6 analyses  
7  
8  
9

10  
11 **Key results**  
12  
13

14 [#18](#) Summarise key results with reference to study objectives n/a to protocol  
15 paper.  
16 Participant  
17 enrollment is not  
18 finished yet  
19  
20  
21  
22  
23  
24  
25

26 **Limitations**  
27  
28

29 [#19](#) Discuss limitations of the study, taking into account sources of potential bias or imprecision. 21  
30  
31 Discuss both direction and magnitude of any  
32 potential bias.  
33  
34  
35  
36  
37  
38

39 **Interpretation**  
40  
41

42 [#20](#) Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, 22  
43 results from similar studies, and other relevant  
44 evidence.  
45  
46  
47  
48  
49  
50  
51

52 **Generalisability**  
53  
54

55 [#21](#) Discuss the generalisability (external validity) of the study results 22  
56  
57  
58

## Funding

#22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

None The STREGA checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)