04/13 update

- Preliminary results on a small, **balanced** subsample (5000 cases, 5000 controls).
- Training set of 9000 IDs, test set of 1000 IDs.
- Imputed missing variables with median.
- Lab data (blood tests, FOBT) and colonoscopies converted to longitudinal summaries (mean,max,min,...).
- Lab data restricted to time interval from 'indexdate - 3 years' to 'indexdate - 1 year'.
- No ICD code information, no medication information, no smoking status records (smoking status at index is in demographic variables).
- Logistic regression.

Predictors ($p =$ # of predictors)	**Training AUC**	**Test AUC**
Demographic ($p = 10$)	0.814	0.818
Charlson ($p = 18$)	0.705	0.693
Demographic + Charlson ($p = 28$)	0.863	0.862
Labs ($p = 210$)	0.824	0.824
Demographic + Charlson + Labs ($p = 238$)	0.913	0.910

04/20 update

- Preliminary results on a small, **balanced** subsample (5000 cases, 5000 controls).
- Training set of 9000 IDs, test set of 1000 IDs.
- Imputed missing variables with median.
- **Sets of predictors:**
  - Demographic data includes race, age, weight, etc. (**Demographic**).
  - Charlson score inputs plus GERD diagnosis (**Charlson**).
  - Lab data (blood tests, FOBT) and colonoscopy data converted to longitudinal summaries (mean,max,min,...) (**Labs**).
  - Medication (H2R and PPI) converted to longitudinal summaries (mean,max,...) (**Meds**).
- Lab and medication data restricted to time interval from ‘indexdate - 3 years’ to ‘indexdate - 1 year’.
- Logistic regression.

Predictors (p = # of predictors)	**Training AUC**	**Test AUC**
Demographic ($p = 10$)	0.814	0.818
Charlson ($p = 18$)	0.705	0.693
Meds ($p = 10$)	0.604	0.598
Demographic + Charlson + Labs + Meds ($p = 240$)	0.915	0.912

04/27 update

- Baseline logistic regression on entire sample (no blood labs, no medication data).
- Full sample contains $n = 6,649,108$ observations, with $n_{\text{control}} = 6,637,713$ and $n_{\text{case}} = 11,395$.
- Imputed numeric variables with medians, imputed smoking status at random, proportional to non-missing in sample (45% current, 41% former, 14% never).

Predictors (p = # of predictors)	**Training AUC**	**Test AUC**
Demographic ($p = 10$)	0.670	0.675
Charlson ($p = 18$)	0.684	0.705
Demographic + Charlson ($p = 28$)	0.760	0.770

Smoking status missingness.

In the entire sample:

Smoking Status	Current	Former	Never	Missing
Count	1696052	1521806	537727	2893523
Probability	0.26	0.23	0.08	0.44

Among cases:

Smoking Status	Current	Former	Never	Missing
Count	3901	3546	594	3354
Probability	0.34	0.31	0.05	0.29

Among controls:

Smoking Status	Current	Former	Never	Missing
Count	1692151	1518260	537133	2890169
Probability	0.25	0.23	0.08	0.44

05/04 update

- Preliminary results on a balanced **random sample** of 5000 cases and 5000 controls.
- Most missing variables imputed with their median, SmokeStatus imputed at random proportional to non-missing.
- Training on 9000 observations, testing on 1000 observations.
- Baseline logistic regression fit with subsets of predictors, and all predictors.
- Random forest fit with all predictors.

Model/predictors (p = # of predictors)	**Training AUC**	**Test AUC**
Logistic regression	-	-
Demographic ($p = 10$)	0.669	0.676
Charlson ($p = 18$)	0.689	0.659
Meds ($p = 10$)	0.515	0.513
Colonoscopies ($p = 2$)	0.513	0.502
Labs ($p = 200$)	0.671	0.621
All ($p = 240$)	**0.814**	**0.778**
Random forest	-	-
All ($p = 240$)	**0.985**	**0.844**

Random forest variable importance. Most important blood lab measurements (all means of measurements over the 2 year window):

1. Hematocrit value (CBC labs)
2. MCH value (CBC labs)
3. ALT value (LFT labs)
4. Alk. Phos. value (LFT labs)
5. AST value (LFT labs)
6. White blood cells (WBC) value (CBC labs)
7. Glucose value (BMP labs)

Next steps:

- Better approaches to impute missing variables (esp. SmokeStatus).
- Improved non-linear classifiers for subsample.
- Logistic regression baselines for the full sample of 6M observations.

05/11 update

- Baseline logistic regression on full sample (no medication data).
- $n = 6,649,108$ observations, with $n_{\text{control}} = 6,637,713$ and $n_{\text{case}} = 11,395$.
- Most missing variables imputed with their median, SmokeStatus imputed at random proportional to non-missing.
- For lab information, only means of each measurement, no longitudinal information so far.
- 05/27 update: Charlson and Demographic+Charlson updated to exclude Cancer and Metastatic Carcinoma.

