Supplementary Material

for

Nationwide prediction of type 2 diabetes comorbidities

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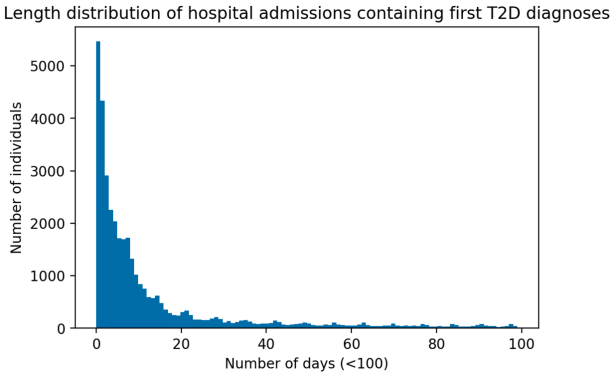
Supplementary Note 1: Death as a competing risk

Individuals who died during the prediction horizon before potentially being diagnosed with the comorbidity were categorized as non-cases. Consequently, death constituted a competing risk to the comorbidity diagnosis. To investigate the extent to which death censoring could impact predictions of the baseline and gradient boosting models we conducted two analyses. First, for each comorbidity and the gradient boosting and the reference model, we investigated five-year incidence of all-cause mortality in each population percentile (in the distribution derived by ranking individuals based on their predicted risk of a given comorbidity). We observed that for all comorbidities incidence of all-cause mortality was generally increasing with the predicted risk of the comorbidity (see Supplementary Fig. 8b for the results for CKD and Supplementary Fig. 9 for the other four comorbidities). Second, we trained and evaluated prediction performance for all-cause mortality using the same procedure as for T2D comorbidities. We found that gradient boosting significantly outperformed all other models (Supplementary Table 10) with AUROCs substantially higher compared to the best AUROCs observed for the T2D comorbidities (AUROC=0.87 vs. HF AUROC=0.80). Furthermore, the gradient boosting feature importances for all-cause mortality, in contrast to the comorbidity prediction feature importances, suggested a more prominent role of hospital diagnoses (among top 7 features three were diagnoses of malignant neoplasms) compared to canonical features and prescriptions (cumulative importances of 32%, 19% and 29%, compared to average cumulative importances of 24.2%, 22.2% and 36.8%, respectively; Supplementary Fig. 8c). These results show that competing risk of death is especially prominent among individuals predicted to be at highest comorbidity risk and that Danish health registers contain information highly predictive of all-cause mortality.

The register-based ML models, due to their high flexibility, could potentially better account for this risk as firstly, the health registers may contain variables, such as diagnoses of terminal diseases e.g. cancers, highly predictive of death. Secondly, more flexible models such as random forest or gradient boosting can better leverage non linear relationships between the features and the outcome by accounting that e.g. very advanced age, otherwise typically positively correlated with a comorbidity risk, may decrease overall comorbidity risk due to increased risk of mortality. In the analogous task of five-year all-cause mortality prediction at first T2D diagnosis, gradient boosting significantly outperformed the reference model achieving a relatively high AUROC of 0.87 when identifying subgroups at high (95th percentile risk ratio of 4.53) risk of death. Furthermore, the best all-cause mortality prediction model was able to identify relatively rare but highly predictive hospital diagnosis features such as cancer diagnoses. Lastly, for HF, CVD, and CKD individuals predicted to be at highest risk of developing a given comorbidity by a register-based model had a lower incidence of all-cause mortality than their counterparts selected by the reference model. This indicates that ML register-based models can outperform the reference model through better estimation of individuals risk of death and weighing it against the risk of a given comorbidity.



Supplementary Figure 1. Histogram of lengths of hospital admissions during which individuals received their first hospital diagnosis of T2D. Individuals with a prior T2D prescription-based diagnosis were excluded. The hospital admissions were limited to those lasting less than 100 days. T2D, type 2 diabetes.

	T2D population	**Chronic kidney disease (BPL 30 days)**	**Chronic kidney disease (BPL 60 days)**
# Individuals	203,517	200,646	200,508
# Cases	-	5,617 (2.80%)	5,605 (2.80%)
# Non-cases	-	195,029 (97.20%)	194,903 (97.20%)
% Women	47.03	47.18	47.18
Median age at T2D diagnosis	61.44	61.32	61.31
# Days until outcome	-	2065.30	2089.20
# Features in RFV	-	6,155	6,155

Supplementary Table 1. Overview of study population characteristics among all newly diagnosed type 2 diabetics (T2D population) and two chronic kidney disease comorbidity populations with buffer period set to 30 and 60 days respectively. RFV, register feature vector; #, number of; BPL, buffer period length.

Chronic kidney disease (BPL 30 days) (incidence: 0.03)

	$AUROC$	$\Delta AUROC_{RLR}$	$\Delta AUROC_{LR}$	$\Delta AUROC_{RF}$
Reference, logistic regression (RLR)	0.71 (0.69 — 0.73)			
Logistic regression (LR)	0.74 (0.72 — 0.76)	0.04 (0.02 — 0.05)		
Random forest (RF)	0.74 (0.72 — 0.76)	0.03 (0.01 — 0.05)	0.00 (-0.02 — 0.01)	
Gradient boosting (GB)	0.77 (0.76 — 0.79)	0.07 (0.05 — 0.08)	0.03 (0.02 — 0.04)	0.04 (0.02 — 0.05)

Chronic kidney disease (BPL 60 days) (incidence: 0.03)

	$AUROC$	$\Delta AUROC_{RLR}$	$\Delta AUROC_{LR}$	$\Delta AUROC_{RF}$
Reference, logistic regression (RLR)	0.70 (0.68 — 0.72)			
Logistic regression (LR)	0.74 (0.72 — 0.76)	0.04 (0.03 — 0.06)		
Random forest (RF)	0.73 (0.71 — 0.75)	0.03 (0.01 — 0.05)	-0.01 (-0.03 — 0.01)	
Gradient boosting (GB)	0.77 (0.75 — 0.78)	0.07 (0.05 — 0.08)	0.03 (0.02 — 0.04)	0.04 (0.02 — 0.05)

Supplementary Table 2. Comparison of AUROC measures for each prediction models best parameterization between chronic kidney disease comorbidity populations with buffer period set to 30 and 60 days respectively. We applied a reference- and three register-based models on fifteen years of health register data comprising hospital diagnoses, hospital procedures, drug prescriptions and interactions with primary care contractors to predict five-year risk for chronic kidney disease comorbidity. For each comorbidity, prediction was performed on a T2D population free of that comorbidity at the date of prediction (date of individuals first T2D diagnosis). The reference model was a logistic ridge regression based on canonical features: age, sex, country or region of birth and date of first T2D diagnosis as well as their interactions, while the register-based models were logistic ridge regression, random forest and gradient boosting based on the canonical features as well as hospital diagnoses, hospital procedures, drug prescriptions and interactions with primary care extracted from Danish health registers. Incidences are proportions of cases within comorbidities sub-population at the end of the prediction horizon. Value ranges in brackets represent 95% confidence intervals based on bootstrap sampling. AUROC, area under receiver operating characteristic curve.

