

Supplement to the manuscript:

Predicting physician consultations for low back pain using claims data and population-based cohort data – an interpretable machine learning approach.

Adrian Richter, Julia Truthmann, Jean François Chenot, Carsten Oliver Schmidt

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List of ICD-10 codes

The following list contains all ICD-10 codes used for the definition of low back pain.

Table S1: List of ICD-10 Codes associated with low back pain.

ICD-10 codes	Code label
M40	Kyphosis and lordosis
M41	Scoliosis
M42	Spinal osteochondrosis
M43	Other deforming dorsopathies
M45	Ankylosing spondylitis
M46	Other inflammatory spondylopathies
M47	Spondylosis
M48	Other spondylopathies
M49	Spondylopathies (not elsewhere classified)
M51	Other intervertebral disc disorders
M53	Other dorsopathies (not elsewhere classified)
M54	Back pain (not elsewhere classified)

We excluded all codes starting with 3-character ICD-10 codes *M50.XX*, which are used in cases of *cervical disc damages*. From the remaining ICD-10 codes, we have further removed:

M42.12, M42.13, M42.92, M42.93, M43.02, M43.12, M43.22, M43.3, M43.4, M43.6, M47.12, M47.14, M47.21, M47.22, M47.23, M47.24, M47.82, M47.83, M47.84, M47.91, M47.92, M47.93, M47.94, M48.02, M48.03, M48.04, M50.-, M50.0, M50.1, M50.2, M50.3, M50.8, M50.9, M53.0, M53.1, M53.22, M53.23, M53.24, M53.82, M53.83, M53.92, M53.94, M54.01, M54.02, M54.03, M54.04, M54.11, M54.12, M54.13, M54.14, M54.82, M54.83, M54.84, M54.91, M54.92, M54.93, M54.94

as they all related to cervical or thoracic diagnoses.

List of physicians' fee schedules

The following list of the physicians' fee schedule have been selected and divided into five groups.

Table S2: List of physicians' fee positions related to back pain

Group	Codes	Label
General practitioner	03000	Specific code for treatment within standby
	03003	19th to 54th year of age
	03004	55th to 75th year of age
	03005	from 76th year of age
	03111	between 2005 - 2013: 6th to 59th year of age
	03112	between 2005 - 2013: from 60th year of age
Neurologist	16211	6th to 59th year of age
	16212	from 60th year of age
	16232	Additional fee for diagnostic/treatment
Orthopedist	18211	6th to 59th year of age
	18212	from 60th year of age
	18331	Additional fee for diagnostic/treatment
Interventions	30201	Manual therapy
	30700, 30702	Special pain therapy
	30724, 34503, 30731, 02360	Injection therapy
	30790, 30791	Acupuncture
	02510	Thermotherapy
	02511	Electrotherapy
Imaging	34221, 34222	X-ray
	34223, 34311	CT
	34411	MRI

Methods

Distribution of the primary outcome

The primary outcome (number of ICD-10 codes for back pain) has a highly skewed distribution with a considerable quantity of zero's (Figure S1 below).

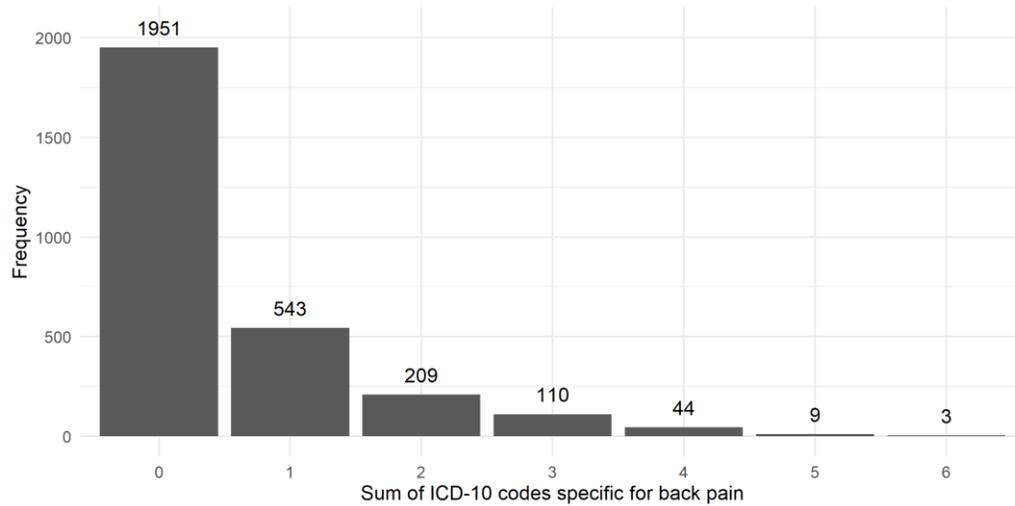


Figure S1: Frequency of ICD-10 codes for back pain observed in the training data.

The score test rejected the hypothesis of no zero inflation ($p < 0.001$).

```
## Score test for zero inflation
##
## Chi-square = 661.56823
## df = 1
## pvalue: < 2.22e-16
```

Candidate variables

We selected a broad sequence of variables from both data sources, which were presumably related to the frequency of low back pain episodes as indicated by ICD-10 codes. Table S4 in [Exploratory variable selection](#) shows the selected candidate variables after revision of univariate associations and interaction terms. In addition to these variables, we examined univariate associations of the following variables with the outcome:

- job type (e.g. farmer, freelancer)
- average von Korff back pain severity
- comorbidities: diabetes (yes vs. no), diabetes with complications (no vs. diabetes without complications vs. diabetes with complications), heart failure, atrial fibrillation, myocardial infarction, stroke, cancer
- interaction terms: PHQ-9 strata: sex.

Compared to the employment/workability status (Table S4), the job type was hardly associated with the outcome. Instead of the average of two von Korff items (back pain severity, impairment due to back pain), we used the original items in the modelling process. The above mentioned comorbidities (diabetes, cardiovascular disease, and cancer) origin from interviews of the SHIP participants and represent self-reported diseases. We summarized them into a single variable named *competing diseases* (none, one, >one of: diabetes, cardiovascular disease, and cancer) as all univariate coefficients indicated a negative association with the number of ICD-10 codes. Using claims data, we were able to compute the Charlson comorbidity index based on the approach from [1].

Non-linear associations

The presence of non-linear associations was examined using a generalized additive model [2] provided by the R package *mgcv*. To discriminate nonlinear effects in the zero-part from those in the count-part we applied two types of models: (a) a binomial distribution for the zero-part and (b) negative binomial for the count-part.

Table S3: Results of a generalized additive model for nonlinear associations.

Terms	edf	Ref.df	Chi.sq	p-value	Model
s(age)	5.1	6.2	68.101	0.000	Zero
s(bmi)	2.2	2.8	5.485	0.153	Zero
s(height)	1.0	1.0	0.625	0.429	Zero
s(weight)	1.0	1.0	0.167	0.685	Zero
s(sf12_pcs)	2.2	2.8	19.183	0.000	Zero
s(phq_sum_score)	5.7	6.6	10.114	0.179	Zero
s(house_income)	2.2	2.8	22.143	0.000	Zero
s(age)	1.2	1.4	6.043	0.019	Count
s(bmi)	1.0	1.0	1.171	0.279	Count
s(height)	1.0	1.0	1.246	0.264	Count
s(weight)	1.0	1.0	1.123	0.289	Count
s(sf12_pcs)	1.0	1.0	9.613	0.002	Count
s(phq_sum_score)	1.2	1.3	0.041	0.909	Count
s(house_income)	1.0	1.0	0.985	0.321	Count