Model/predictors ($p =$ # of predictors)	**Training AUC**	**Test AUC**
Demographic ($p = 10$)	0.670	0.675
Charlson ($p = 16$)	0.684	0.705
Demographic + Charlson ($p = 26$)	0.760	0.770
Colonoscopies ($p = 2$)	0.511	0.504
Labs ($p = 34$)	0.604	0.601
Meds ($p = 10$)	0.523	0.512

Next steps:

- Process medication data.
- Approaches to impute missing variables (esp. SmokeStatus).
- Non-linear classifiers for subsample, plots/graphics to interpret predictor effects.

05/18 update

- Medication data processed for full sample, new line (red) added to last week's table of baseline logistic regression AUCs.
- Gradient boosting implemented for the random sample of 5000 cases and 5000 controls.

Model/predictors (p = # of predictors)	**Training AUC**	**Test AUC**
Logistic regression	-	-
All ($p = 240$)	0.814	0.778
Random forest	-	-
All ($p = 240$)	**0.985**	0.844
Gradient boosting	-	-
All ($p = 240$), no interactions	0.900	0.847
All ($p = 240$), 2-way interactions	0.924	0.857
All ($p = 240$), 3-way interactions	0.937	**0.864**

Same gradient boosting results without Charlson score inputs or GERD at index:

Model/predictors (p = # of predictors)	**Training AUC**	**Test AUC**
Gradient boosting	-	-
No Charlson inputs ($p = 222$), no interactions	0.881	0.811
No Charlson inputs ($p = 222$), 2-way interactions	0.898	0.820
No Charlson inputs ($p = 222$), 3-way interactions	0.909	0.817

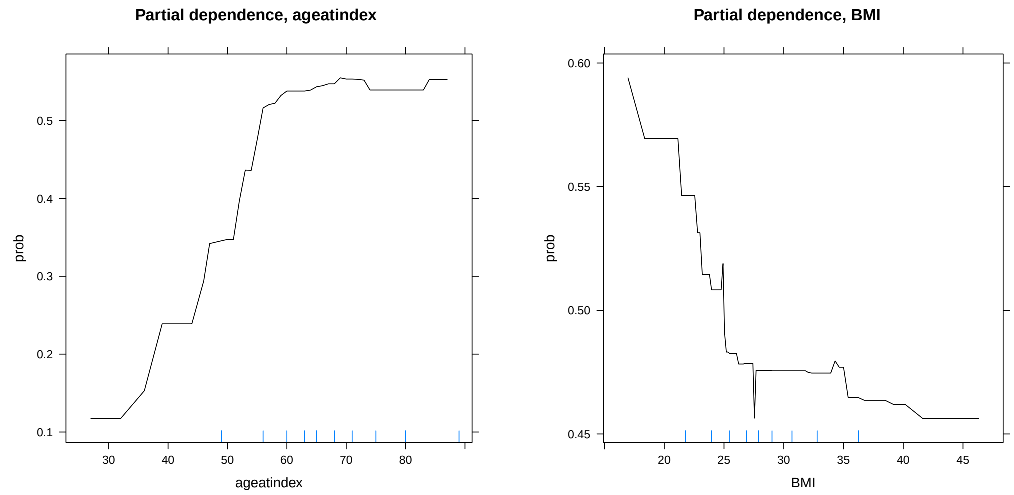
Next steps

- Scaling up gradient boosting, dealing with unbalanced classes in full sample.
- Plots/graphics to interpret black box models.

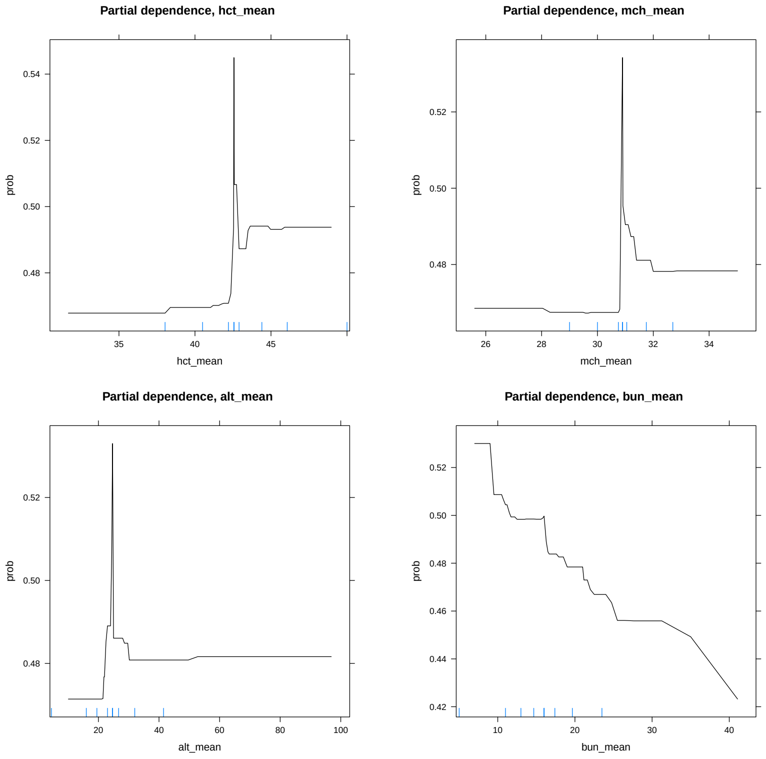
05/25 update

- Results now without Cancer and Metastatic Carcinoma inputs to Charlson score.
- Implemented scalable `xgboost` model, test AUC **0.860**.