	T2D population	HF	MI
# Individuals	181,100	169,729	169,972
# Cases	-	8,222 (4.84%)	6,039 (3.55%)
# Non-cases	-	161,507 (95.16%)	163,933 (96.45%)
% Women	46.98	47.53	48.13
Median age at T2D diagnosis	61.71	60.95	61.24
# Days until outcome	-	1672.90	1546.60
# Features in RFV	-	6,093	6,093
	ST	**CVD**	**CKD**
# Individuals	169,870	103,971	178,586
# Cases	7,467 (4.40%)	28,638 (27.54%)	5,361 (3.00%)
# Non-cases	162,403 (95.60%)	75,333 (72.46%)	173,225 (97.00%)
% Women	47.37	49.99	47.13
Median age at T2D diagnosis	61.07	57.53	61.61
# Days until outcome	1636.50	1465.00	2060.20
# Features in RFV	6,093	6,093	6,093

(a) one year after first T2D diagnosis

	T2D population	HF	MI
# Individuals	165,482	154,684	154,997
# Cases	-	8,019 (5.18%)	5,814 (3.75%)
# Non-cases	-	146,665 (94.82%)	149,183 (96.25%)
% Women	46.89	47.42	48.05
Median age at T2D diagnosis	62.35	61.56	61.85
# Days until outcome	-	1659.20	1562.80
# Features in RFV	-	5,929	5,929
	ST	**CVD**	**CKD**
# Individuals	154,683	92,455	163,069
# Cases	7,232 (4.68%)	26,302 (28.45%)	5,318 (3.26%)
# Non-cases	147,451 (95.32%)	66,153 (71.55%)	157,751 (96.74%)
% Women	47.28	49.90	47.04
Median age at T2D diagnosis	61.66	58.17	62.25
# Days until outcome	1625.90	1452.00	2036.50
# Features in RFV	5,929	5,929	5,929

(b) two years after first T2D diagnosis

	T2D population	HF	MI
# Individuals	150,228	140,053	140,418
# Cases	-	7,667 (5.47%)	5,492 (3.91%)
# Non-cases	-	132,386 (94.53%)	134,926 (96.09%)
% Women	46.73	47.26	47.88
Median age at T2D diagnosis	62.90	62.11	62.41
# Days until outcome	-	1652.20	1560.40
# Features in RFV	-	5,773	5,773
	ST	**CVD**	**CKD**
# Individuals	139,877	81,858	147,830
# Cases	6,896 (4.93%)	23,993 (29.31%)	5,178 (3.50%)
# Non-cases	132,981 (95.07%)	57,865 (70.69%)	142,652 (96.50%)
% Women	47.18	49.69	46.91
Median age at T2D diagnosis	62.22	58.77	62.78
# Days until outcome	1592.60	1434.60	2012.60
# Features in RFV	5,773	5,773	5,773

(c) three years after first T2D diagnosis

	T2D population	HF	MI
# Individuals	137,240	127,580	127,930
# Cases	-	7,403 (5.80%)	5,298 (4.14%)
# Non-cases	-	120,177 (94.20%)	122,632 (95.86%)
% Women	46.38	46.89	47.51
Median age at T2D diagnosis	63.56	62.75	63.07
# Days until outcome	-	1625.90	1543.10
# Features in RFV	-	5,624	5,624
	ST	**CVD**	**CKD**
# Individuals	127,240	72,742	134,874
# Cases	6,666 (5.24%)	22,236 (30.57%)	5,070 (3.76%)
# Non-cases	120,574 (94.76%)	50,506 (69.43%)	129,804 (96.24%)
% Women	46.83	49.25	46.55
Median age at T2D diagnosis	62.84	59.52	63.44
# Days until outcome	1571.40	1404.90	2018.10
# Features in RFV	5,624	5,624	5,624

(d) four years after first T2D diagnosis

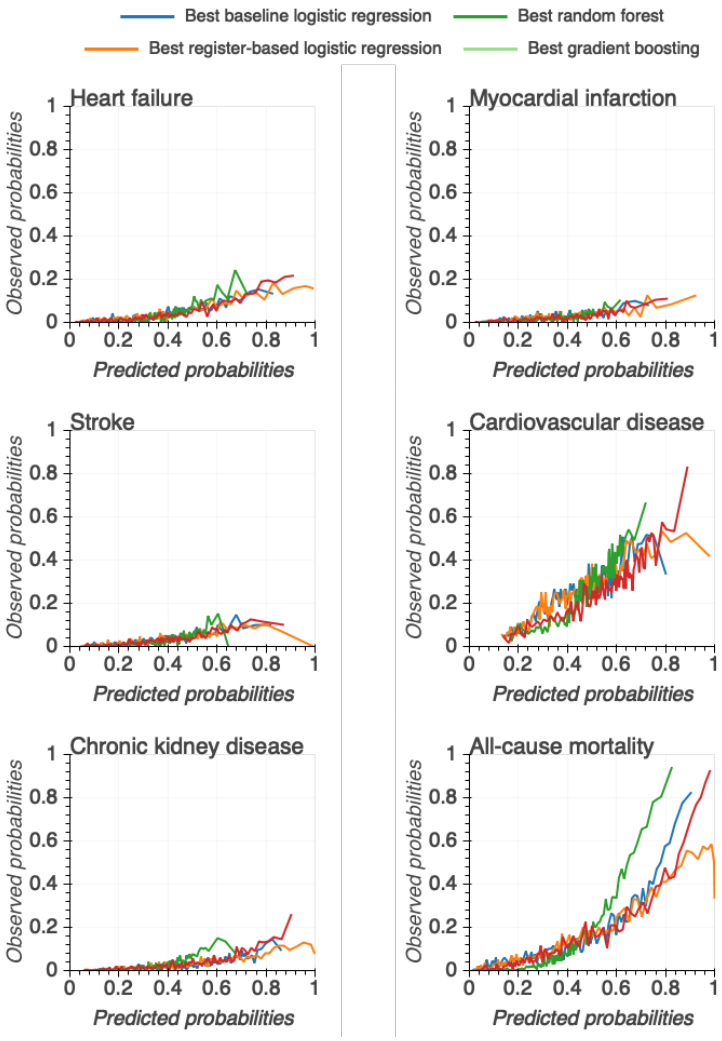
Supplementary Table 3. Population characteristics at different dates of prediction. T2D, type 2 diabetes; HF, heart failure; MI, myocardial infarction; ST, stroke; CVD, cardiovascular disease; CKD, chronic kidney disease; RFV, register feature vector; #, number of.

Logistic regression (LR)	
penalty	L2
solver	lbfgs
C	0.6, 0.7, 0.8
max_iter	300, 400, 500

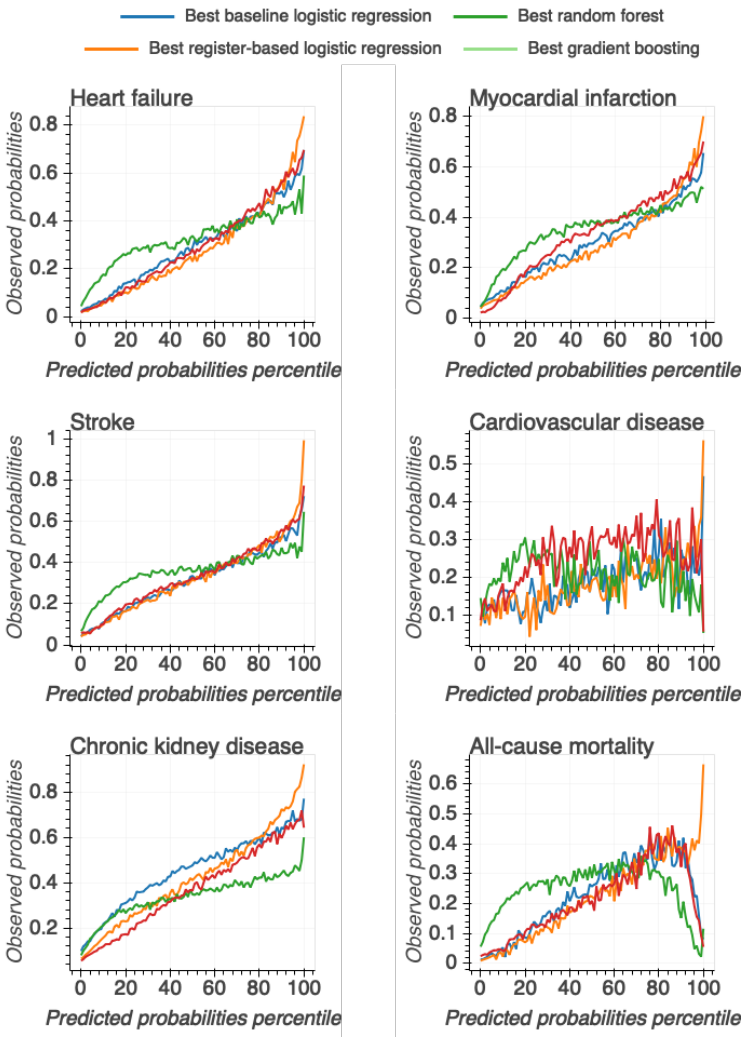
Random forest (RF)	
max_features	sqrt
criterion	gini
n_estimators	1000, 1500
max_depth	12, 14, 16

Gradient boosting (GB)	
n_estimators	200
booster	gbtree
eval_metric	auc
learning_rate	0.025, 0.05, 0.1
max_depth	2, 3, 4, 5