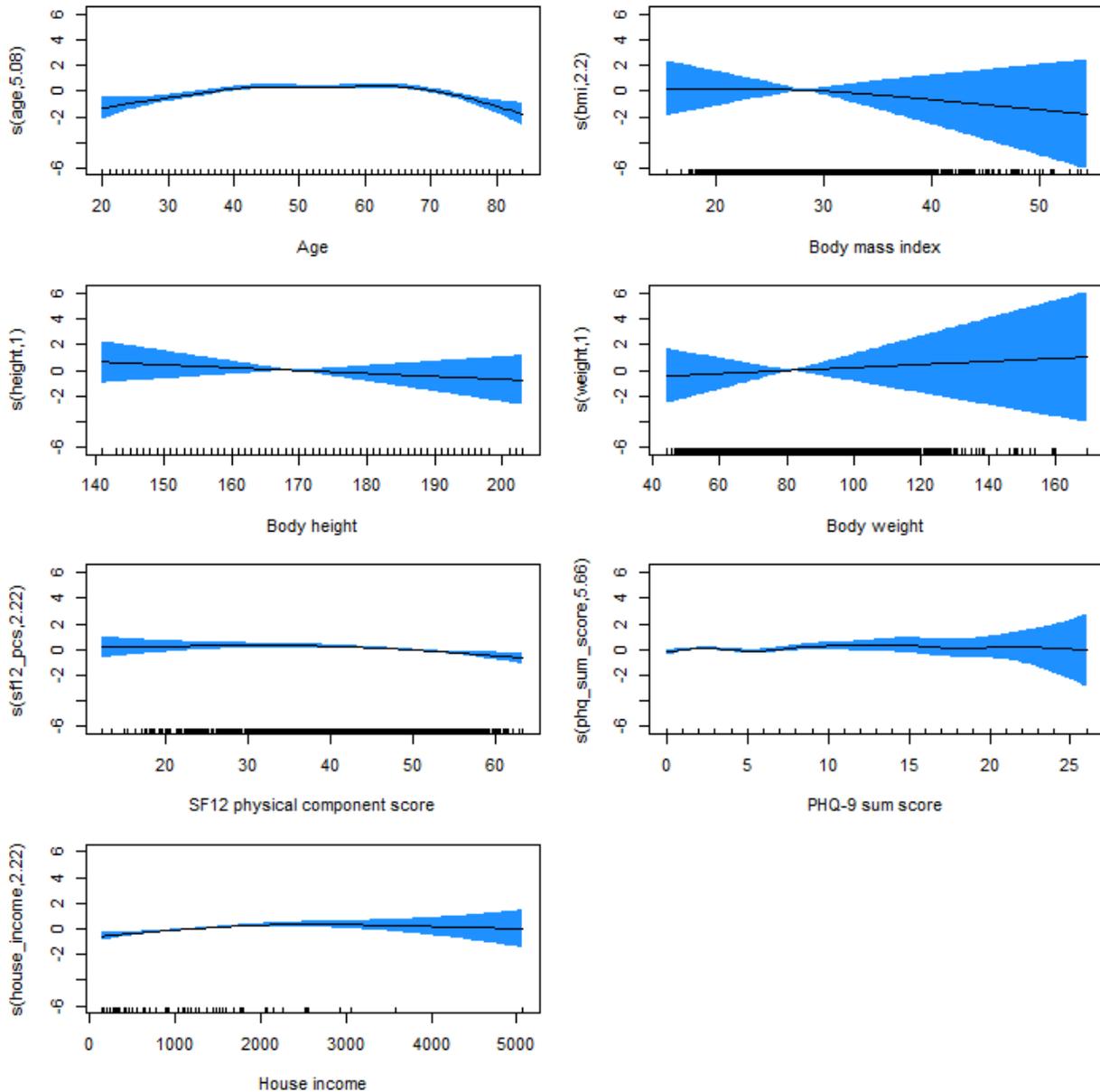


Figure S2: Nonlinear associations of covariates with the presence of ICD-10 codes for back pain (yes/no).

The results from this model suggest non-linear associations in the zero-part of the model for age, SF12 PCS, PHQ-9 sum score, and house income. Regarding the count-part none of the candidate variables appears to have non-linear associations, as effective degrees of freedom are all close to 1.

There are some caveats: the household income in the SHIP data represents a transformed variable. Participants of the SHIP study were asked about their income in non-equidistant

categories $[[[0; 500), [500; 900), [900; 1300), [1300; 1800), [1800; 2300), [2300; 2800), [2800; 3300), [3300; 3800), 3800; \text{Inf})$. These categories were then transformed along the interval means and standardized according the number of individuals living in the respective household ($\sqrt{\# \text{ individuals}}$). The respective values appear to be continuous, but base in fact on categorical values. Please see also Figure S4 below where we made use of the R package *dataquieR* to illustrate possible outliers [3]. We therefore decided to not model a nonlinear functional form (spline) of this variable.

In summary, based on AIC information criteria, we considered restricted natural splines for age (degrees of freedom $df=4$) and SF12 physical component scale ($df=2$) as candidate variables.

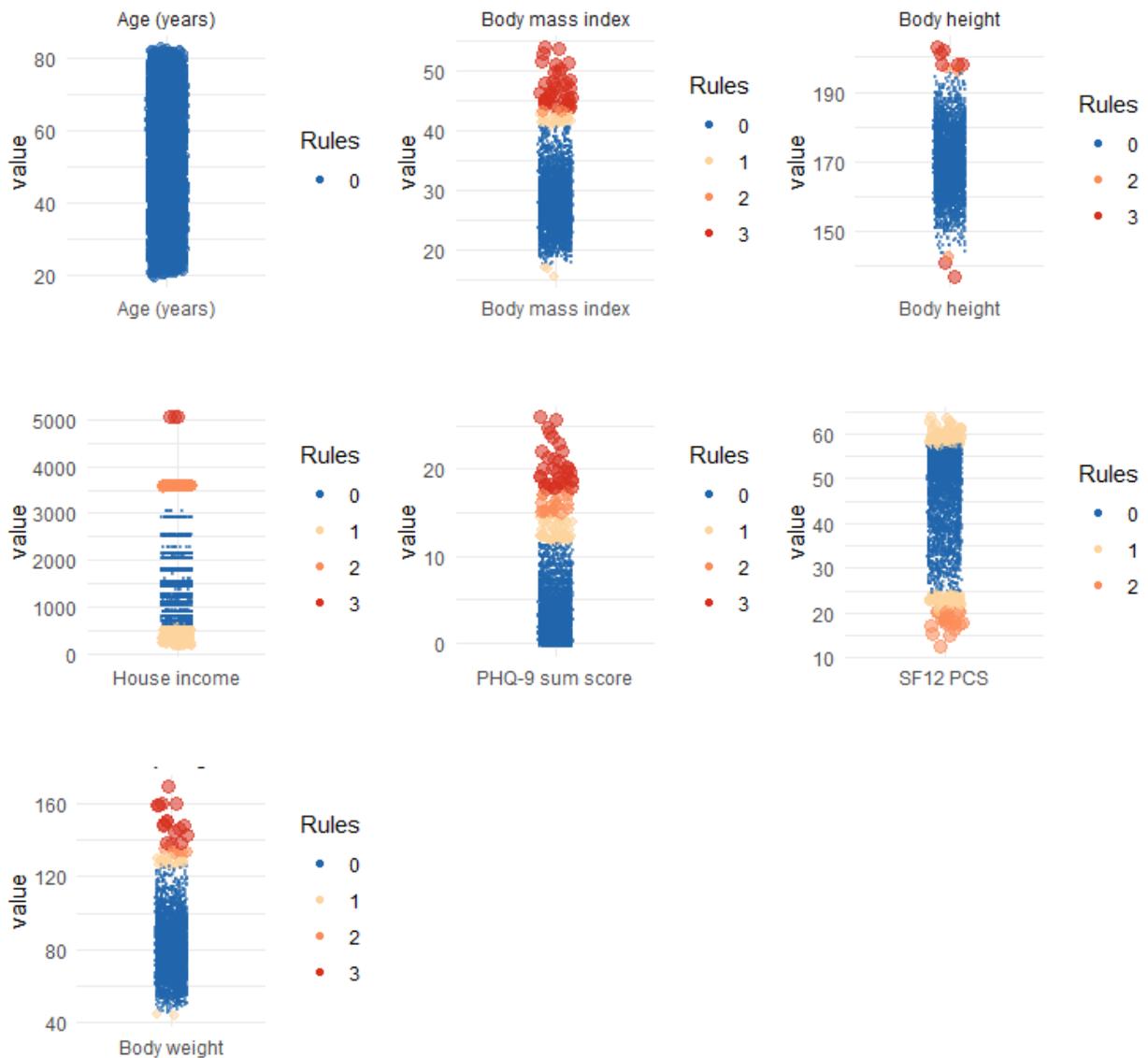


Figure S3: Distributional plots of all continuous candidate variables and the classification of outliers. Please see this [website](#) for annotation of the different outlier classification rules.

Exploratory variable selection

Best subset selection is computationally expensive with $2^p - 1$ possible combinations of covariates. To minimize computational time, we applied *model-based boosting* (MBB) to conduct an explorative variable selection for the SHIP data. MBB is applicable in high-dimensional settings ($n \ll p$) and in the presence of multi-collinearity [4]. The latter is of particular interest for our approach since we examined some variables in alternative forms, e.g. age (original, discretized, smoothed).

In brief, MBB starts from an intercept model in which each *base-learner* or candidate variable is iteratively evaluated in terms of fitting a loss function (negative log-likelihood) best. In each iteration only the best base-learner, with respect to minimizing residual sum of squares, will be used to update the model [4]. The R package *mboost* [5] has been used to build the MBB model in 2000 iterations (maximum *mstop*). Usually the best model is then identified via resampling. However, we applied stability selection [6] after model building to select covariates being predictive in 20% of the resampled data, i.e. contributing to the model in at least 20% of resampled data. This setting is less restrictive, i.e. more variables are retained, recommendations suggest to choose a threshold of 50% or higher [6]. However, we pursued an initial set of promising candidate variables and to remove competing effect definitions, we omitted the evaluation of the optimal MBB model. All predictors as specified in Table S4 were examined as candidate learners.