Partial dependence plots (from xgboost model). Demographic variables:



Most influential blood lab variables:



Missingness rates for blood lab variables (where 'missing' means zero measurements of that variable in the 2 year window):

Proportion missing	controls	cases
A1c_mean (A1C Labs)	0.51	0.52
bun_mean (BMP Labs)	0.17	0.30
hct_mean (CBC Labs)	0.20	0.50
CRP_mean (CRP Labs)	0.95	0.94
alkphos_mean (LFT Labs)	0.23	0.47
chol_mean (Lipid Labs)	0.19	0.32

08/20: now with the new data, 4 year window from index-1 to index-5

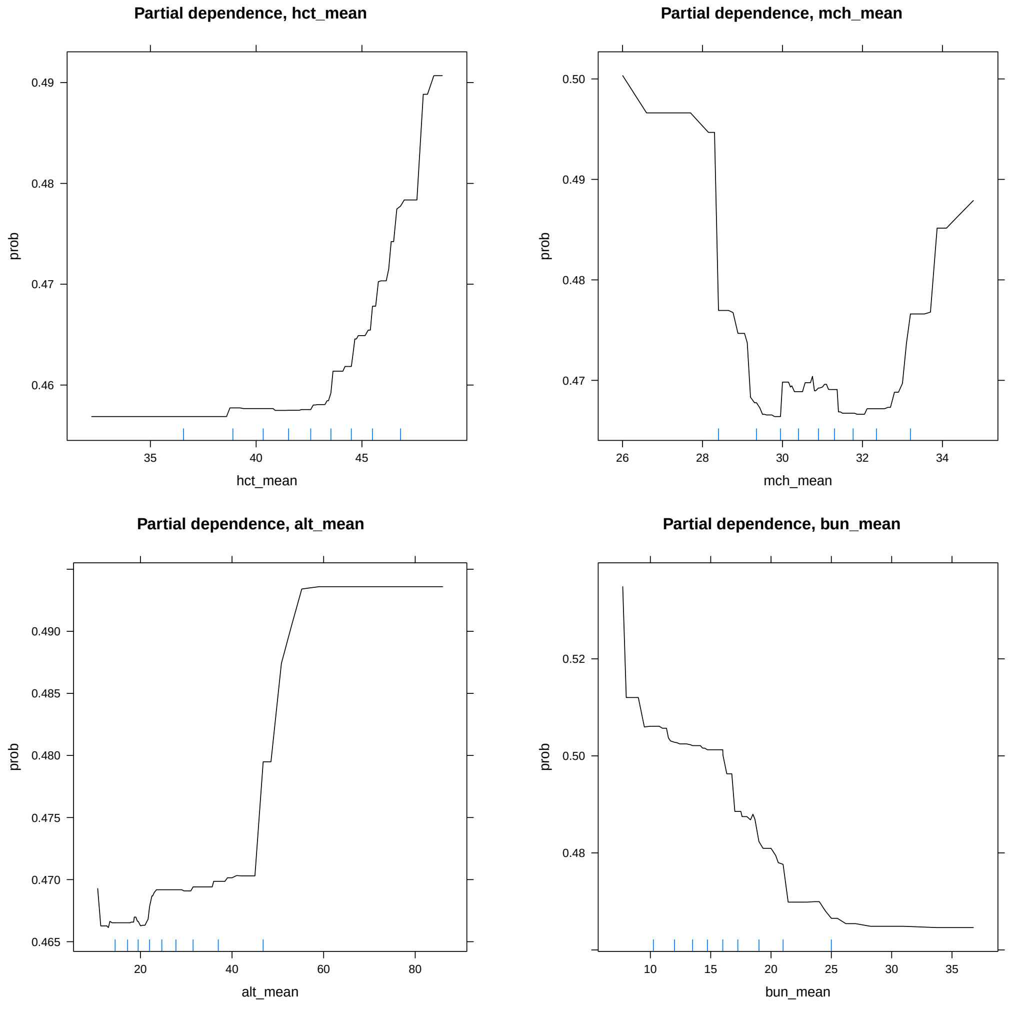
Proportion missing	controls	cases
A1c_mean (A1C Labs)	0.43	0.47
bun_mean (BMP Labs)	0.11	0.26
hct_mean (CBC Labs)	0.12	0.46
CRP_mean (CRP Labs)	0.93	0.91
alkphos_mean (LFT Labs)	0.15	0.42
chol_mean (Lipid Labs)	0.12	0.29

uniformly fewer missing, but rates are not cut in half, moreover heterogeneity of missingness between cases and controls is not fixed.