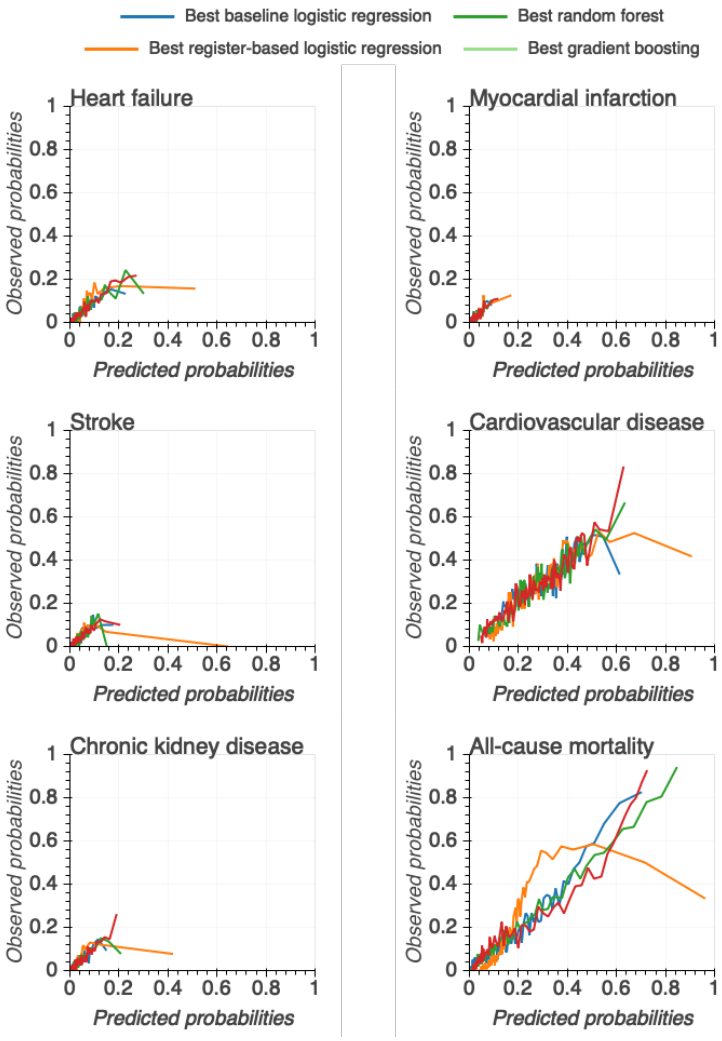
Supplementary Table 4. Overview of model hyperparameters that were evaluated. For each model type, all combinations of listed hyperparameters were tested to identify those that led to the best average AUROC using 3-fold cross validation on the training set. Parameter names listed correspond to naming in software implementation (Python modules scikit-learn for LR and RF and xgboost for GB). Due to class imbalance (difference between number of cases and non-cases in each population) training error for class representing cases was scaled up by the inverse proportion between cases and non-cases.



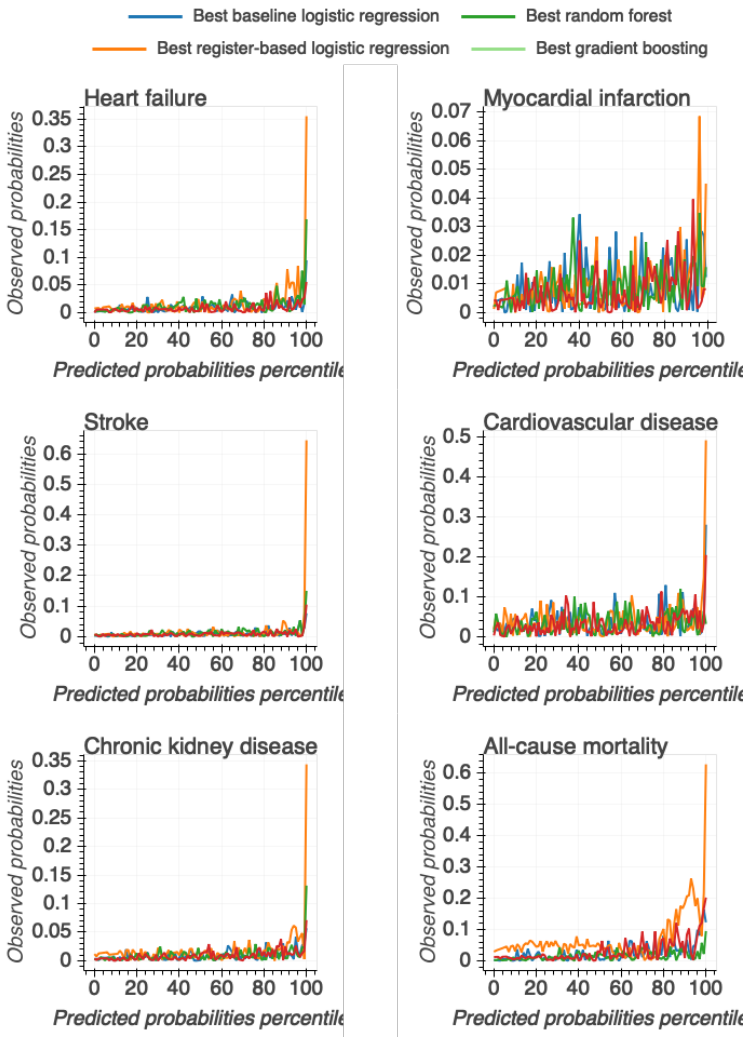
Supplementary Figure 2. Validation set calibration curves of uncalibrated best models for each comorbidity and all-cause mortality with date of prediction set to an individual's first type 2 diabetes diagnosis.



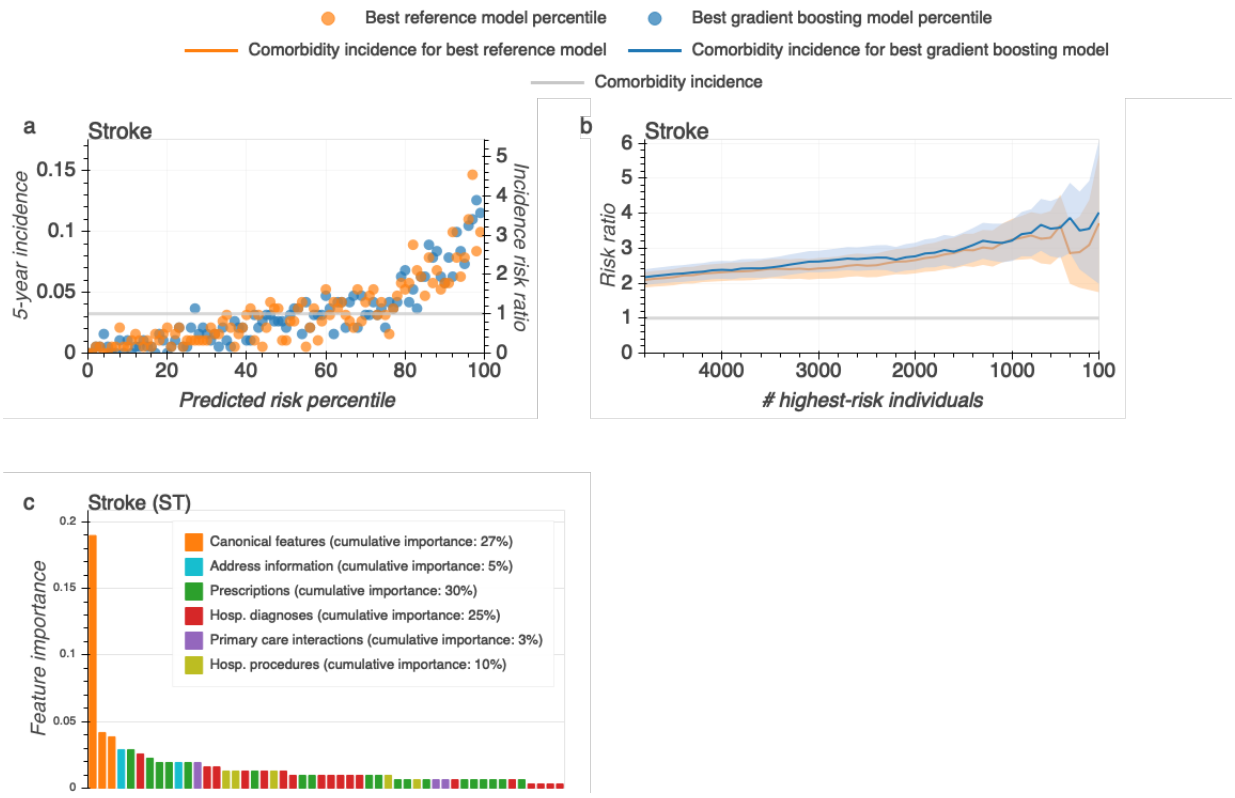
Supplementary Figure 3. Validation set calibration error (average difference between observed and predicted outcome probabilities for each predicted probability percentile) of uncalibrated best models for each comorbidity and all-cause mortality with date of prediction set to an individual's first type 2 diabetes diagnosis.