In case of alternative effect definition, e.g. regarding age, we chose the effect with highest selection frequency in MBB.

Table S4: Candidate variables and results of explorative variable selection.

Characteristic	Data type and if required categories and explanation	Model part	Selection frequency ZERO	Selection frequency COUNT
Sex	female male	zero	0.68	0.00
Age	integer	count	0.00	0.61
Age (categorized)	[20; 40); [40; 70); [70;Inf): age has been categorized based on clinical hypotheses	zero	1.00	0.55
Age (spline)	B-splines with 5 degrees of freedom (knots at quintiles)		0.10	n.a.
Use of opioids	no yes	count	0.03	0.38
Use of benzodiazepine	no yes		0.01	0.01
Use of NSAR	no yes; self-reported use of NSAR (over-the-counter-drug)		0.10	0.11
Use of antidepressants	no yes		0.00	0.04
No. of drugs used in last 7d	integer	count	0.00	0.71
Family status	single married divorced widowed	zero, count	0.57	0.27
BMI	float		0.00	0.02
Back pain in last 3 month (NRS)	integer	zero, count	0.99	0.41
Impairment by back pain in last 3 month (NRS)	integer	count	0.03	0.99
PHQ-9	Sum score		0.00	0.00
SF12 Physical component scale	float		0.00	0.16
SF12 Physical component scale (spline)	B-splines with 2 degrees of freedom (knot at median)		0.08	n.a.
Sport activities	<1h a week 1-2h a week > 2h a week	count	0.03	0.35
Physician visits (last year)	None GP only Specialist only GP and specialist (visits can be unrelated to back pain)	zero, count	1.00	0.73
Body height	float		0.00	0.01
Body weight	float		0.03	0.02
Household income	float	zero	0.85	0.09
School years	<10 10 >10	count	0.06	0.20
Physical demanding job	no yes		0.04	0.04
Workability status	employable retired unemployed	count	0.00	0.34
Competing diseases	0 = None 1 = one 2 = >1 (of diabetes, cardiovascular disease, cancer)	zero	0.21	0.09
Depression (self-reported)	no yes		0.00	0.08
Inflammatory joint disease	no yes		0.04	0.01
Osteoarthritis	no yes	zero, count	0.57	0.28
Disc prolapse	no yes	zero, count	0.96	0.81
Pressure pain (related to back pain)	no yes	zero	0.31	0.01
Dysesthesia (tingling, related to back pain)	no yes	zero, count	0.43	0.38
Radiating back pain	0 = none 1 = yes, gluteal only 2 = yes, to knee 3 = yes, to lower leg	zero, count	0.53	0.41
Interactions:				
depression: sex			0.08	0.04
depression: PHQ-9			0.06	0.15
disc prolapse: radiating back pain		zero, count	0.22	0.63

*n.a.: not applicable as non-linear associations were not necessary to model the count part of the hurdle model. All variables marked with a gray background were removed by model-based boosting under stability selection.

Best subset

From a vector of candidate variables (in the following example A, B, C) we specified a matrix of all their possible combinations in the following manner:

```
# Variables: A, B, and C
covars <- c("A", "B", "C")

# each of these variables can be selected (1) or not (0)
ps <- rep(list(0:1), length(covars))

# create all possible combinations
ps_claims <- expand.grid(ps)

# remove row in which all variables are "NULL"
ps_claims <- ps_claims[-1, ]
names(ps_claims) <- covars
```

Table S5: Matrix of all possible variable combinations.

A	B	C
1	0	0
0	1	0
1	1	0
0	0	1
1	0	1
0	1	1
1	1	1

The validation algorithm iterated in each bootstrap sample over the rows of this matrix and selected the model-formula according to binary values in this matrix (1 = *TRUE*).

Model training algorithm

Model training and evaluation were conducted in separate data to avoid overfitting [7]. In absence of external (independent) validation data, a so-called internal validation of a model should be applied, i.e. using a subsample of the same data source, which is not involved in model training. This approach is inferior to an external validation but a crucial model evaluation step [8].

We adapted a common approach of model validation as described by Filzmoser et. al [8]. Therefore, the SHIP-TREND-0 data were randomly splitted into *training-data* and *validation-data* in a ratio of 3:1 (n=2869:968). Figure S4 shows the scheme of this approach:

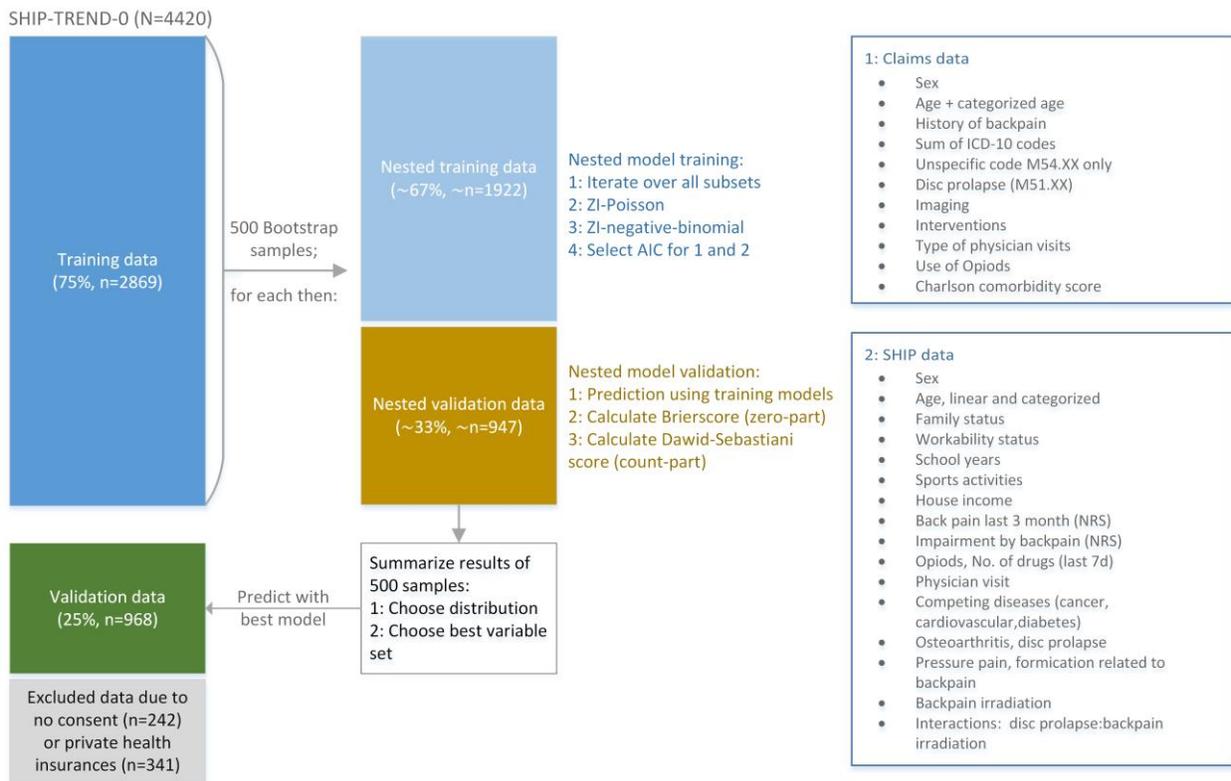


Figure S4: Scheme of the Validation algorithm to assess model prediction accuracy.

In each step of the nested model training we iterated over a matrix of predictors (please see [Best subset](#) for explanation) and conducted zero-inflated *Poisson* and negative-binomial count data models for all possible combinations of covariates. Respective information criteria (AIC) have been saved in each iteration to choose the most appropriate distribution type after completion of the nested model training. Each model result was used to predict the outcome of interest in the nested validation data.

The accuracy of the nested prediction performance has been evaluated using the strictly proper scoring rules of *Brier score* and the *Dawid-Sebastiani score* [10–12]. The calculation and notation

of these scores is mentioned under [Scores for model calibration](#) and has been applied using the R package *surveillance* [13].

Overall, this scheme was applied three times:

- 1st for the claims data
- 2nd for the SHIP data
- 3rd for the joined data using only the best subset from either claims and SHIP.

Due to the computational complexity, e.g. 8.191.000 models ($2^{13} - 1$ subsets * 500 samples * 2 distributions) were calculated for the claims data alone, we used the R package *doParallel* [14] to apply parallel computations. Further, we used the high-performance-cluster provided by the computation center of the University of Greifswald [15].