06/08 update

- Re-coded BMI/weight measurements?
- Re-run xgboost on balanced subsample with `NA`s, test AUC **0.880**, but it is using missing values to identify cases.
- Source of missingness? More detailed breakdown for LFT Labs.

Updated partial dependence plots for blood lab variables. Using new xgboost model on subsample.



Detailed breakdown of missingness for LFT labs. (Prediction window is second and third years before index)

Mean # of labs	controls	cases
First year before index	1.87	2.42
Second year before index	1.47	1.52
Third year before index	1.42	1.34

Detailed breakdown for the prediction window (index minus 3 years to index minus 1 year):

Proportion	controls	cases
At least 1 lab	0.83	0.69
At least 2 labs	0.67	0.59
At least 3 labs	0.45	0.44
At least 4 labs	0.30	0.31
At least 5 labs	0.18	0.21

Next Steps:

- Imputation with xgboost
- Implement xgboost for entire sample

06/22 update

- Set up code on GitLab (waljee-zhu-ml-projects/hosea-project).
- Received updated sample with recoded BMIs. BMIs are more likely to be missing for cases (14%) than controls (8%).
- Continuing to code imputation following Deng and Lumley (2021).

BMI comparison on the original sample data:

Original BMI	< 20	$\in (20, 25]$	$\in (25, 30]$	$\in (30, 35]$	$\in (35, 40]$	> 40
$\mathbb{P}(Control \vert BMI)$	0.9960	0.9978	0.9985	0.9985	0.9986	0.9986
$\mathbb{P}(Case \vert BMI)$	0.0040	0.0022	0.0015	0.0015	0.0014	0.0014

With the re-coded sample data:

New BMI	< 20	$\in (20, 25]$	$\in (25, 30]$	$\in (30, 35]$	$\in (35, 40]$	> 40
$\mathbb{P}(Control \vert BMI)$	0.9983	0.9985	0.9985	0.9984	0.9981	0.9979
$\mathbb{P}(Case \vert BMI)$	0.0017	0.0015	0.0015	0.0016	0.0019	0.0021

06/29 update

- Now using updated data (new BMIs, Charlson scores).
- For subsample, comparison of baseline logistic regression and xgboost models for different imputation approaches:

  1. **No imputation**: leave NAs in the data, learn a classification for subjects with missing data (only compatible with xgboost).
  2. **Median imputation**: impute all variables with median/most common class.
  3. **Regression imputation**: impute by (linear) regression of each predictor variable on the others (similar to MICE).
  4. **Random sample imputation**: impute each predictor by sampling at random from the non-missing entries.

AUC results for xgboost/logistic regression for different imputation approaches. Results still on balanced subsample.

Imputation method/model	**Training AUC**	**Test AUC**	**Test AUC (complete records)**
No imputation	-	-	-
xgboost	0.977	0.942	0.643
Median imputation	-	-	-
logistic regression	0.834	0.810	0.585
xgboost	0.970	0.857	0.623
Regression imputation	-	-	-
logistic regression	0.805	0.760	0.557
xgboost	0.948	0.815	0.705
Random sample imputation	-	-	-
logistic regression	0.724	0.689	0.724
xgboost	0.919	0.729	**0.745**

Regression imputation still has ‘regression to mean’ effect for imputed values, imputed values have smaller variance than the true values (with observation error). Maybe try a version that imputes a rank then resamples from observed values.

07/06 update

- Source of missingness in the data? About 85% of cases missing Charlson score inputs (compared to about 47% of controls).
- Missingness in test set/use case?
- Updated (in red) last weeks results with a test set of 1000 complete records (226 cases, 774 controls).
  - Poor generalization to complete cases for no imputation, median imputation implies that those models are fitting to the missingness, patterns won't continue to hold with fully observed data.
  - Regression imputation still has 'regression to mean' effect for imputed values, imputed values have smaller variance than the observed values (observation error).
  - Good generalization of random sample imputation implies that there is no bias introduced from training on data with missingness.

07/13 update

- Should we evaluate the model on complete records or missing/imputed records?
- Recall: previous results with an additional test set of 1000 complete records (226 cases, 774 controls).
  - New comparison for **multiple** random sample imputation: imputes by sampling from non-missing entries several times (reps) for each missing value, training on the multiple imputed records.
- Memory issues fitting xgboost on the full data, implementing "batched" training.

AUC's for xgboost/logistic regression for different imputation approaches. Results still on balanced subsample.