Supplementary Figure 4. Validation set calibration curves of calibrated best models for each comorbidity and all-cause mortality with date of prediction set to an individual's first type 2 diabetes diagnosis. Each best model was calibrated using Platt scaling method on the test set.



Supplementary Figure 5. Validation set calibration error (average difference between observed and predicted outcome probabilities for each predicted probability percentile) of calibrated best models for each comorbidity and all-cause mortality with date of prediction set to an individual's first type 2 diabetes diagnosis. Each best model was calibrated using Platt scaling method on the test set.



Supplementary Figure 6. (**a**) five-year incidence of hospital diagnosis of stroke for population percentiles ranked by risk as predicted by the best gradient boosting (blue) and the best baseline (orange) models. (**b**) Individuals were ranked according to their predicted risk of stroke by the best gradient boosting (blue) and the best baseline (orange) models. For a number of thresholds, shown are risk ratios, calculated as the stroke incidence of individuals ranking above that thresholds over ST incidence in the entire study population. 95% confidence interval (shaded areas) were obtained through bootstrap sampling. (**c**) 50 most predictive features for stroke according to the best gradient boosting models feature importances.

Heart failure

Model	Hyperparameters	AUROC
GB	max_depth: 2 learning_rate: 0.1 n_estimators: 200	0.803
GB	max_depth: 3 learning_rate: 0.05 n_estimators: 200	0.803
GB	max_depth: 4 learning_rate: 0.05 n_estimators: 200	0.803
GB	max_depth: 3 learning_rate: 0.1 n_estimators: 200	0.803
GB	max_depth: 2 learning_rate: 0.05 n_estimators: 200	0.802
GB	max_depth: 4 learning_rate: 0.025 n_estimators: 200	0.802
GB	max_depth: 4 learning_rate: 0.1 n_estimators: 200	0.802
GB	max_depth: 5 learning_rate: 0.025 n_estimators: 200	0.801
GB	max_depth: 5 learning_rate: 0.05 n_estimators: 200	0.801
GB	max_depth: 3 learning_rate: 0.025 n_estimators: 200	0.801
GB	max_depth: 5 learning_rate: 0.1 n_estimators: 200	0.800
GB	max_depth: 2 learning_rate: 0.025 n_estimators: 200	0.798
RF	n_estimators: 1500 max_depth: 12	0.790
RF	n_estimators: 1000 max_depth: 12	0.790
RF	n_estimators: 1500 max_depth: 14	0.787
RF	n_estimators: 1000 max_depth: 14	0.786
LR	C: 0.8 max_iter: 500	0.782
LR	C: 0.6 max_iter: 500	0.782
LR	C: 0.7 max_iter: 500	0.781
RF	n_estimators: 1500 max_depth: 16	0.781
RF	n_estimators: 1000 max_depth: 16	0.781
LR	C: 0.7 max_iter: 400	0.780
LR	C: 0.6 max_iter: 400	0.780
LR	C: 0.8 max_iter: 400	0.780
LR	C: 0.6 max_iter: 300	0.779
LR	C: 0.7 max_iter: 300	0.778
LR	C: 0.8 max_iter: 300	0.778
RLR	C: 0.6 max_iter: 300	0.748
RLR	C: 0.6 max_iter: 400	0.748
RLR	C: 0.6 max_iter: 500	0.748
RLR	C: 0.7 max_iter: 300	0.748
RLR	C: 0.7 max_iter: 400	0.748
RLR	C: 0.7 max_iter: 500	0.748
RLR	C: 0.8 max_iter: 300	0.748
RLR	C: 0.8 max_iter: 400	0.748
RLR	C: 0.8 max_iter: 500	0.748

Myocardial infarction

Model	Hyperparameters	AUROC
GB	max_depth: 2 learning_rate: 0.1 n_estimators: 200	0.730
GB	max_depth: 2 learning_rate: 0.05 n_estimators: 200	0.730
GB	max_depth: 3 learning_rate: 0.025 n_estimators: 200	0.729
GB	max_depth: 3 learning_rate: 0.1 n_estimators: 200	0.729
GB	max_depth: 4 learning_rate: 0.025 n_estimators: 200	0.729
GB	max_depth: 3 learning_rate: 0.05 n_estimators: 200	0.729
GB	max_depth: 4 learning_rate: 0.05 n_estimators: 200	0.728
GB	max_depth: 4 learning_rate: 0.1 n_estimators: 200	0.727
GB	max_depth: 2 learning_rate: 0.025 n_estimators: 200	0.727
GB	max_depth: 5 learning_rate: 0.025 n_estimators: 200	0.727
GB	max_depth: 5 learning_rate: 0.05 n_estimators: 200	0.726
GB	max_depth: 5 learning_rate: 0.1 n_estimators: 200	0.725
LR	C: 0.6 max_iter: 400	0.723
LR	C: 0.8 max_iter: 500	0.722
LR	C: 0.6 max_iter: 500	0.722
LR	C: 0.7 max_iter: 500	0.722
LR	C: 0.7 max_iter: 400	0.722
LR	C: 0.8 max_iter: 300	0.722
LR	C: 0.8 max_iter: 400	0.722
LR	C: 0.6 max_iter: 300	0.721
LR	C: 0.7 max_iter: 300	0.721
RF	n_estimators: 1500 max_depth: 12	0.712
RF	n_estimators: 1000 max_depth: 12	0.712
RLR	C: 0.6 max_iter: 300	0.703
RLR	C: 0.6 max_iter: 400	0.703
RLR	C: 0.6 max_iter: 500	0.703
RLR	C: 0.7 max_iter: 300	0.703
RLR	C: 0.7 max_iter: 400	0.703
RLR	C: 0.7 max_iter: 500	0.703
RLR	C: 0.8 max_iter: 300	0.703
RLR	C: 0.8 max_iter: 400	0.703
RLR	C: 0.8 max_iter: 500	0.703
RF	n_estimators: 1000 max_depth: 14	0.703
RF	n_estimators: 1500 max_depth: 14	0.703
RF	n_estimators: 1000 max_depth: 16	0.691
RF	n_estimators: 1500 max_depth: 16	0.691

Stroke

Model	Hyperparameters	AUROC
GB	max_depth: 2 learning_rate: 0.1 n_estimators: 200	0.734
GB	max_depth: 2 learning_rate: 0.05 n_estimators: 200	0.733
GB	max_depth: 3 learning_rate: 0.05 n_estimators: 200	0.733
GB	max_depth: 3 learning_rate: 0.1 n_estimators: 200	0.733
GB	max_depth: 3 learning_rate: 0.025 n_estimators: 200	0.733
GB	max_depth: 4 learning_rate: 0.025 n_estimators: 200	0.732
GB	max_depth: 4 learning_rate: 0.05 n_estimators: 200	0.731
GB	max_depth: 4 learning_rate: 0.1 n_estimators: 200	0.731
GB	max_depth: 2 learning_rate: 0.025 n_estimators: 200	0.730
GB	max_depth: 5 learning_rate: 0.025 n_estimators: 200	0.730
GB	max_depth: 5 learning_rate: 0.05 n_estimators: 200	0.729
GB	max_depth: 5 learning_rate: 0.1 n_estimators: 200	0.728
LR	C: 0.8 max_iter: 500	0.726
LR	C: 0.6 max_iter: 300	0.725
LR	C: 0.8 max_iter: 400	0.725
LR	C: 0.6 max_iter: 500	0.725
LR	C: 0.6 max_iter: 400	0.725
LR	C: 0.8 max_iter: 300	0.725
LR	C: 0.7 max_iter: 300	0.725
LR	C: 0.7 max_iter: 500	0.725
LR	C: 0.7 max_iter: 400	0.725
RLR	C: 0.6 max_iter: 300	0.717
RLR	C: 0.6 max_iter: 400	0.717
RLR	C: 0.6 max_iter: 500	0.717
RLR	C: 0.7 max_iter: 300	0.717
RLR	C: 0.7 max_iter: 400	0.717
RLR	C: 0.7 max_iter: 500	0.717
RLR	C: 0.8 max_iter: 300	0.717
RLR	C: 0.8 max_iter: 400	0.717
RLR	C: 0.8 max_iter: 500	0.717
RF	n_estimators: 1500 max_depth: 12	0.713
RF	n_estimators: 1000 max_depth: 12	0.713
RF	n_estimators: 1500 max_depth: 14	0.707
RF	n_estimators: 1000 max_depth: 14	0.707
RF	n_estimators: 1500 max_depth: 16	0.699
RF	n_estimators: 1000 max_depth: 16	0.699