Scores for model calibration

We used two strictly proper scoring rules to evaluate a model's prediction accuracy. For the *zero-part* of the zero-inflated count data regression we used the *Brier score* [16] and for the *count-part* the *Dawid-Sebastiani score* [11] proposed by [10]. The *Brierscore* has the following notation:

$$BS = \frac{1}{N} \sum_{i=1}^N (p_i - o_i)^2.$$

where p_i is the predicted probability for individual i and o_i the observed event of individual i .

The *Dawid-Sebastiani score* has the following notation for a negative-binomial [11] count data regression:

$$DSS_{(NBB)} = \frac{1}{N} \sum_{i=1}^N \left(\frac{(y_i - \mu_i)^2}{\mu_i(1 + \frac{\mu_i}{\theta})} + \log(\mu_i(1 + \frac{\mu_i}{\theta})) \right).$$

and in terms of a Poisson distribution with $\mu = \sigma^2 = \lambda$:

$$DSS_{(Poi)} = \frac{1}{N} \sum_{i=1}^N \left(\frac{(y_i - \lambda_i)^2}{\lambda_i} + \log(\lambda_i) \right).$$

The calculation of these scores is implemented in the R package *surveillance* [12].

Missing data

Imputation setting

The overall frequency of missing values was low (<5%). Nevertheless, we first applied multiple imputations using chained equations provided by the R package *mice* ([17]). The imputation was conducted independently for training data and validation data.

Transformed variables, such as body mass index and strata of the PHQ score, were not imputed; instead passive imputation has been used, which was defined as:

```
# mice::methods for imputation
meths["bmi"] <- "~I(weight/((height/100)^2))"

# a customized function to categorize phq score into strata
mycutfun <- function(x) {
  x <- cut(x,
           right = FALSE,
           breaks = c(0, 1, 5, 10, 15, Inf),
           labels = c("no signs", "minimal", "mild", "moderate", "severe"))
}

# mice::methods for imputation
meths["phq_strata"] <- "~I(mycutfun(phq_sum_score))"
```

Imputation diagnostics

We used inbuilt functions of the R package mice for imputation diagnostics. Further, variance increase (%) by using Rubins' rule [18] for calculating the pooled variance from the variance between and within the imputed data sets.

Overall, the increase in variance was very low, for most covariates <1%. Due the small increase in variance and in line with recommendations for the application of multiple imputations in case of missingness < 5% [19] we restricted the imputations to $m = 1$ in the training data.

However, the validation data contained $m=20$ imputations.

Table S6: Imputation diagnostics.

Variable	Category	Location	Before imputations	After imputations	V increase
Household income		Mean	1,296.77	1,297.83	4.58
BMI		Mean	28.28	28.29	0.38
Body weight		Mean	81.26	81.27	0.12
Body height		Mean	169.37	169.37	0.28
Back pain (NRS)		Mean	2.72	2.73	0.28
Impairment due to back pain (NRS)		Mean	1.05	1.06	0.38
SF12 PCS		Mean	46.97	46.90	1.24
PHQ-9 sum score		Mean	3.97	3.97	3.74
Use of medication (last 7d)		Mean	2.49	2.49	0.46
Family status	Single	Proportion	0.10	0.10	0.00
	Married/Partner	Proportion	0.77	0.78	0.00
	Separated	Proportion	0.06	0.06	0.00
	Widowed	Proportion	0.06	0.06	0.00
Work categories	Never working	Proportion	0.01	0.01	0.00
	At desktop, not physically	Proportion	0.30	0.30	0.02
	At desktop and physically demanding	Proportion	0.13	0.14	0.02
	Not at desktop, not physically	Proportion	0.20	0.22	0.11
Physical demanding job	Not at desktop but physically demanding	Proportion	0.32	0.34	0.14
	yes	Proportion	0.45	0.47	0.16
Work status	no	Proportion	0.51	0.53	0.16
	employable	Proportion	0.54	0.55	0.01
School years	retired	Proportion	0.32	0.36	0.00
	unemployed	Proportion	0.09	0.10	0.01
	<10	Proportion	0.25	0.25	0.00
Physical activity	10	Proportion	0.53	0.53	0.00
	>10	Proportion	0.22	0.22	0.00
	No sport	Proportion	0.22	0.22	0.01
Radiating back pain	1-2h/week	Proportion	0.57	0.58	0.01
	>2h/week	Proportion	0.20	0.20	0.00
	no	Proportion	0.68	0.68	0.00
Pressure pain	gluteal only	Proportion	0.16	0.16	0.00
	to knee	Proportion	0.10	0.10	0.00
	to lower leg	Proportion	0.06	0.06	0.00
NSAR	yes	Proportion	0.17	0.17	0.01
	no	Proportion	0.82	0.83	0.01
Tingling, prickling	yes	Proportion	0.90	0.90	0.00
	no	Proportion	0.10	0.10	0.00
Claudication	yes	Proportion	0.12	0.12	0.00
	no	Proportion	0.88	0.88	0.00
Osteoarthritis	yes	Proportion	0.02	0.02	0.08
	no	Proportion	0.95	0.98	0.08
	yes	Proportion	0.29	0.30	0.01

Variable	Category	Location	Before imputations	After imputations	V increase
Disc prolapse	no	Proportion	0.69	0.70	0.01
	yes	Proportion	0.09	0.09	0.00
Inflammatory joint disease	no	Proportion	0.90	0.91	0.00
	yes	Proportion	0.05	0.06	0.01
Competing disease	no	Proportion	0.93	0.94	0.01
	None	Proportion	0.79	0.79	0.00
	One	Proportion	0.16	0.16	0.00
Physician visit	>1	Proportion	0.04	0.04	0.00
	No physician visit	Proportion	0.18	0.19	0.01
	GP visit only	Proportion	0.56	0.56	0.01
	Specialist only	Proportion	0.03	0.03	0.01
Use of medication (last 7d, y/n)	GP and specialist	Proportion	0.21	0.21	0.01
	yes	Proportion	0.71	0.71	0.00
Depression	no	Proportion	0.28	0.29	0.00
	yes	Proportion	0.69	0.71	0.02
Opioids	no	Proportion	0.28	0.29	0.02
	yes	Proportion	0.98	0.98	0.00
Benzodiazepine	no	Proportion	0.02	0.02	0.00
	yes	Proportion	0.98	0.98	0.00
Antidepressants	no	Proportion	0.01	0.01	0.00
	yes	Proportion	0.94	0.94	0.00
	yes	Proportion	0.06	0.06	0.00

Comparative analyses

For comparative analysis we applied *randomforest* (RF) in this study, which has been shown to provide excellent prediction accuracy [20,21]. In RF, bootstraps of original data, i.e. random samples of the data with replacement, are used to build ensembles of uncorrelated decision trees on so-called in-bag observations.

It is advised to build a high number of trees (*ntree*) in RF but the number of trees is not considered a tuning parameter [22]. The following parameters have a higher impact on prediction accuracy:

- the number of variables (*mtry*) considered for splitting the trees
- the minimum terminal node size (*nodesize*), and
- the sample size of inner bootstraps (*sampsiz*).

We used the R package *tuneRanger* to conduct this tuning [22].