Imputation method/ prediction model	**Training AUC**	**Test AUC (imputed records)**	**Test AUC (complete records)**
No imputation	-	-	-
xgboost	0.977	0.942	0.643
Median imputation	-	-	-
logistic regression	0.834	0.810	0.585
xgboost	0.970	0.857	0.623
Regression imputation	-	-	-
logistic regression	0.805	0.760	0.557
xgboost	0.948	0.815	0.705
Random sample imputation	-	-	-
logistic regression	0.724	0.689	0.724
xgboost	0.919	0.729	0.745
Multiple rand. samp.	-	-	-
xgboost, 10 reps	0.909	0.742	0.781
xgboost, 20 reps	0.939	0.765	0.820
xgboost, 30 reps	0.948	0.768	0.781

Final two columns suggest two different evaluation metrics, ensuring the model performs well on **both** (A) new patients with imputed data and (B) new patients with fully observed blood labs, etc.

07/20 update

- Continuing to test/tune imputation approaches.
- Notes on decision curve analysis.

Imputation method/ prediction model	**Training AUC**	**Test AUC (imputed records)**	**Test AUC (complete records)**
Separate class	-	-	-
xgboost	0.977	0.942	0.643
Median	-	-	-
logistic regression	0.834	0.810	0.585
xgboost	0.970	0.857	0.623
Regression	-	-	-
logistic regression	0.805	0.760	0.557
xgboost	0.948	0.815	0.705
Regression v2	-	-	-
logistic regression	0.769	0.706	0.564
xgboost	0.928	0.722	0.764
Random sample	-	-	-
logistic regression	0.724	0.689	0.724
xgboost	0.919	0.729	0.756
Multiple rand. samp.	-	-	-
xgboost, 10 imputes × 50 trees	0.909	0.742	0.781
xgboost, 20 imputes × 25 trees	0.906	0.750	0.778
xgboost, 30 imputes × 20 trees	0.909	0.765	0.788
xgboost, 100 imputes × 5 trees	0.898	0.762	0.806

07/27 update

- Continuing to tweak regression imputation approaches.
- Comparing parameters/number of imputations needed for multiple sample imputation.
- Notes on decision curve analysis.

Next steps:

- Re-process new data when available

Imputation method/ prediction model	**Training AUC**	**Test AUC** **(imputed records)**	**Test AUC** **(complete records)**
Separate class	-	-	-
xgboost	0.977	0.942	0.643
Median	-	-	-
logistic regression	0.834	0.810	0.585
xgboost	0.970	0.857	0.623
Regression	-	-	-
logistic regression	0.759	0.704	0.657
xgboost	0.902	0.742	0.757
Single rand. samp.	-	-	-
logistic regression	0.724	0.689	0.724
xgboost	0.919	0.729	0.756
Multiple rand. samp.	-	-	-
xgboost, 10 imputes	0.909	0.742	0.781
xgboost, 20 imputes	0.906	0.750	0.778
xgboost, 30 imputes	0.909	0.765	0.788
xgboost, 100 imputes	0.898	0.762	0.806

08/03 update

- Received new data, loading/processing files
- Still issues with missing Charlson scores (0's vs NAs), relationship between CaseControl indicator and number of visits.

08/17 update

- Processed longitudinal summaries for BMP labs. Missingness rates down but still different for cases and controls. Continuing to process new blood lab data.
- Incidence rates for some example Charlson inputs: Peptic Ulcer Disease, Renal Disease, GERD. Full tables for all inputs are on the next page.

Variable **(ignoring NA's)**	Among cases	Among controls
pud	6.8% (120/1762)	3.8% (142821/3803451)
RD	11.8% (208/1762)	12.1% (460302/3803451)
GERD	-	-

Variable **(impute NA's as 0's)**	Among cases	Among controls
pud	1.1% (120/11395)	2.2% (142821/6637713)
RD	1.8% (208/11395)	6.9% (460302/6637713)
GERD	17.9% (2044/11395)	15.7% (1039206/6637713)

Cross-classified by number of BMP lab results (0, 1 or 2+):

Peptic Ulcer Disease, **controls**:

Number of BMP labs	0	1	NA
0	29.3%	0.9%	69.8%
1	32.2%	0.9%	66.8%
2+	61.5%	2.5%	36.0%

Peptic Ulcer Disease, **cases**:

Number of BMP labs	0	1	NA
0	8.6%	0.7%	90.8%
1	10.7%	0.4%	88.8%
2+	17.0%	1.3%	81.7%

Full tables for all Charlson indicators (red indicates these variables have been dropped from past models):

Variable **(ignoring NA's)**	Among cases	Among controls
CANCER	30.5% (538/1762)	18.3% (695558/3803451)
CHF	12.3% (217/1762)	11.8% (450090/3803451)
CTD	2.9% (51/1762)	3.0% (115492/3803451)
DEM	1.4% (24/1762)	2.3% (85704/3803451)
DIAB_C	15.5% (273/1762)	13.8% (525226/3803451)
HIV	0.3% (6/1762)	0.8% (30507/3803451)
MET_CAR	6.6% (117/1762)	1.3% (47696/3803451)
MLD	9.1% (160/1762)	8.0% (305462/3803451)
MSLD	0.7% (13/1762)	0.8% (29495/3803451)
PARA	1.9% (33/1762)	1.9% (72051/3803451)
RD	11.8% (208/1762)	12.1% (460302/3803451)
cd	16.3% (287/1762)	15.3% (582328/3803451)
copd	43.1% (759/1762)	35.9% (1365577/3803451)
diab_nc	44.6% (786/1762)	44.8% (1702629/3803451)
mi	9.1% (161/1762)	7.0% (264731/3803451)
pud	6.8% (120/1762)	3.8% (142821/3803451)
pvd	20.1% (354/1762)	16.0% (609425/3803451)
GERD	-	-