Cardiovascular disease

Model	Hyperparameters	AUROC
GB	max_depth: 4 learning_rate: 0.05 n_estimators: 200	0.698
GB	max_depth: 2 learning_rate: 0.1 n_estimators: 200	0.698
GB	max_depth: 3 learning_rate: 0.05 n_estimators: 200	0.698
GB	max_depth: 3 learning_rate: 0.1 n_estimators: 200	0.698
GB	max_depth: 5 learning_rate: 0.05 n_estimators: 200	0.698
GB	max_depth: 5 learning_rate: 0.025 n_estimators: 200	0.698
GB	max_depth: 4 learning_rate: 0.1 n_estimators: 200	0.698
GB	max_depth: 5 learning_rate: 0.1 n_estimators: 200	0.697
GB	max_depth: 4 learning_rate: 0.025 n_estimators: 200	0.697
GB	max_depth: 2 learning_rate: 0.05 n_estimators: 200	0.697
GB	max_depth: 3 learning_rate: 0.025 n_estimators: 200	0.695
GB	max_depth: 2 learning_rate: 0.025 n_estimators: 200	0.691
RF	class_weight: balanced_subsample n_estimators: 1000 max_depth: 14	0.687
RF	class_weight: balanced_subsample n_estimators: 1500 max_depth: 16	0.687
RF	class_weight: balanced_subsample n_estimators: 1500 max_depth: 14	0.687
RF	class_weight: balanced_subsample n_estimators: 1000 max_depth: 16	0.687
RF	class_weight: balanced_subsample n_estimators: 1500 max_depth: 12	0.687
RF	class_weight: balanced_subsample n_estimators: 1000 max_depth: 12	0.687
LR	class_weight: balanced C: 0.6 max_iter: 400	0.682
LR	class_weight: balanced C: 0.7 max_iter: 500	0.682
LR	class_weight: balanced C: 0.8 max_iter: 500	0.682
LR	class_weight: balanced C: 0.6 max_iter: 500	0.682
LR	class_weight: balanced C: 0.7 max_iter: 400	0.682
LR	class_weight: balanced C: 0.7 max_iter: 300	0.681
LR	class_weight: balanced C: 0.8 max_iter: 400	0.681
LR	class_weight: balanced C: 0.8 max_iter: 300	0.680
LR	class_weight: balanced C: 0.6 max_iter: 300	0.680
RLR	class_weight: balanced C: 0.6 max_iter: 300	0.666
RLR	class_weight: balanced C: 0.6 max_iter: 400	0.666
RLR	class_weight: balanced C: 0.6 max_iter: 500	0.666
RLR	class_weight: balanced C: 0.7 max_iter: 300	0.666
RLR	class_weight: balanced C: 0.7 max_iter: 400	0.666
RLR	class_weight: balanced C: 0.7 max_iter: 500	0.666
RLR	class_weight: balanced C: 0.8 max_iter: 300	0.666
RLR	class_weight: balanced C: 0.8 max_iter: 400	0.666
RLR	class_weight: balanced C: 0.8 max_iter: 500	0.666

Supplementary Table 5. Area under receiver operating characteristic curve (AUROC) performance for each tested parametrization for heart failure, myocardial infarction, stroke and cardiovascular disease. Date of prediction was set to date of first type 2 diabetes diagnosis. Hyperparameter names correspond to parameter names from the python sklearn package. GB, gradient boosting; RF, random forest; LR, register-based logistic regression; RLR, reference logistic regression.