Variable importance in joined data using a tuned randomforest approach

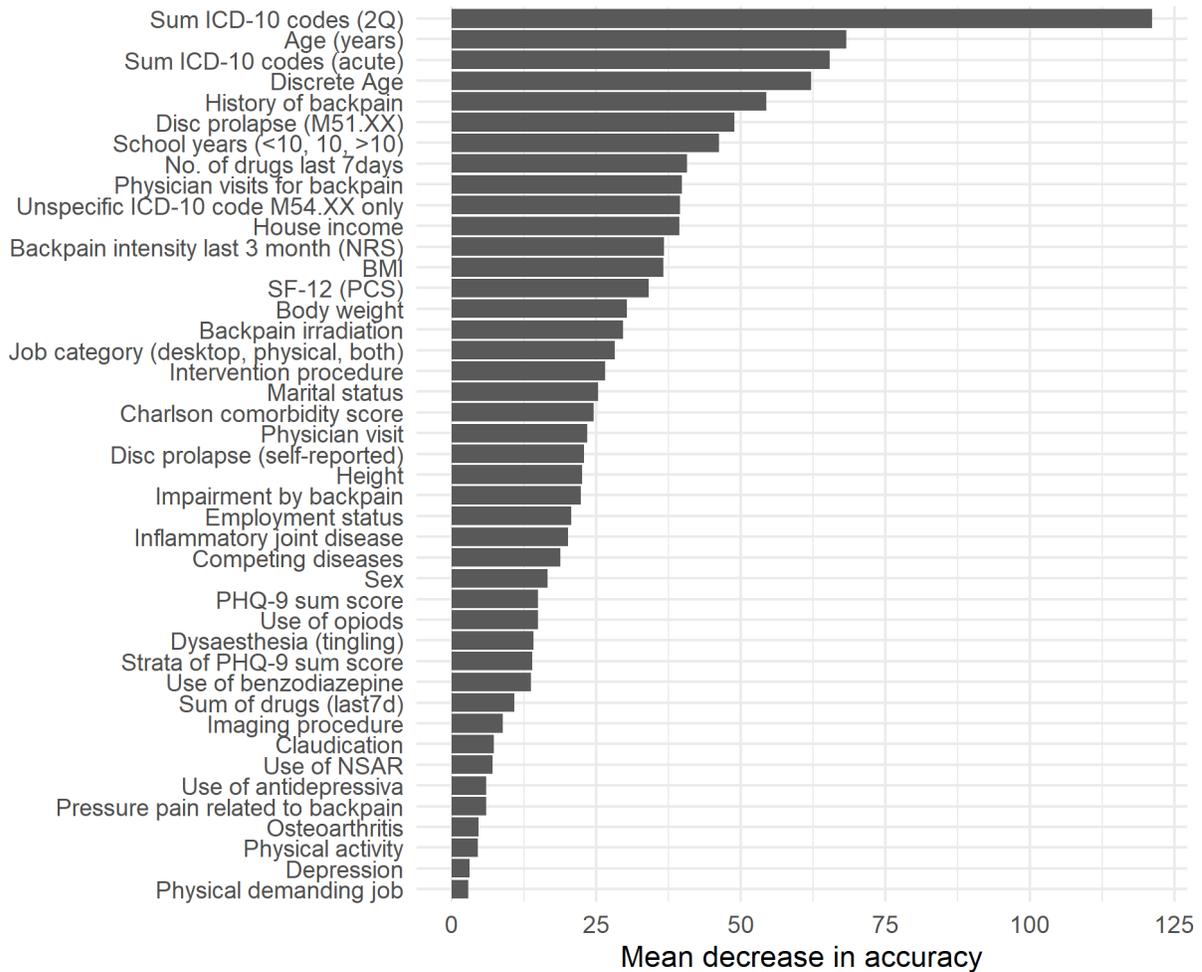


Figure S5: Joined data means claims data and SHIP data analyzed together. Variable importance resulting from a tuned random forest approach (mtry=9, nodesize=60, sampsize = 1674, ntree=10000).

Results

Association of covariates

For most continuous or count variables we found low to moderate associations. Particularly the association of self-reported back pain (SHIP-data) with the frequency of ICD-10 codes for back pain (claims data) was low.

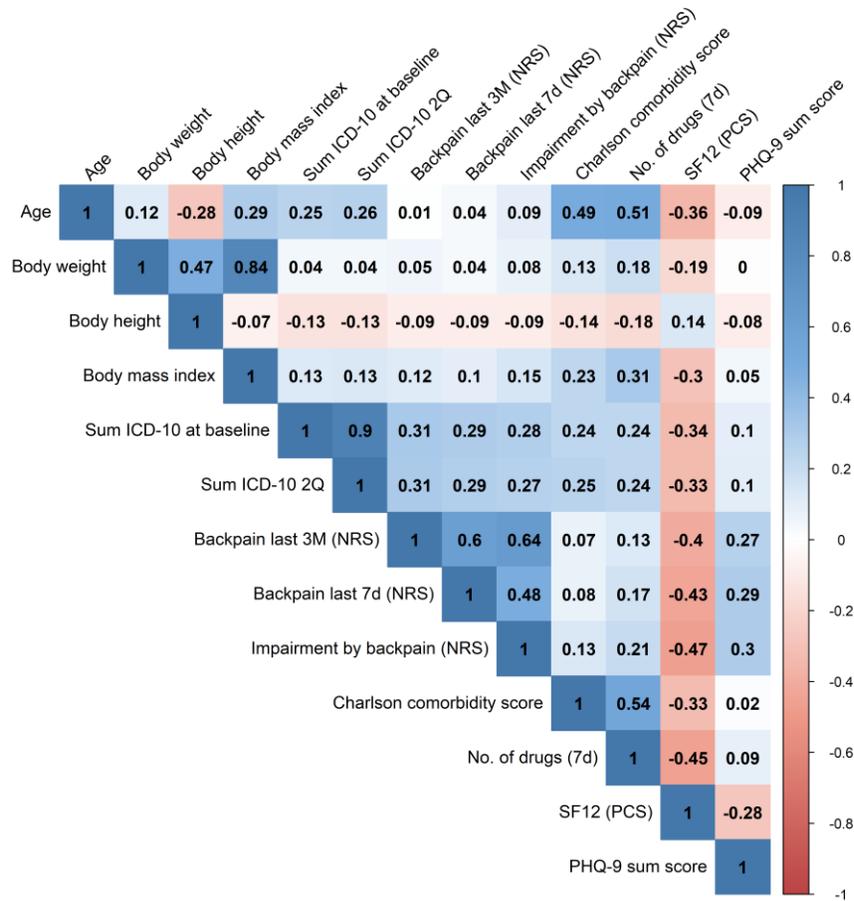


Figure S6: Correlation plot of continuous or count data.

Best subset selection

In this section, the distribution of mean scores across all 500 bootstrap samples is shown for the individual candidate variable, the full set and the best subset of all candidate variables. The scores obtained for the models in the claims data are much lower on average, i.e. the predictive value of these variables is higher than those for the SHIP data.

Computational times for best subset were 28h for claims and SHIP data on two nodes à 16 cores, and 21h for joined best subsets on one node à 16 cores.

Brier scores (Zero-part)

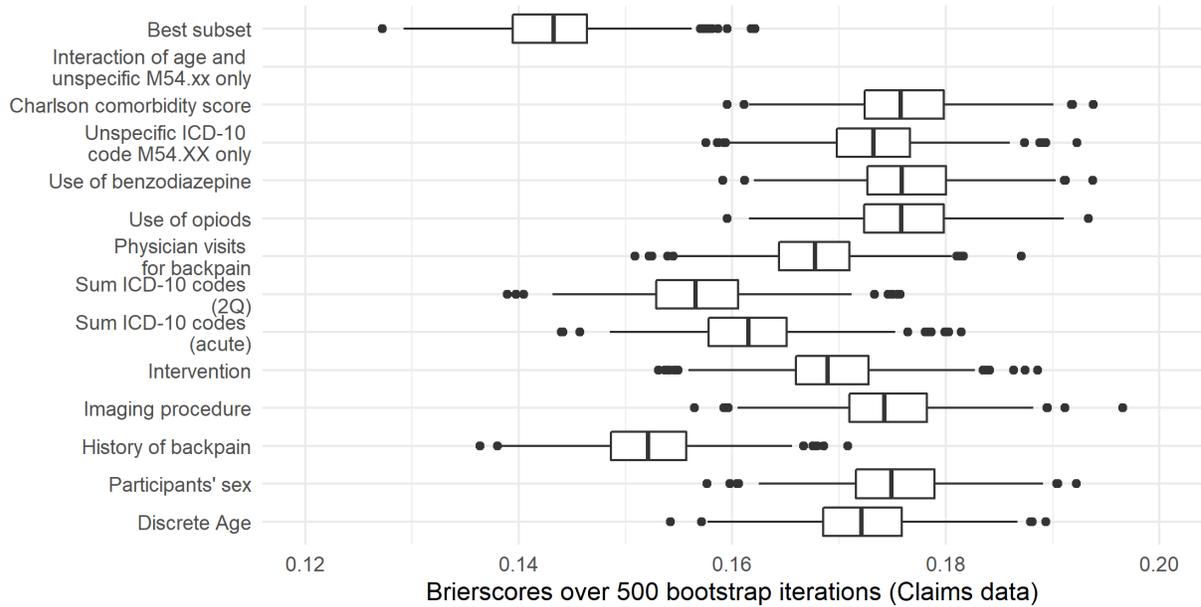


Figure S7: Brier scores claims data.

