

Supplementary Material for Validation of Tools for Predicting Incident Adenocarcinoma of the Esophagus or Esophagogastric Junction

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Supplementary Table 1. Mutually Adjusted Effects of MHC Questions on Odds of Weekly GERD Symptoms as Defined by MBERET Questions from Stepwise Forward Logistic Regression

Step	MHC Question	Odds Ratio (95% Confidence Interval)
1	"In the past 6 months, have you often had trouble with digestion, or heartburn (burning from abdomen into the throat)?"	3.47 (1.66, 7.23)
2	"Before one year ago had you often had heartburn, indigestion or stomach pain?"	3.92 (1.96, 7.85)
3	"In the past 6 months, have you often had heartburn, indigestion or pain in stomach, bad pain in your abdomen?"	2.84 (1.36, 6.00)
4	"That was worse bending over or lying down?" (follow-up to question in Step 1 above)	2.52 (1.16, 5.51)
5	"In the past year or two has a doctor said you had a hiatal (diaphragmatic) hernia?"	9.40 (1.49, 59.3)

Supplementary Table 2. Mutually Adjusted Effects of MHC Questions on Pack-Years of Cigarette Smoking among Former and Current Smokers from Linear Regression

MHC Question	Estimate (Standard Error)
Intercept	70.4 (23.1)
"Have you smoked altogether less than 10 years?" (reference: "Or for more than 20 years?")	-27.2 (8.0)
"For 10 to 20 years?" (reference: "Or for more than 20 years?")	-15.6 (6.9)
"In the past year... or less than 1 pack a day?" (reference: "did you smoke 2 packs a day or more?")	-40.2 (17.0)
"In the past year... or 1 to 2 packs a day?" (reference: "did you smoke 2 packs a day or more?")	-14.6 (17.0)
"Do you usually inhale when you smoke?"	4.6 (16.6)

Supplementary Table 3. Mutually Adjusted Effects of MHC Anthropometrics on Waist-to-Hip Circumference Ratio from Linear Regression

MHC Anthropometric	Estimate (Standard Error)
Intercept	0.8732 (0.0421)
Height (inches)	0.0040 (0.0005)
Weight (pounds)	0.0002 (0.0001)
Waist anterior-posterior diameter (cm)	0.0116 (0.0006)
Thigh anterior-posterior diameter (cm)	-0.0042 (0.0007)
Pelvic trochanteric transverse diameter (cm)	-0.0131 (0.0007)

Supplementary Table 4. Area Under the Receiver Operating Characteristic Curve among Patients with GERD

Tool	AUROC for EAC	AUROC for EGJAC
HUNT	0.639 ^a	0.628
Kunzmann	0.716	0.662 ^c
M-BERET	0.659 ^b	0.648
Thrift	0.649 ^a	0.674 ^c

AUROC: area under the receiver operating characteristic curve

EAC: esophageal adenocarcinoma

EGJAC: esophagogastric junction adenocarcinoma

HUNT: Nord-Trøndelag Health Study

M-BERET: Michigan Barrett's Esophagus pREdiction Tool

a $p < 0.001$ vs. Kunzmann

b $p = 0.01$ vs. Kunzmann

c $p = 0.06$ vs. HUNT

Supplementary Table 5. Unadjusted Cox Proportional Hazard Ratios of Individual Risk Factors for Incident Esophageal Adenocarcinoma and Esophagogastric Junction Adenocarcinoma

Risk Factor	Category	HR (95% CI) for EAC	HR (95% CI) for EGJAC
Age	Per 10 years	0.579 (0.503, 0.667)	0.707 (0.610, 0.820)
	< 50 years	(reference)	(reference)
	50-59 years	0.459 (0.297, 0.709)	0.517 (0.331, 0.808)
	60-69 years	0.165 (0.0678, 0.403)	0.629 (0.375, 1.05)
	≥ 70 years	0.0912 (0.0133, 0.644)	0.0918 (0.0132, 0.663)
Sex	Female	(reference)	(reference)
	Male	7.61 (4.94, 11.7)	3.68 (2.57, 5.32)
Waist-to-hip Circumference Ratio	Per 0.1 increment*	1.62 (1.10, 2.36)	1.43 (1.13, 1.82)
Body mass index	< 25 kg/m ²	(reference)	(reference)
	≥ 25, < 30 kg/m ²	1.81 (1.23, 2.66)	1.22 (0.855, 1.74)
	≥ 30 kg/m ²	1.96 (1.15, 3.32)	1.28 (0.691, 2.37)
Cigarette smoking	Pack-years (per increment of 10)*	1.15 (1.02, 1.30)	1.15 (1.04, 1.26)
	Never Smoker*	(reference)	(reference)
	Ever Smoker*	2.56 (1.77, 3.69)	2.29 (1.52, 3.44)
	Former Smoker*	2.33 (1.49, 3.62)	1.63 (0.972, 2.72)
	Current Smoker	2.68 (1.80, 3.97)	2.65 (0.448, 1.98)
Education	College graduate or post-graduate	(reference)	(reference)
	Technical/business college	1.04 (0.499, 2.18)	0.943 (0.448, 1.98)
	Elementary school, high school, or some college without degree	1.51 (1.09, 2.08)	0.944 (0.654, 1.36)