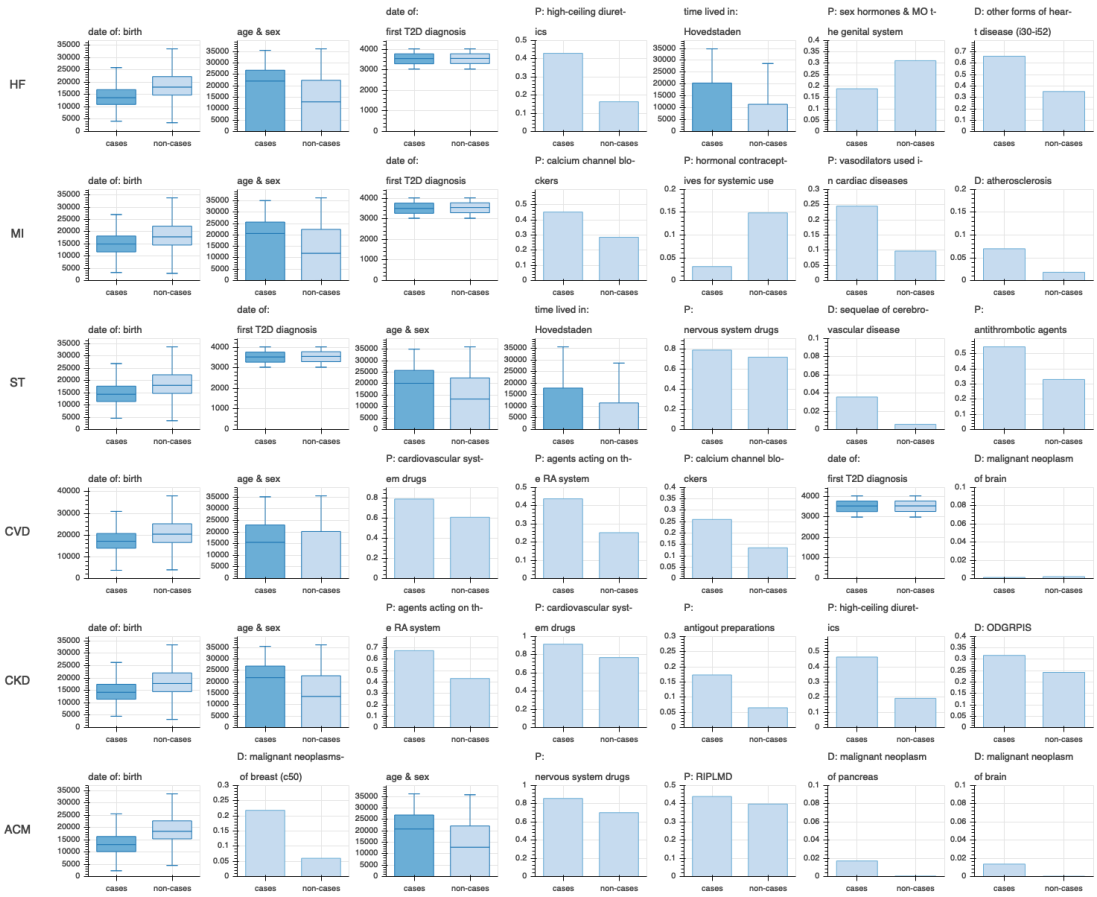
Chronic kidney disease

Model	Hyperparameters	AUROC
GB	max_depth: 2 learning_rate: 0.1 n_estimators: 200	0.754
GB	max_depth: 3 learning_rate: 0.05 n_estimators: 200	0.754
GB	max_depth: 2 learning_rate: 0.05 n_estimators: 200	0.753
GB	max_depth: 3 learning_rate: 0.1 n_estimators: 200	0.753
GB	max_depth: 3 learning_rate: 0.025 n_estimators: 200	0.752
GB	max_depth: 4 learning_rate: 0.05 n_estimators: 200	0.752
GB	max_depth: 4 learning_rate: 0.025 n_estimators: 200	0.751
GB	max_depth: 2 learning_rate: 0.025 n_estimators: 200	0.749
GB	max_depth: 4 learning_rate: 0.1 n_estimators: 200	0.749
GB	max_depth: 5 learning_rate: 0.025 n_estimators: 200	0.749
GB	max_depth: 5 learning_rate: 0.05 n_estimators: 200	0.747
GB	max_depth: 5 learning_rate: 0.1 n_estimators: 200	0.745
LR	C: 0.6 max_iter: 500	0.730
LR	C: 0.6 max_iter: 400	0.729
RF	n_estimators: 1500 max_depth: 12	0.729
LR	C: 0.8 max_iter: 400	0.729
LR	C: 0.8 max_iter: 500	0.729
RF	n_estimators: 1000 max_depth: 12	0.729
LR	C: 0.7 max_iter: 500	0.727
LR	C: 0.7 max_iter: 400	0.727
LR	C: 0.6 max_iter: 300	0.726
LR	C: 0.7 max_iter: 300	0.726
LR	C: 0.8 max_iter: 300	0.724
RF	n_estimators: 1500 max_depth: 14	0.718
RF	n_estimators: 1000 max_depth: 14	0.717
RF	n_estimators: 1500 max_depth: 16	0.701
RF	n_estimators: 1000 max_depth: 16	0.700
RLR	C: 0.6 max_iter: 300	0.693
RLR	C: 0.6 max_iter: 400	0.693
RLR	C: 0.6 max_iter: 500	0.693
RLR	C: 0.7 max_iter: 300	0.693
RLR	C: 0.7 max_iter: 400	0.693
RLR	C: 0.7 max_iter: 500	0.693
RLR	C: 0.8 max_iter: 300	0.693
RLR	C: 0.8 max_iter: 400	0.693
RLR	C: 0.8 max_iter: 500	0.693

All-cause mortality

Model	Hyperparameters	AUROC
GB	max_depth: 4 learning_rate: 0.1 n_estimators: 200	0.864
GB	max_depth: 5 learning_rate: 0.1 n_estimators: 200	0.863
GB	max_depth: 3 learning_rate: 0.1 n_estimators: 200	0.863
GB	max_depth: 5 learning_rate: 0.05 n_estimators: 200	0.863
GB	max_depth: 4 learning_rate: 0.05 n_estimators: 200	0.862
GB	max_depth: 2 learning_rate: 0.1 n_estimators: 200	0.861
GB	max_depth: 3 learning_rate: 0.05 n_estimators: 200	0.860
GB	max_depth: 5 learning_rate: 0.025 n_estimators: 200	0.859
GB	max_depth: 4 learning_rate: 0.025 n_estimators: 200	0.857
GB	max_depth: 2 learning_rate: 0.05 n_estimators: 200	0.856
GB	max_depth: 3 learning_rate: 0.025 n_estimators: 200	0.854
GB	max_depth: 2 learning_rate: 0.025 n_estimators: 200	0.847
RF	n_estimators: 1500 max_depth: 16	0.845
RF	n_estimators: 1000 max_depth: 16	0.845
RF	n_estimators: 1500 max_depth: 14	0.842
RF	n_estimators: 1000 max_depth: 14	0.842
RF	n_estimators: 1500 max_depth: 12	0.838
RF	n_estimators: 1000 max_depth: 12	0.838
LR	C: 0.8 max_iter: 500	0.827
LR	C: 0.7 max_iter: 500	0.827
LR	C: 0.6 max_iter: 500	0.826
LR	C: 0.8 max_iter: 400	0.826
LR	C: 0.7 max_iter: 400	0.826
LR	C: 0.6 max_iter: 400	0.825
LR	C: 0.8 max_iter: 300	0.823
LR	C: 0.6 max_iter: 300	0.822
LR	C: 0.7 max_iter: 300	0.822
RLR	C: 0.6 max_iter: 300	0.796
RLR	C: 0.6 max_iter: 400	0.796
RLR	C: 0.6 max_iter: 500	0.796
RLR	C: 0.7 max_iter: 300	0.796
RLR	C: 0.7 max_iter: 400	0.796
RLR	C: 0.7 max_iter: 500	0.796
RLR	C: 0.8 max_iter: 300	0.796
RLR	C: 0.8 max_iter: 400	0.796
RLR	C: 0.8 max_iter: 500	0.796

Supplementary Table 6. Area under receiver operating characteristic curve (AUROC) performance for each tested parametrization for chronic kidney disease and all cause mortality. Date of prediction was set to date of first type 2 diabetes diagnosis. Hyperparameter names correspond to parameter names from the the python sklearn package. GB, gradient boosting; RF, random forest; RLR, register-based logistic regression; LR, reference logistic regression.



Supplementary Figure 7. Top seven most predictive gradient boosting features. For each comorbidity and ACM shown are the top seven features according to gradient boosting feature importance. Feature importance is an estimate of feature's relative contribution to outcome prediction. Box plots show a distribution of a given continuous feature (e.g. age, an interaction between age and sex) among cases and non-cases within validation set. Box plot whiskers represent lowest and highest observations still within 1.5 inter quantile range. To comply with Danish data protection rules, these values as well as values representing 25th, 50th and 75th percentiles were obtained by averaging five closest observations. Bar plots, describing count based features (e.g. count of a given drug prescription, count of a given diagnosis), show the proportion of validation set cases and non-cases with at least a single observation of that feature. HF, heart failure; MI, myocardial infarction; ST, stroke; CVD, cardiovascular disease; CKD, chronic kidney disease; ACM, all-cause mortality; D, diagnosis of; P, prescription of; MO, modulators of; STE, st elevation; RA, renin-angiotensin; ODGRPIS, other disorders of glucose regulation and pancreatic internal secretion; RIPLMD, hmg coa reductase inhibitors and plain lipid modifying drugs.

Heart failure

t_P	I	Gradient Boosting AUROC	Reference AUROC
0	0.04	0.80 (0.78 — 0.81)	0.74 (0.72 — 0.75)
1	0.04	0.80 (0.78 — 0.81)	0.74 (0.72 — 0.76)
2	0.04	0.80 (0.78 — 0.81)	0.74 (0.72 — 0.76)
3	0.04	0.81 (0.79 — 0.83)	0.75 (0.73 — 0.77)
4	0.04	0.81 (0.79 — 0.82)	0.74 (0.72 — 0.75)

Myocardial infarction

t_P	I	Gradient Boosting AUROC	Reference AUROC
0	0.03	0.71 (0.69 — 0.73)	0.68 (0.65 — 0.70)
1	0.03	0.73 (0.71 — 0.75)	0.68 (0.66 — 0.71)
2	0.03	0.74 (0.71 — 0.76)	0.69 (0.67 — 0.71)
3	0.03	0.72 (0.70 — 0.75)	0.69 (0.67 — 0.72)
4	0.03	0.73 (0.70 — 0.75)	0.68 (0.66 — 0.71)

Stroke

t_P	I	Gradient Boosting AUROC	Reference AUROC
0	0.03	0.72 (0.70 — 0.74)	0.71 (0.69 — 0.73)
1	0.03	0.75 (0.73 — 0.77)	0.70 (0.68 — 0.72)
2	0.03	0.75 (0.73 — 0.77)	0.71 (0.69 — 0.73)
3	0.04	0.75 (0.73 — 0.77)	0.72 (0.70 — 0.74)
4	0.04	0.75 (0.73 — 0.77)	0.72 (0.70 — 0.74)

Cardiovascular disease

t_P	I	Gradient Boosting AUROC	Reference AUROC
0	0.26	0.69 (0.68 — 0.70)	0.66 (0.64 — 0.67)
1	0.25	0.71 (0.70 — 0.73)	0.67 (0.66 — 0.68)
2	0.25	0.72 (0.71 — 0.74)	0.68 (0.67 — 0.70)
3	0.25	0.73 (0.72 — 0.74)	0.68 (0.67 — 0.69)
4	0.26	0.73 (0.72 — 0.74)	0.69 (0.67 — 0.70)

Chronic kidney disease

t_P	I	Gradient Boosting AUROC	Reference AUROC
0	0.03	0.77 (0.76 — 0.79)	0.71 (0.69 — 0.73)
1	0.03	0.77 (0.75 — 0.78)	0.68 (0.66 — 0.70)
2	0.03	0.77 (0.75 — 0.79)	0.70 (0.68 — 0.72)
3	0.04	0.79 (0.77 — 0.80)	0.72 (0.70 — 0.74)
4	0.04	0.79 (0.77 — 0.81)	0.70 (0.68 — 0.72)

All-cause mortality

t_P	I	Gradient Boosting AUROC	Reference AUROC
0	0.14	0.87 (0.86 — 0.87)	0.80 (0.79 — 0.81)
1	0.14	0.87 (0.87 — 0.88)	0.81 (0.80 — 0.82)
2	0.14	0.88 (0.87 — 0.88)	0.81 (0.80 — 0.82)
3	0.15	0.88 (0.87 — 0.88)	0.82 (0.81 — 0.83)
4	0.16	0.87 (0.87 — 0.88)	0.80 (0.79 — 0.81)

Supplementary Table 7. Prediction performance at one, two, three and four years after individual's first type 2 diabetes diagnosis. t_P, time of prediction counted in years since individual's first type 2 diabetes diagnosis; I, outcome incidence within study population; AUROC, area under receiver operating characteristic curve which confidence intervals were obtained by bootstrap sampling procedure.