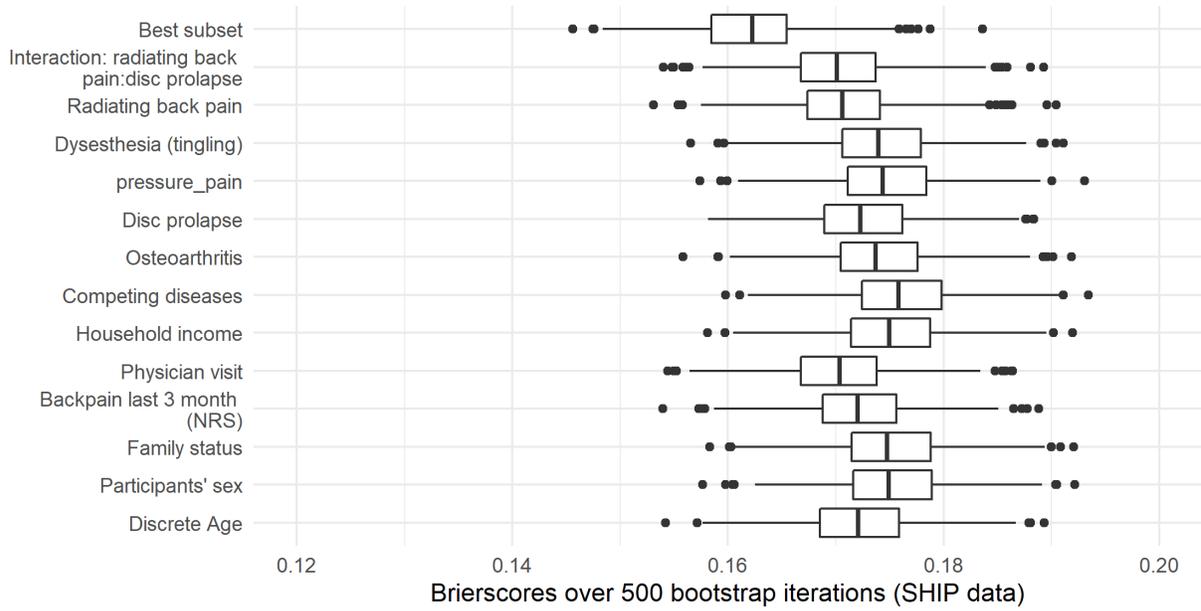


Figure S8: Brier scores SHIP data.

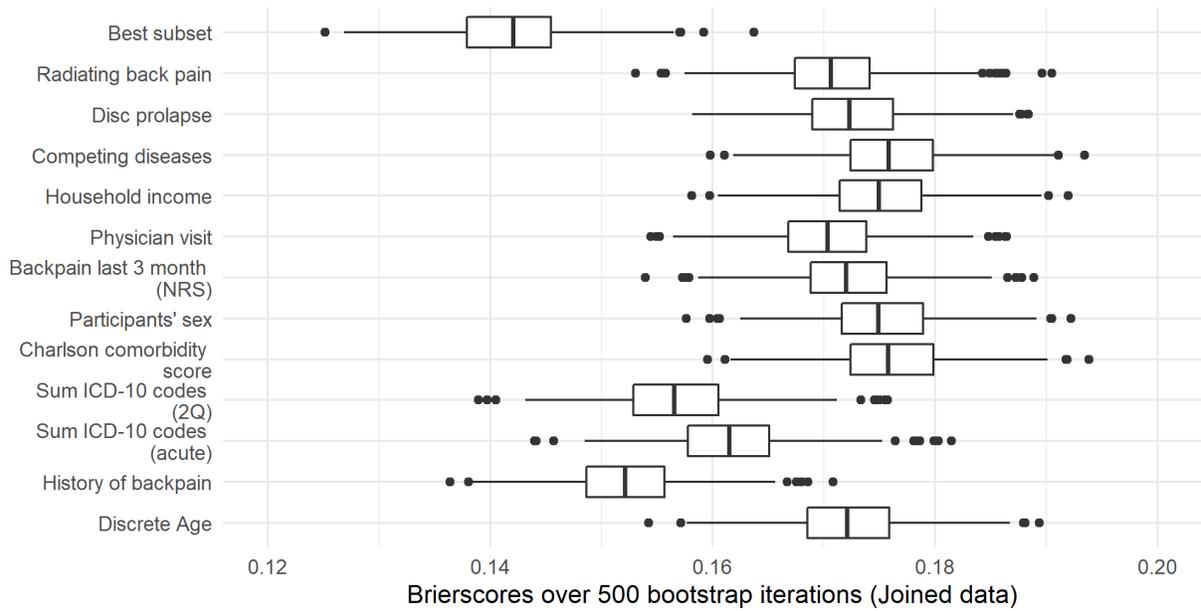


Figure S9: Brier scores joined data.

Dawid-Sebastiani scores (Count-part)

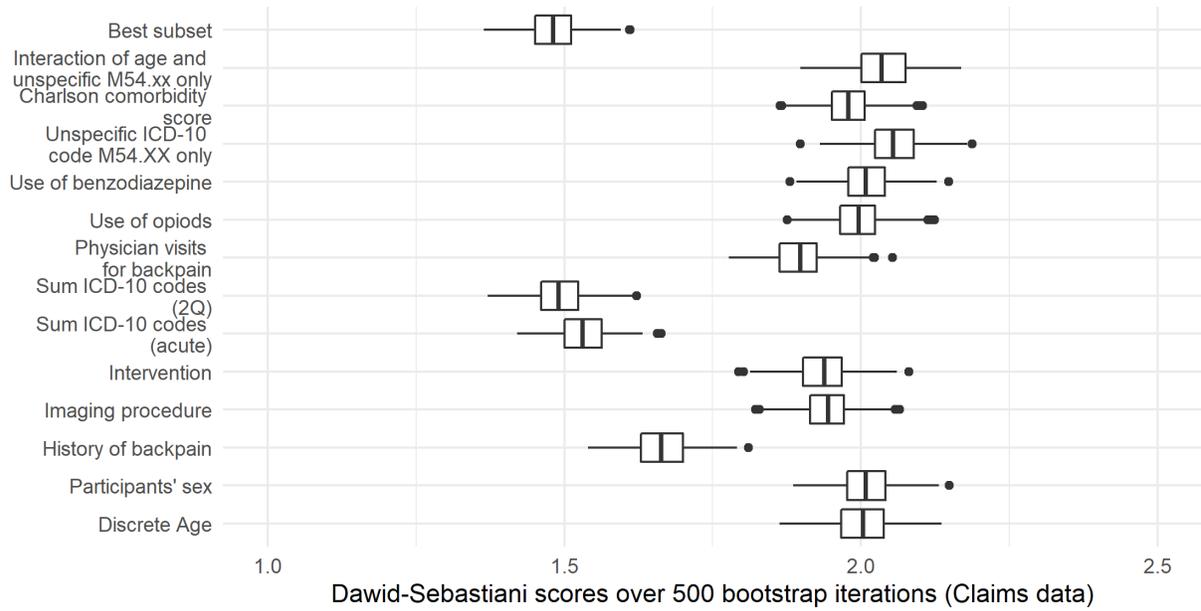


Figure S10: Dawid-Sebastiani scores claims data.

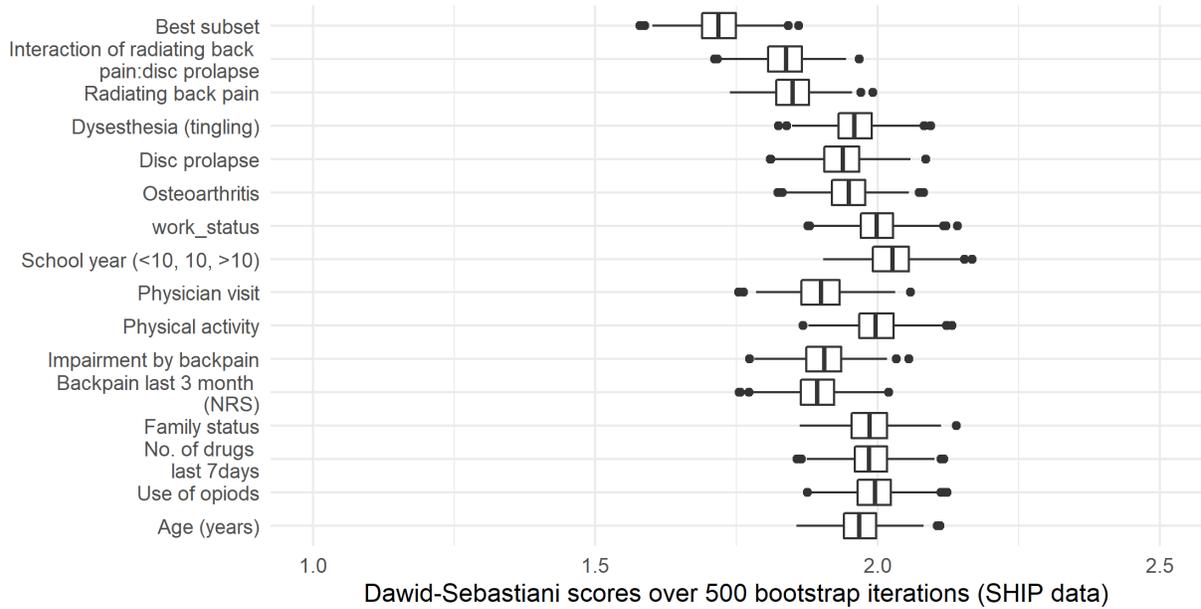


Figure S11: Dawid-Sebastiani scores SHIP data.