Variable **(impute NA's as 0's)**	Among cases	Among controls
CANCER	4.7% (538/11395)	10.5% (69558/6637713)
CHF	1.9% (217/11395)	6.8% (450090/6637713)
CTD	0.4% (51/11395)	1.7% (115492/6637713)
DEM	0.2% (24/11395)	1.3% (85704/6637713)
DIAB_C	2.4% (273/11395)	7.9% (525226/6637713)
HIV	0.1% (6/11395)	0.5% (30507/6637713)
MET_CAR	1.0% (117/11395)	0.7% (47696/6637713)
MLD	1.4% (160/11395)	4.6% (305462/6637713)
MSLD	0.1% (13/11395)	0.4% (29459/6637713)
PARA	0.3% (33/11395)	1.1% (72051/6637713)
RD	1.8% (208/11395)	6.9% (460302/6637713)
cd	2.5% (287/11395)	8.8% (582328/6637713)
copd	6.7% (759/11395)	20.6% (1365577/6637713)
diab_nc	6.9% (786/11395)	25.6% (1702629/6637713)
mi	1.4% (161/11365)	4.0% (264731/6637713)
pud	1.1% (120/11395)	2.2% (142821/6637713)
pvd	3.1% (354/11395)	9.2% (609425/6637713)
GERD	17.9% (2044/11395)	15.7% (1039206/6637713)

08/31 update

- Re-fit xgboost models on new subsampled data (compare to 07/27 results). $n_{\text{train}} = 9000$, $n_{\text{test}} = 1000$, $n_{\text{complete.test}} = 1000$.
- Compare (xgboost) model performance with different groups of variables included.
- Ongoing: a proxy for number of visits to better impute Charlson ICD codes?

Comparing different imputation approaches and prediction models:

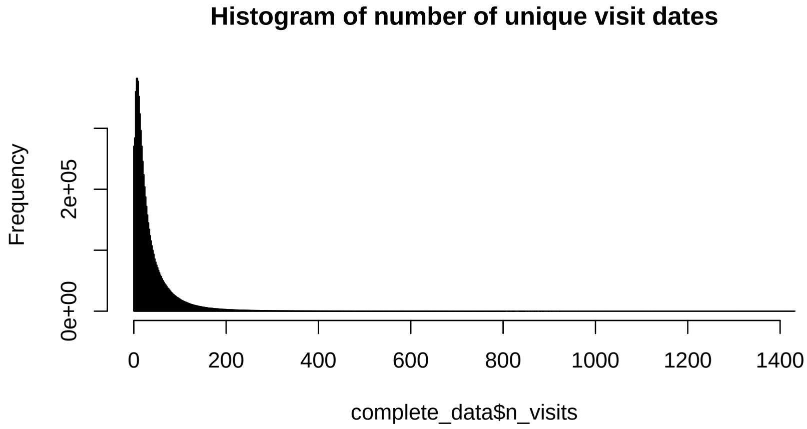
Imputation method/ prediction model	**Training AUC**	**Test AUC** **(imputed records)**	**Test AUC** **(complete records)**
Separate class	-	-	-
xgboost	0.985	0.962	0.582
Median	-	-	-
logistic regression	0.853	0.846	0.583
xgboost	0.963	0.911	0.618
Regression	-	-	-
logistic regression	0.772	0.726	0.651
xgboost	0.911	0.750	0.798
Single rand. samp.	-	-	-
logistic regression	0.739	0.695	0.703
xgboost	0.916	0.780	0.833
Multiple rand. samp.	-	-	-
xgboost, 10 imputes	0.942	0.824	0.885
xgboost, 20 imputes	0.935	0.820	0.872
xgboost, 30 imputes	0.943	0.810	0.879
xgboost, 100 imputes	0.931	0.824	0.891

Comparing different included variables (imputing with single random sampling, fit with xgboost):

Variables included	**Training AUC**	**Test AUC** **(imputed records)**	**Test AUC** **(complete records)**
Demographic ($p = 11$)	0.743	0.700	0.663
Charlson + GERD ($p = 16$)	0.600	0.542	0.530
Medications ($p = 10$)	0.594	0.501	0.539
Labs ($p = 202$)	0.903	0.687	0.829