EAC: esophageal adenocarcinoma, EGJAC: esophagogastric junction adenocarcinoma

* Imputed variable

Supplementary Table 6. Published Effect Estimates of Individual Risk Factors from the Development of the Prediction Tools

Risk Factor	HUNT HR for EAC	Kunzmann OR for EAC	M-BERET OR for BE	Thrift OR for BE
Age	< 50: (reference) 50-59: 2.1 60-69: 3.2 ≥ 70: 3.1	50-55: (reference) 55-60: 2.0 60-65: 2.8 ≥ 65: 4.0	Per 10 years: 1.5	Per 10 years: 1.3
Sex	Female: (reference) Male: 1.9	Female: (reference) Male: 5.2	Female: (reference) Male: 2.6	Female: (reference) Male: 2.2
GERD	No: (reference) Yes: 3.7	No: (reference) Yes: 1.9	No: (reference) Yes: 2.3	Not applicable
Waist-to-hip Circumference Ratio	Not applicable	Not applicable	Per 0.1 increment: 1.4	Not applicable
Body mass index (kg/m ²)	< 30: (reference) ≥ 30: 1.8	< 25: (reference) 25-30: 1.5 30-35: 1.9 ≥ 35: 3.0	Not applicable	< 25: (reference) 25-30: 1.0 ≥ 30: 1.4
Cigarette smoking	Never: (reference) Ever: 2.1	Never: (reference) Former: 2.0 Current: 3.8	per 10 pack-years: 1.1	Never: (reference) Former: 1.4 Current: 1.9
Education	Not applicable	Not applicable	Not applicable	University: (reference) Technical college/diploma: 1.3 School only: 2.1

BE: Barrett's esophagus, EAC: esophageal adenocarcinoma, GERD: gastroesophageal reflux disease, HR: hazard ratio, HUNT: Nord-Trøndelag Health Study, M-BERET: Michigan Barrett's Esophagus pREdiction Tool, OR: odds ratio

Supplementary Figures

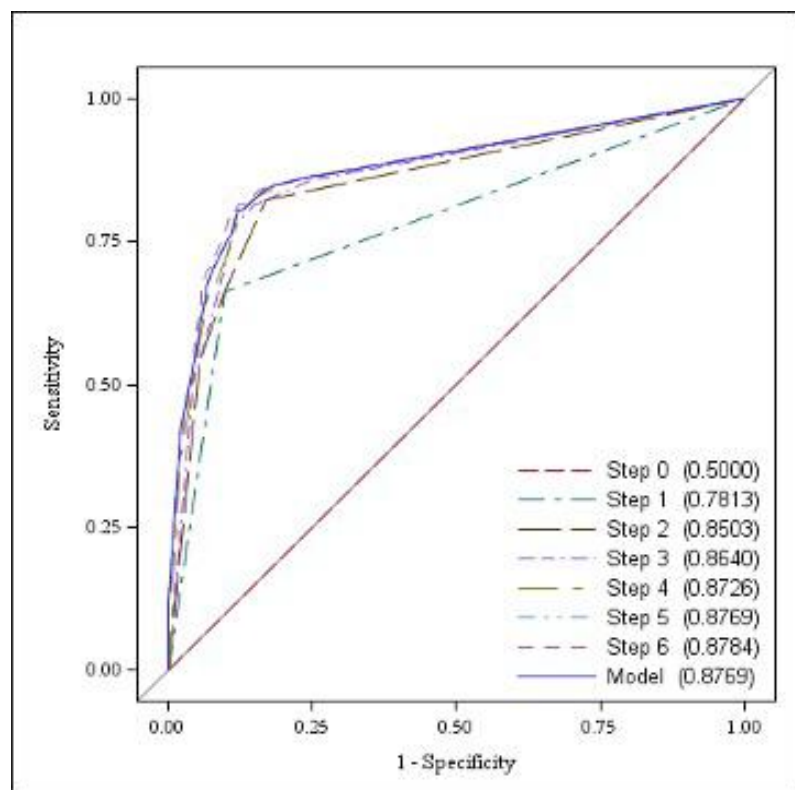
Supplementary Figure 1. Schematic Diagram of Datasets for Imputation.