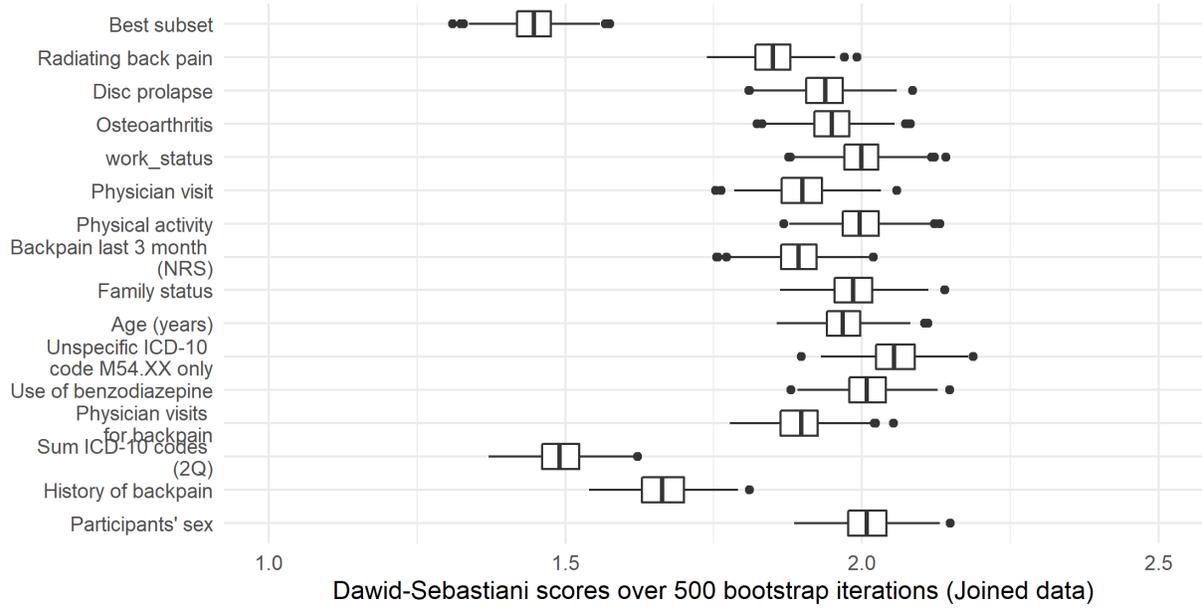


Figure S12: Dawid-Sebastiani scores joined data.

Goodness of fit

To visualize the fit of the optimal model obtained from the joined data we used rootograms [23]. The bars in Figure S13 correspond to the observed counts of ICD-10 codes. The red line indicates the fitted response of the hurdle model from a Poisson distribution.

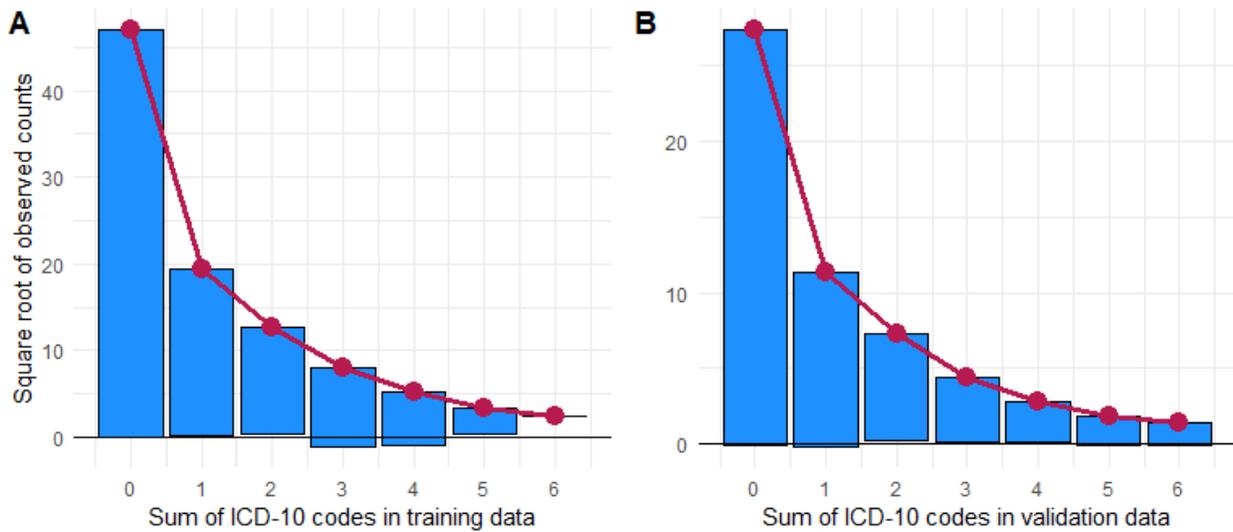


Figure S13: Rootograms of the optimal model from the joined data evaluated in training data and the validation data.

By design, the counts of the zero-part are perfectly fitted in the training data and slightly overestimated in the validation data, i.e. in the validation data the actual counts are slightly lower than what has been estimated by the model. The model fit is very reasonable.

Prediction accuracy and missing data

In Figure S14 we have depicted the ROC curves of predictions in the validation data for each imputed data set ($m=20$).

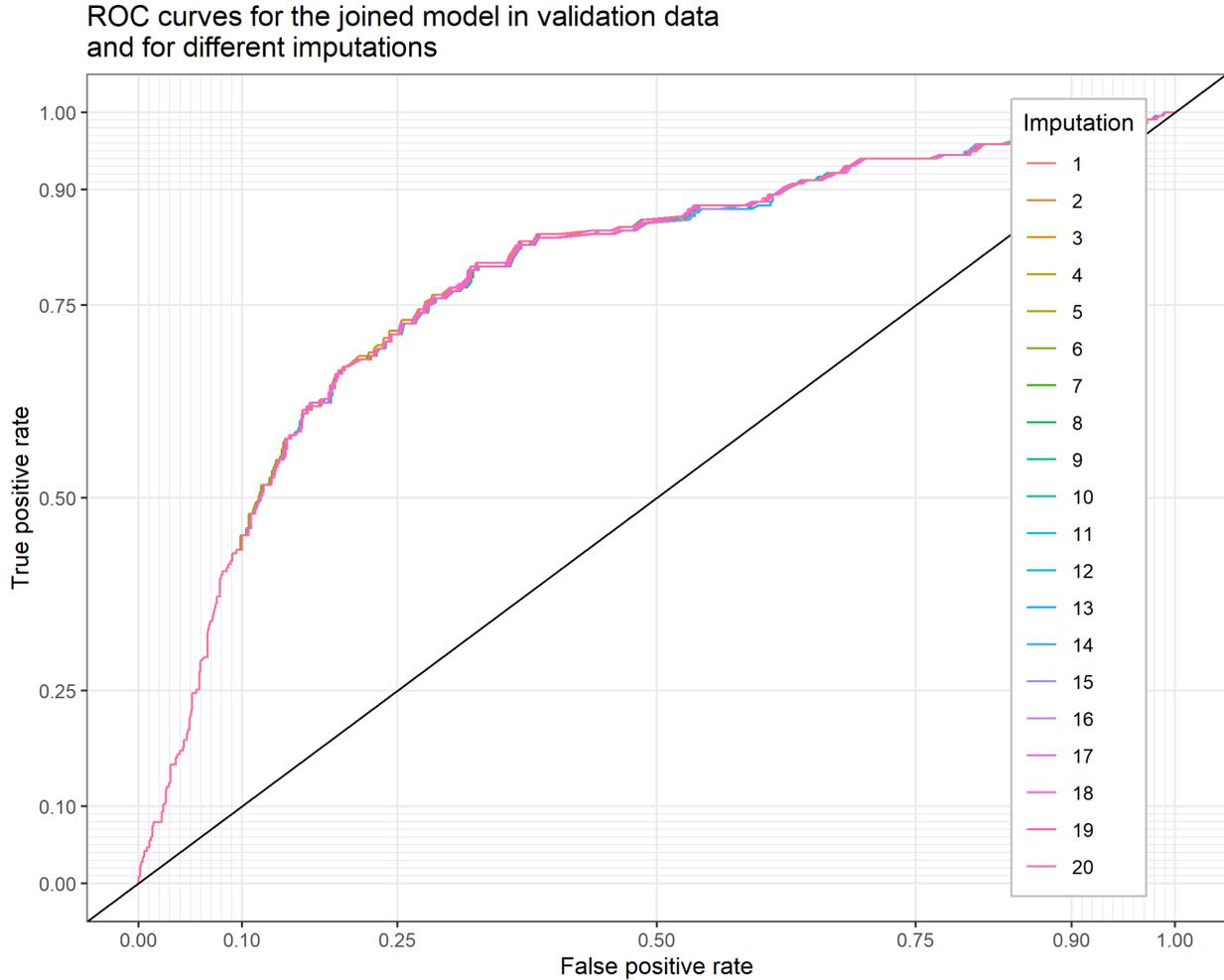


Figure S14: ROC curves for the best subset model applied on validation data with multiple imputations.