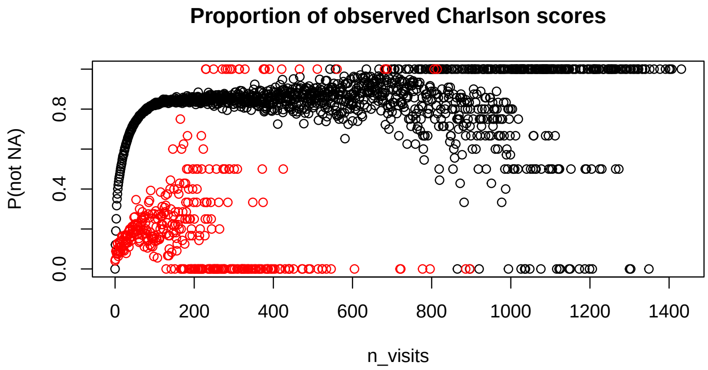
09/21 update

Overall missingness of Charlson score inputs. A histogram of the total number of visits in the 4-year prediction window:

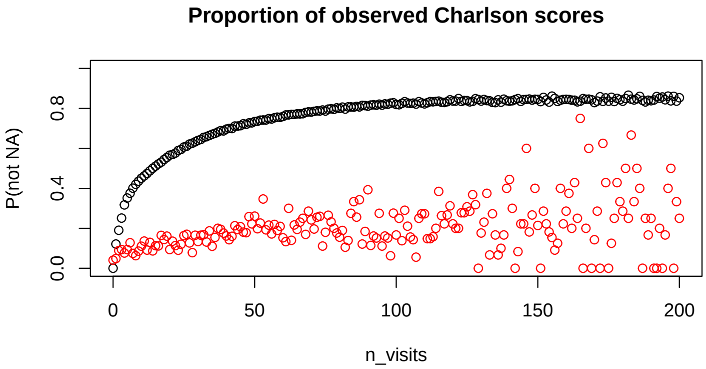


The median control has 22 visits, while the median case has 33 visits.

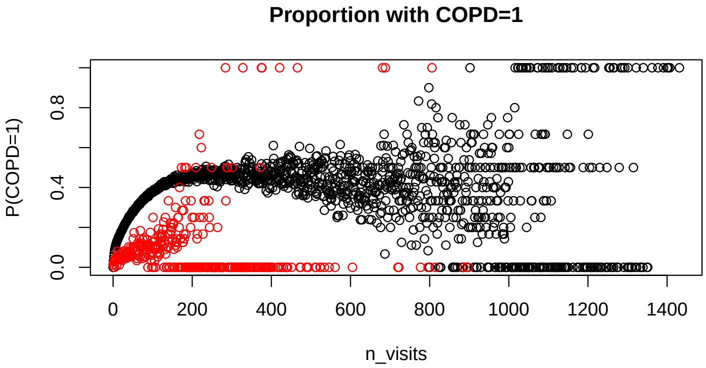
Proportion of observed Charlson scores plotted against number of visits, separating controls (black) and cases (red):



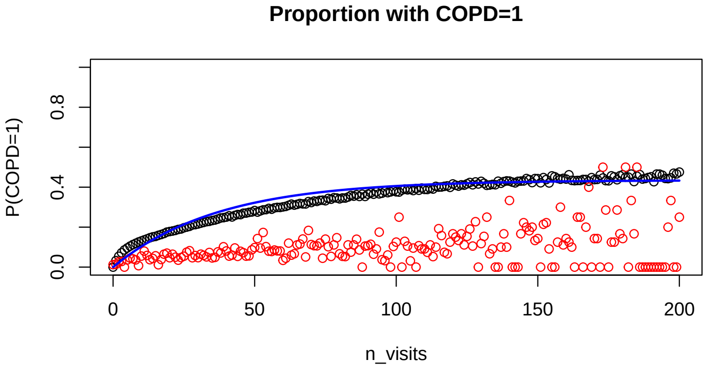
The same plot restricted to ≤ 200 visits.



Example: missingness of COPD. Proportion of patients coded COPD=1, plotted against number of visits, separating controls (black) and cases (red):



The same plot restricted to ≤ 200 visits. The blue line is a model-based estimate of $\mathbb{P}(\text{COPD} = 1|\text{n\_visits})$ using pooled case and control data.

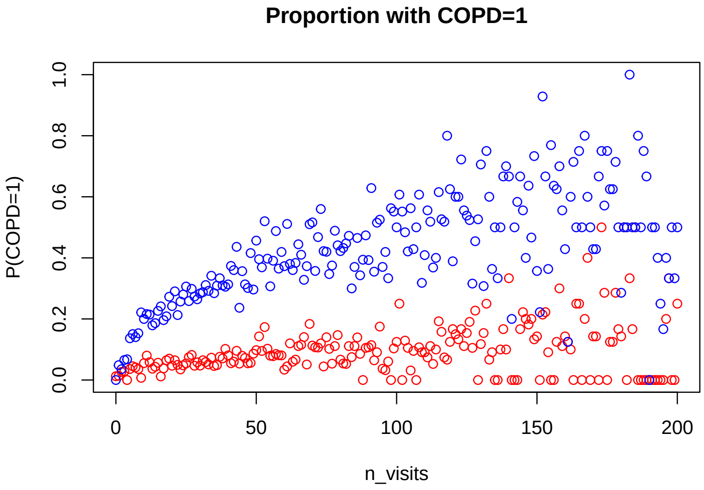


For cases only, created a new COPD indicator based on the ‘alldxscx’ table. For ICD9, 1 means you have a code ‘49x’, for ICD10, 1 means you have a code starting with ’J44’.