Heart failure (incidence: 0.04)

	AUROC
Reference, logistic regression	0.74 (0.72 — 0.76)
Gradient boosting	0.80 (0.78 — 0.81)

Myocardial infarction (incidence: 0.03)

	AUROC
Reference, logistic regression	0.68 (0.66 — 0.71)
Gradient boosting	0.73 (0.71 — 0.75)

Stroke (incidence: 0.03)

	AUROC
Reference, logistic regression	0.70 (0.68 — 0.72)
Gradient boosting	0.75 (0.73 — 0.77)

Cardiovascular disease (incidence: 0.24)

	AUROC
Reference, logistic regression	0.67 (0.66 — 0.68)
Gradient boosting	0.71 (0.70 — 0.73)

Chronic kidney disease (incidence: 0.03)

	AUROC
Reference, logistic regression	0.68 (0.66 — 0.70)
Gradient boosting	0.77 (0.75 — 0.78)

(a) one years after first T2D diagnosis

Heart failure (incidence: 0.04)

	AUROC
Reference, logistic regression	0.74 (0.72 — 0.76)
Gradient boosting	0.80 (0.78 — 0.81)

Myocardial infarction (incidence: 0.03)

	AUROC
Reference, logistic regression	0.69 (0.67 — 0.71)
Gradient boosting	0.74 (0.71 — 0.76)

Stroke (incidence: 0.04)

	AUROC
Reference, logistic regression	0.71 (0.69 — 0.73)
Gradient boosting	0.75 (0.73 — 0.77)

Cardiovascular disease (incidence: 0.25)

	AUROC
Reference, logistic regression	0.68 (0.67 — 0.70)
Gradient boosting	0.72 (0.71 — 0.74)

Chronic kidney disease (incidence: 0.04)

	AUROC
Reference, logistic regression	0.70 (0.68 — 0.72)
Gradient boosting	0.77 (0.75 — 0.79)

(b) two years after first T2D diagnosis

Heart failure (incidence: 0.04)

	AUROC
Reference, logistic regression	0.75 (0.73 — 0.77)
Gradient boosting	0.81 (0.79 — 0.83)

Myocardial infarction (incidence: 0.03)

	AUROC
Reference, logistic regression	0.69 (0.67 — 0.72)
Gradient boosting	0.72 (0.70 — 0.75)

Stroke (incidence: 0.04)

	AUROC
Reference, logistic regression	0.72 (0.70 — 0.74)
Gradient boosting	0.75 (0.73 — 0.77)

Cardiovascular disease (incidence: 0.25)

	AUROC
Reference, logistic regression	0.68 (0.67 — 0.69)
Gradient boosting	0.73 (0.72 — 0.74)

Chronic kidney disease (incidence: 0.04)

	AUROC
Reference, logistic regression	0.72 (0.70 — 0.74)
Gradient boosting	0.79 (0.77 — 0.80)

(c) three years after first T2D diagnosis

Heart failure (incidence: 0.04)

	AUROC
Reference, logistic regression	0.74 (0.72 — 0.75)
Gradient boosting	0.81 (0.79 — 0.82)

Myocardial infarction (incidence: 0.03)

	AUROC
Reference, logistic regression	0.68 (0.66 — 0.71)
Gradient boosting	0.73 (0.70 — 0.75)

Stroke (incidence: 0.04)

	AUROC
Reference, logistic regression	0.72 (0.70 — 0.74)
Gradient boosting	0.75 (0.73 — 0.77)

Cardiovascular disease (incidence: 0.25)

	AUROC
Reference, logistic regression	0.69 (0.67 — 0.70)
Gradient boosting	0.73 (0.72 — 0.74)

Chronic kidney disease (incidence: 0.04)

	AUROC
Reference, logistic regression	0.70 (0.68 — 0.72)
Gradient boosting	0.79 (0.77 — 0.81)

(d) four years after first T2D diagnosis

Supplementary Table 8. Gradient boosting and baseline model prediction performance for different dates of prediction. Incidence is the proportion of cases within the population. AUROC is area under receiver operating characteristic curve which confidence intervals were obtained by bootstrap sampling procedure. T2D, type 2 diabetes.

Heart failure (I_{ts}: 0.04, I_{no-ts}: 0.05)

	$AUROC_{ts}$	$AUROC_{no-ts}$
Reference, logistic regression	0.74 (0.72 — 0.75)	0.76 (0.74 — 0.77)
Logistic regression	0.77 (0.76 — 0.79)	0.78 (0.77 — 0.80)
Random forest	0.77 (0.75 — 0.78)	0.80 (0.79 — 0.81)
Gradient boosting	0.80 (0.78 — 0.81)	0.81 (0.80 — 0.83)

Myocardial infarction (I_{ts}: 0.02, I_{no-ts}: 0.03)

	$AUROC_{ts}$	$AUROC_{no-ts}$
Reference, logistic regression	0.68 (0.65 — 0.70)	0.69 (0.67 — 0.71)
Logistic regression	0.70 (0.68 — 0.73)	0.71 (0.69 — 0.73)
Random forest	0.67 (0.64 — 0.69)	0.71 (0.69 — 0.73)
Gradient boosting	0.71 (0.69 — 0.73)	0.72 (0.70 — 0.74)

Stroke (I_{ts}: 0.03, I_{no-ts}: 0.04)

	$AUROC_{ts}$	$AUROC_{no-ts}$
Reference, logistic regression	0.71 (0.69 — 0.73)	0.72 (0.70 — 0.73)
Logistic regression	0.72 (0.70 — 0.74)	0.72 (0.70 — 0.74)
Random forest	0.69 (0.67 — 0.71)	0.71 (0.69 — 0.73)
Gradient boosting	0.72 (0.70 — 0.74)	0.73 (0.72 — 0.75)

Cardiovascular disease (I_{ts}: 0.25, I_{no-ts}: 0.28)

	$AUROC_{ts}$	$AUROC_{no-ts}$
Reference, logistic regression	0.66 (0.64 — 0.67)	0.67 (0.66 — 0.68)
Logistic regression	0.68 (0.67 — 0.69)	0.69 (0.68 — 0.70)
Random forest	0.68 (0.67 — 0.69)	0.70 (0.69 — 0.71)
Gradient boosting	0.69 (0.68 — 0.70)	0.71 (0.70 — 0.72)

Chronic kidney disease (I_{ts}: 0.03, I_{no-ts}: 0.03)

	$AUROC_{ts}$	$AUROC_{no-ts}$
Reference, logistic regression	0.71 (0.69 — 0.73)	0.71 (0.69 — 0.73)
Logistic regression	0.74 (0.72 — 0.76)	0.75 (0.73 — 0.77)
Random forest	0.74 (0.72 — 0.76)	0.76 (0.74 — 0.78)
Gradient boosting	0.77 (0.76 — 0.79)	0.78 (0.76 — 0.80)