There is almost no difference between the different data sets which relates (a) to the low magnitude of missing data in most covariates and (b) that particularly in those variables selected as the best subset missingness was $<1\%$.

Subgroup analyses

Table S7: Subgroup analyses through stratification for seek of care.

Characteristic	Seek of care for low back pain*			
	0 0	0 1	1 1	1 0
N	2229	267	601	740
Age (years)				
Mean (SD)	49.9 (16.0)	49.8 (13.1)	56.3 (12.3)	58.7 (15.2)
Age discrete				
<40 years	670 (30.1%)	64 (24.0%)	58 (9.7%)	102 (13.8%)
40 to 69 years	1239 (55.6%)	186 (69.7%)	448 (74.5%)	419 (56.6%)
> 69 years	320 (14.4%)	17 (6.4%)	95 (15.8%)	219 (29.6%)
Sex				
male	1142 (51.2%)	110 (41.2%)	247 (41.1%)	316 (42.7%)
female	1087 (48.8%)	157 (58.8%)	354 (58.9%)	424 (57.3%)
Workability status				
Employable	1333 (59.8%)	174 (65.2%)	301 (50.1%)	298 (40.3%)
Retired	663 (29.7%)	66 (24.7%)	253 (42.1%)	378 (51.1%)
Unemployed	233 (10.5%)	27 (10.1%)	47 (7.8%)	64 (8.6%)
Physical demanding job				
Yes	1005 (45.1%)	120 (44.9%)	285 (47.4%)	400 (54.1%)
No	1224 (54.9%)	147 (55.1%)	316 (52.6%)	340 (45.9%)
Household income				
Mean (SD)	1290 (656)	1410 (707)	1400 (632)	1200 (538)
Missing	1100 [167, 5070]	1450 [149, 3580]	1360 [149, 3580]	1100 [167, 3580]
Competing diseases				
None	1815 (81.4%)	229 (85.8%)	470 (78.2%)	514 (69.5%)
One	335 (15.0%)	32 (12.0%)	115 (19.1%)	171 (23.1%)
>One	79 (3.5%)	6 (2.2%)	16 (2.7%)	55 (7.4%)
Inflammatory joint disease				
Yes	77 (3.5%)	10 (3.7%)	56 (9.3%)	66 (8.9%)
No	2152 (96.5%)	257 (96.3%)	545 (90.7%)	674 (91.1%)
Disc prolapse				
Yes	82 (3.7%)	13 (4.9%)	117 (19.5%)	106 (14.3%)
No	2147 (96.3%)	254 (95.1%)	484 (80.5%)	634 (85.7%)
Dysesthesia (tingling)				
Yes	174 (7.8%)	26 (9.7%)	130 (21.6%)	136 (18.4%)
No	2055 (92.2%)	241 (90.3%)	471 (78.4%)	604 (81.6%)
Back pain in last 3 month (NRS)				
Mean (SD)	2.07 (2.38)	2.56 (2.38)	3.79 (2.68)	3.76 (2.81)
Back pain irradiation (ref: no)				
no	1761 (79.0%)	190 (71.2%)	281 (46.8%)	393 (53.1%)
gluteal only	274 (12.3%)	40 (15.0%)	144 (24.0%)	146 (19.7%)
to knee	136 (6.1%)	21 (7.9%)	102 (17.0%)	114 (15.4%)
to lower leg	58 (2.6%)	16 (6.0%)	74 (12.3%)	87 (11.8%)
Medication (NSAIDs, Opioids, Benzodiazepine)				
Yes	183 (8.2%)	26 (9.7%)	118 (19.6%)	151 (20.4%)
No	2046 (91.8%)	241 (90.3%)	483 (80.4%)	589 (79.6%)
Physician visit (last 4 weeks, self-reported)				
No physician visit	567 (25.4%)	50 (18.7%)	43 (7.2%)	57 (7.7%)
GP visit only	1381 (62.0%)	169 (63.3%)	275 (45.8%)	358 (48.4%)
Specialist only	42 (1.9%)	5 (1.9%)	43 (7.2%)	44 (5.9%)
GP and specialist	239 (10.7%)	43 (16.1%)	240 (39.9%)	281 (38.0%)

*Seek of care:

0|0 = no ICD-10 codes suggestive for LBP in any of the analysis periods,

0|1 = ICD-10 codes suggestive for LBP only during follow-up,

1|1 = ICD-10 codes suggestive for LBP in all analysis periods,

1|0 = history of back pain prior baseline and/or ICD-10 codes suggestive for LBP at baseline but not in the follow-up

References

1. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the charlson comorbidity index predicted in-hospital mortality. *Journal of clinical epidemiology*. Elsevier; 2004;57:1288–94.
2. Wood SN. Stable and efficient multiple smoothing parameter estimation for generalized additive models. *Journal of the American Statistical Association*. Taylor & Francis; 2004;99:673–86.
3. Richter A, Schmidt CO, Krüger M, Struckmann S. dataquieR: Assessment of data quality in epidemiological research. *Journal of Open Source Software* [Internet]. The Open Journal; 2021;6:3093. Available from: <https://doi.org/10.21105/joss.03093>
4. Mayr A, Hofner B, Waldmann E, Hepp T, Meyer S, Gefeller O. An update on statistical boosting in biomedicine. *Computational and mathematical methods in medicine*. Hindawi; 2017;2017.
5. Hothorn T, Buehlmann P, Kneib T, Schmid M, Hofner B. mboost: Model-based boosting [Internet]. 2020. Available from: <https://CRAN.R-project.org/package=mboost>
6. Hofner B, Boccuto L, Göker M. Controlling false discoveries in high-dimensional situations: Boosting with stability selection. *BMC bioinformatics*. Springer; 2015;16:1–7.
7. Hastie T, Tibshirani R, Friedman J. *The elements of statistical learning: Data mining, inference, and prediction*. Springer Science & Business Media; 2009.
8. Steyerberg EW, Harrell Jr FE. Prediction models need appropriate internal, internal-external, and external validation. *Journal of clinical epidemiology*. NIH Public Access; 2016;69:245.
9. Filzmoser P, Liebmann B, Varmuza K. Repeated double cross validation. *Journal of Chemometrics* [Internet]. 2009;23:160–71. Available from: <https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/abs/10.1002/cem.1225>
10. Dawid AP, Sebastiani P. Coherent dispersion criteria for optimal experimental design. *The Annals of Statistics* [Internet]. Institute of Mathematical Statistics; 1999;27:65–81. Available from: <http://www.jstor.org/stable/120118>
11. Gneiting T, Raftery AE. Strictly proper scoring rules, prediction, and estimation. *Journal of the American Statistical Association* [Internet]. Taylor & Francis; 2007;102:359–78. Available from: <https://doi.org/10.1198/01621450600001437>
12. Wei W, Held L. Calibration tests for count data. *TEST* [Internet]. 2014;23:787–805. Available from: <https://doi.org/10.1007/s11749-014-0380-8>
13. Meyer S, Held L, Höhle M. Spatio-temporal analysis of epidemic phenomena using the r package surveillance. *Journal of Statistical Software, Articles* [Internet]. 2017;77:1–55. Available from: <https://www.jstatsoft.org/v077/i11>
14. Corporation M, Weston S. doParallel: Foreach parallel adaptor for the 'parallel' package [Internet]. 2020. Available from: <https://CRAN.R-project.org/package=doParallel>
15. University of Greifswald. HPC brain cluster [Internet]. Available from: <https://rz.uni-greifswald.de/dienste/allgemein/sonstiges/high-performance-computing/>

16. Czado C, Gneiting T, Held L. Predictive model assessment for count data. *Biometrics* [Internet]. 2009;65:1254–61. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1541-0420.2009.01191.x>
17. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in r. *Journal of Statistical Software* [Internet]. 2011;45:1–67. Available from: <https://www.jstatsoft.org/v45/i03/>
18. Rubin DB. Multiple imputation after 18+ years. *Journal of the American statistical Association*. Taylor & Francis Group; 1996;91:473–89.
19. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials—a practical guide with flowcharts. *BMC medical research methodology*. BioMed Central; 2017;17:1–0.
20. Breiman L. Random forests. *Machine learning*. 2001;45:5–32.
21. Biau G, Scornet E. A random forest guided tour. *Test*. Springer; 2016;25:197–227.
22. Probst P, Wright MN, Boulesteix A-L. Hyperparameters and tuning strategies for random forest. *WIREs Data Mining and Knowledge Discovery* [Internet]. 2019;9:e1301. Available from: <https://wires.onlinelibrary.wiley.com/doi/abs/10.1002/widm.1301>
23. Kleiber C, Zeileis A. Visualizing count data regressions using rootograms. *The American Statistician*. 2016;70:296–303.