Missing data among the historic Kaiser Permanente Northern California Multiphase Health Checkup (KPNC MHC) subjects was imputed using data from modern cohorts (data available represented by X). The KPNC MHC enrolled patients from 1964 to 1973, and did not have questions specific for weekly GERD symptoms, queried only current smoking and parameterized it as categorical values, and did not measure waist and hip circumferences. Patients and their chaperones enrolled in 2014 at a University of Michigan endoscopy waiting room answered the historic MHC questions potentially relevant to GERD symptoms and tobacco use, as well as the Michigan Barrett's Esophagus pREdiction Tool (MBERET) GERD and tobacco questions. Patients enrolled from 2015 to 2018 at UM or the Ann Arbor Veterans Affairs Medical Center at the time of their first upper endoscopy for the Validation and Extension of the MBERET Study answered MBERET GERD and tobacco questions and had waist and hip circumferences measured in addition to anthropometrics using the MHC historic protocols.

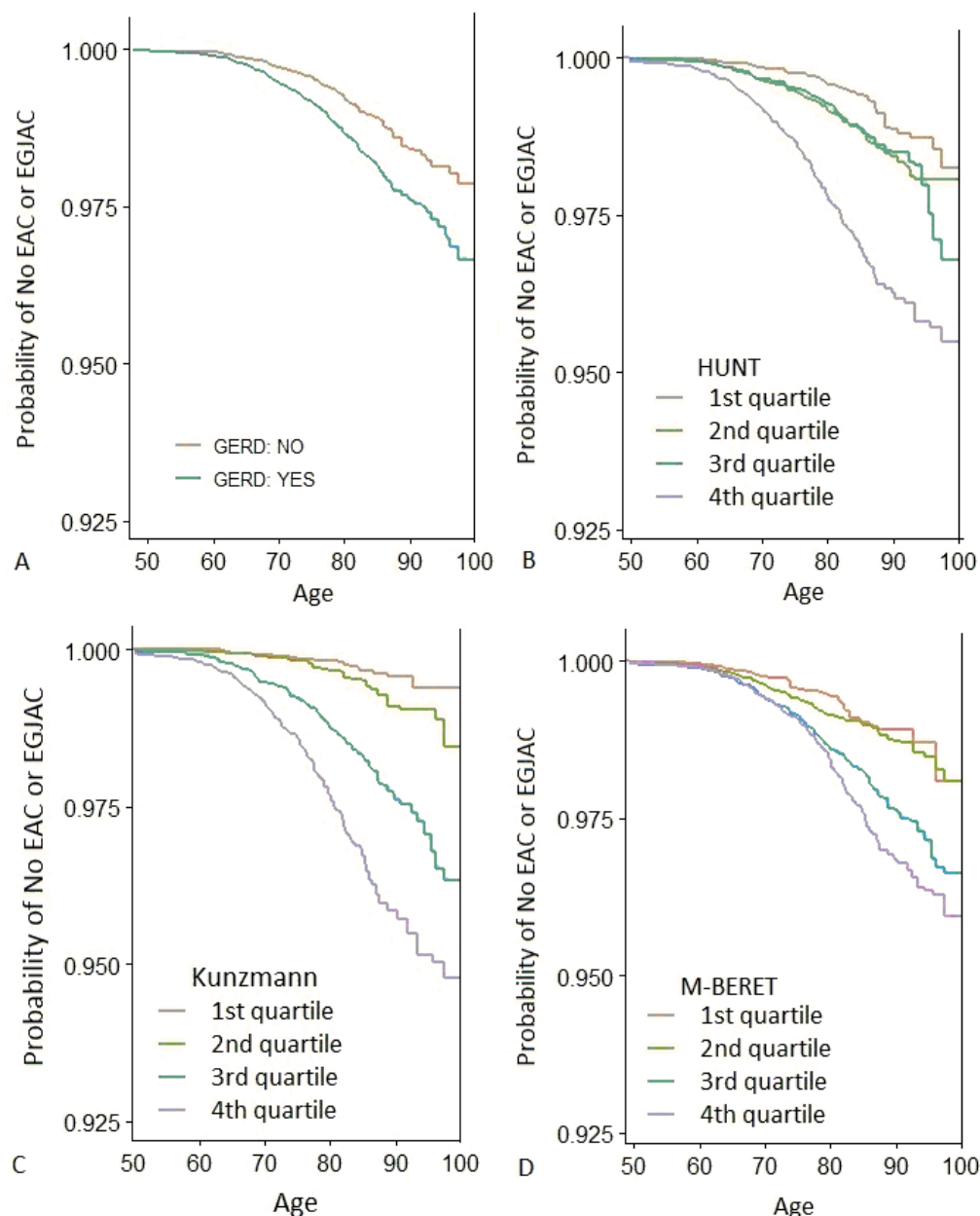
Dataset	Years of Enrollment	MHC symptom questions	MHC tobacco questions	MHC anthropometrics	MBERET GERD questions	MBERET pack-years cigarette & former smoking	Waist-to-hip circumference ratio
KPNC MHC	1964-1973	X	X	X			
UM Waiting Room	2014	X	X		X	X	
MBERET Validation	2015-2018			X	X	X	X