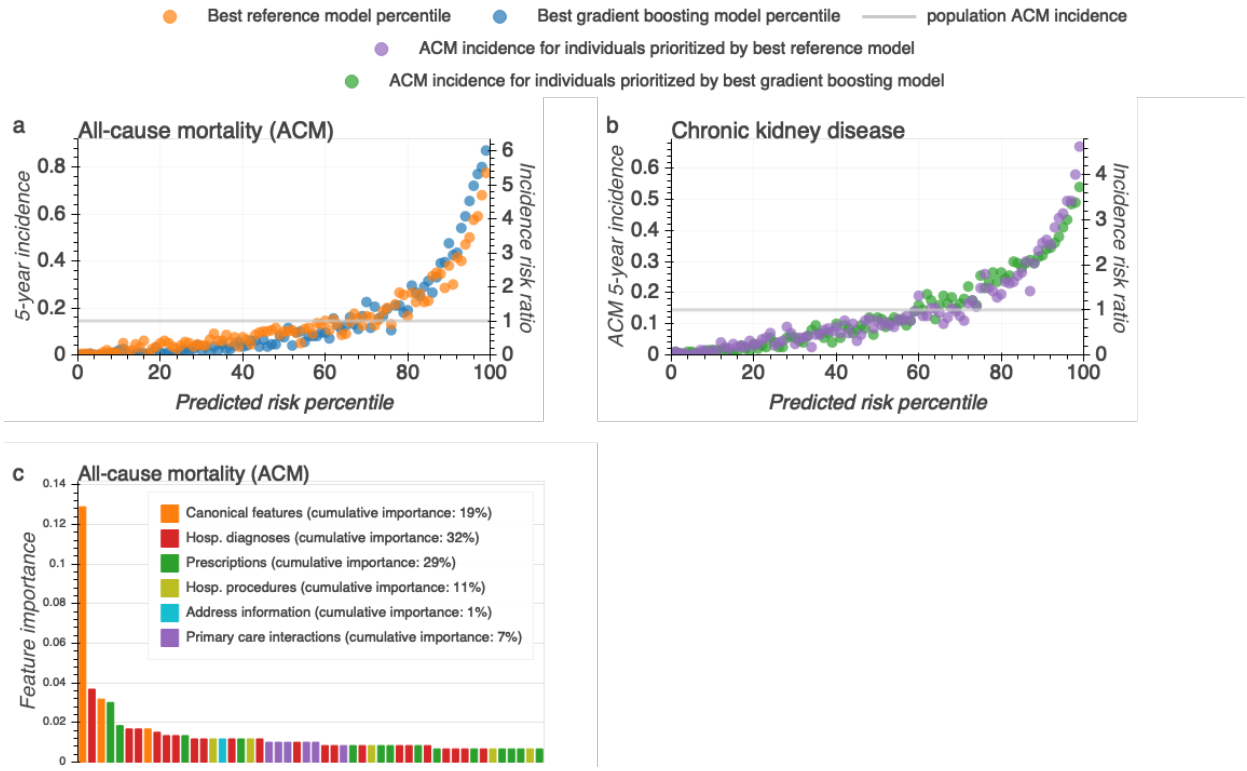
All-cause mortality (I_{ts}: 0.14, I_{no-ts}: 0.17)

	$AUROC_{ts}$	$AUROC_{no-ts}$
Reference, logistic regression	0.80 (0.79 — 0.81)	0.80 (0.79 — 0.81)
Logistic regression	0.83 (0.82 — 0.83)	0.83 (0.82 — 0.83)
Random forest	0.85 (0.85 — 0.86)	0.84 (0.84 — 0.85)
Gradient boosting	0.87 (0.86 — 0.87)	0.86 (0.86 — 0.87)

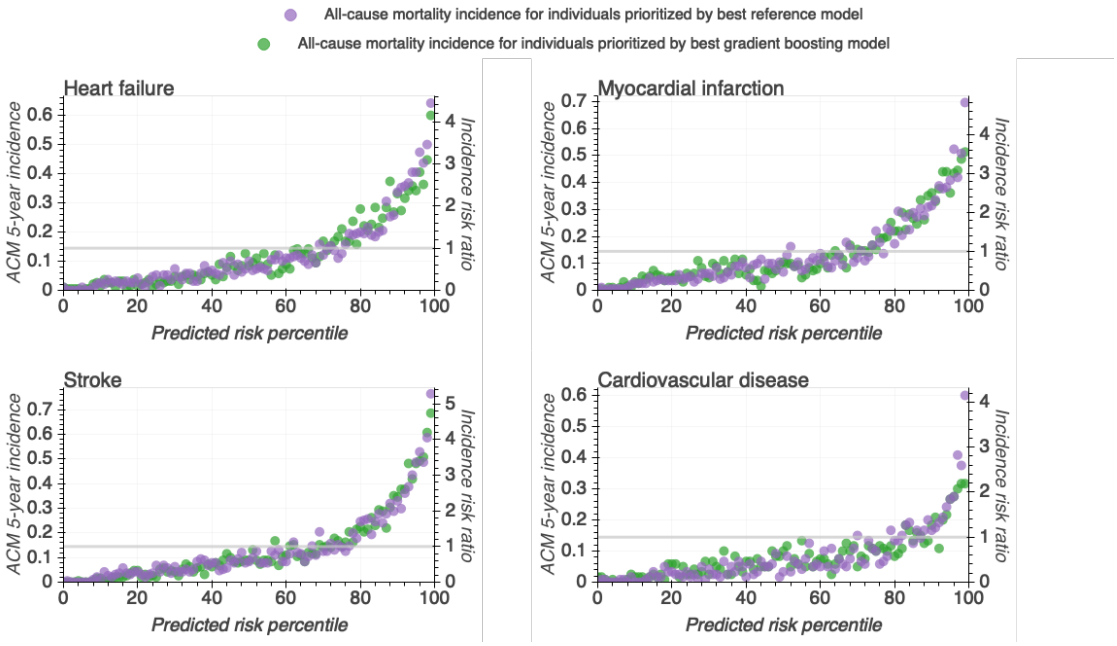
Supplementary Table 9. Comparison of model performance between time-split and non-time-split models. AUROC measure for each prediction model types best parametrization (according to AUROC measure) for all outcomes compared between time-split ($AUROC_{ts}$; training, test and validation sets were split so that the model is trained on individuals diagnosed with type 2 diabetes historically earlier and evaluated on individuals diagnosed later) and non-time-split model ($AUROC_{no-ts}$; training, test and validation sets were split at random without accounting for date of prediction). I_{ts} and I_{no-ts}, outcome incidence within time-split and non-time-split study populations, respectively. AUROC, area under receiver operating characteristic curve which confidence intervals were obtained through bootstrap sampling procedure.

	All-cause mortality (incidence: 0.14)			
	$AUROC$	$\Delta AUROC_{RLR}$	$\Delta AUROC_{LR}$	$\Delta AUROC_{RF}$
Reference, logistic regression (RLR)	0.80 (0.79 — 0.81)			
Logistic regression (LR)	0.83 (0.82 — 0.83)	0.03 (0.02 — 0.03)		
Random forest (RF)	0.85 (0.85 — 0.86)	0.05 (0.05 — 0.06)	0.03 (0.02 — 0.03)	
Gradient boosting (GB)	0.87 (0.86 — 0.87)	0.07 (0.06 — 0.07)	0.04 (0.04 — 0.05)	0.01 (0.01 — 0.02)

Supplementary Table 10. Area under receiver operating characteristic curve for prediction of all-cause mortality by the best reference and register-based models. Compared to the prediction of T2D comorbidities, all models achieved relatively high AUROCs, with all register-based models outperforming the reference model and gradient boosting outperforming the other register-based models. T2D, type 2 diabetes; AUROC, area under receiver operating characteristic curve.



Supplementary Figure 8. Death is a competing risk for diagnosing T2D comorbidities and its effect may be estimated by ML models implicitly. We investigated whether health register data and machine learning model could predict five-year risk of all-cause mortality (ACM) using the same procedure as for T2D comorbidities. (**a**) five-year incidence of ACM for population percentiles ranked by ACM risk predicted by gradient boosting (blue) and reference (orange) models. At the 95th percentile, both models identified individuals ranking multiples above the overall population incidence (ACM risk ratio of 4.53, and 3.46, respectively). (**b**) Incidence of ACM among population percentiles according to predicted risk of chronic kidney disease. Individuals stratified by the register-based model had a similar or lower risk of ACM than those binned into top percentiles by the reference model. (**c**) 50 register features most predictive of ACM according to the gradient boosting models feature importances. Unlike the case of the investigated T2D comorbidities, hospital diagnoses features were the most important followed by prescriptions second and canonical features third.



Supplementary Figure 9. All-cause mortality five-year incidence in population percentiles ranked by predicted type 2 diabetes comorbidity risk by the best gradient boosting (green) and best baseline (violet) models.