Cross-classification of old and new indicator for total of 11,395 cases (overall proportions in parentheses).

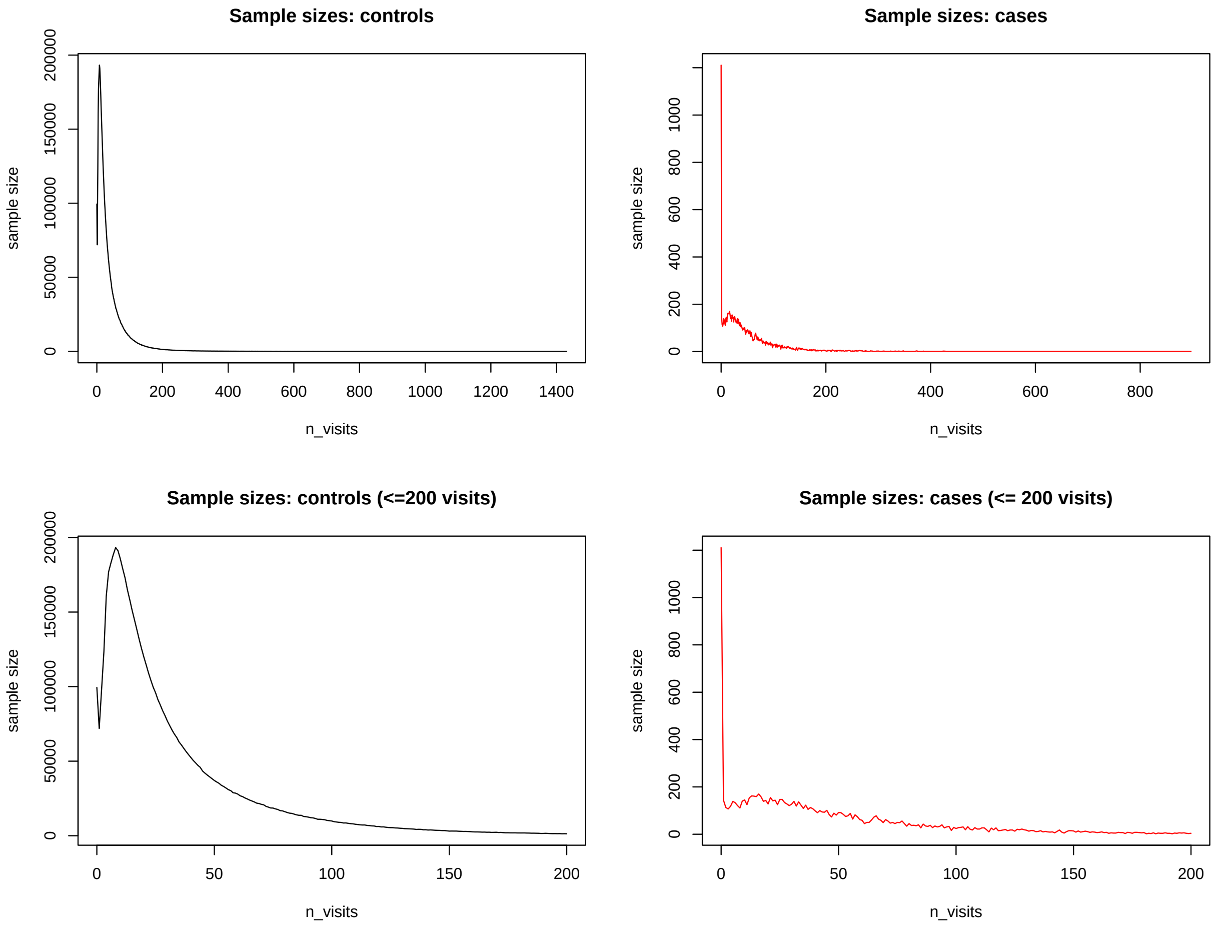
	New COPD=1	New COPD=0/NA
Old COPD=1	7845 (0.688)	2791 (0.245)
New COPD=0/NA	160 (0.014)	599 (0.053)

Proportion of patients with COPD=1 plotted against number of visits, restricted to ≤ 200 visits, with the old indicator in red and the new indicator in blue.



Next steps: similarly code a new indicator for controls, see if it changes results. Generalize to other Charlson inputs (or other entirely new ICD codes), and look at ways to impute by incorporating n_visits.

Sample sizes for controls and cases for calculating the proportions in the above plots.


Sample sizes: controls
sample size
n_visits
Sample sizes: cases
sample size
n_visits
Sample sizes: controls (<=200 visits)
sample size
n_visits
Sample sizes: cases (<= 200 visits)
sample size
n_visits