Supplementary Figure 2. Receiver Operating Characteristic (ROC) Curves for Weekly GERD Symptoms.

Steps are MHC questions outlined in Supplementary Table 1. Step 6 (question removed from model) was “In the past year, have you often had trouble swallowing liquids?” Area under the ROC curves are in parentheses.



Supplementary Figure 3. Kaplan-Meier Survival Curves for Time to Either Esophageal Adenocarcinoma or Esophagogastric Junction Adenocarcinoma.



Panel A: GERD symptoms, B: HUNT, C: Kunzmann, and D: M-BERET. X-axis is age at time of cancer diagnosis or censoring due to death or loss to follow-up. GERD is categorized as yes/no, and the other predictors are categorized into quartiles. Survival proportion has been inflated to reflect the total number of controls from which the 20% random sample were drawn.

Please answer each question to the best of your ability.

1. What is your age? _____ years
2. What is your sex? ☐ Male ☐ Female
3. Are you having a procedure today, or chaperoning someone else who is?
 - ☐ I am having an upper endoscopy (EGD)
 - ☐ I am having a colonoscopy
 - ☐ I am having a different procedure
 - ☐ I am not having any procedure today

Heartburn is a burning sensation in the chest, behind the breastbone, that rises up toward the neck or mouth.

Regurgitation is the *effortless* movement of stomach contents up into the chest, throat, or mouth.

4. If you *do not* take any of your prescription or over-the-counter medications, how often would you have *either* heartburn or regurgitation in a *typical* week?

please write down the number of days per week: _____ (0-7)

or

if not every week, write the number of days per month: _____ (0-31)

5. If you *do not* take any of your prescription or over-the-counter medications, how would rate the intensity of your heartburn and regurgitation?
 - ☐ None
 - ☐ Very mild
 - ☐ Mild
 - ☐ Moderate
 - ☐ Moderately Severe
 - ☐ Severe

Please fill in the table if you are **currently** taking any of the following medications:

<u>Medication</u> (brand name)	<u>Milligrams</u> <u>(mg)</u>	<u>Number of pills</u> <u>each time</u>	<u>Frequency of Use</u> (number of times each week)
cimetidine (Tagamet)			
dexlansoprazole (Dexilant)			
esomeprazole (Nexium)			
famotidine (Pepcid)			
lansoprazole (Prevacid)			
nizatidine (Axid)			
omeprazole (Prilosec, Zegerid)			
pantoprazole (Protonix)			
rabeprazole (Aciphex)			
ranitidine (Zantac)			

6. Have you taken any of those medications in the last 5 years?

☐ YES ☐ NO

7. Treatment effect: If you do take any of those medications, overall, has there been any change in your heartburn and regurgitation since before you started taking *any* of those medications?

- ☐₁ A very great deal worse.
- ☐₂ A great deal worse.
- ☐₃ A good deal worse.
- ☐₄ Moderately worse.
- ☐₅ Somewhat worse.
- ☐₆ A little worse.
- ☐₇ Almost the same, hardly worse at all.
- ☐₈ About the same.
- ☐₉ Almost the same, hardly better at all.
- ☐₁₀ A little better.
- ☐₁₁ Somewhat better.
- ☐₁₂ Moderately better.
- ☐₁₃ A good deal better.
- ☐₁₄ A great deal better.
- ☐₁₅ A very great deal better.
- ☐₁₆ I do not take any of those medications.

8. Have you smoked at least 100 cigarettes in your life?

☐ YES ☐ NO

a. If yes, how old were you the first time you smoked? _____ years old

b. If yes, are you still smoking?

☐ YES ☐ NO

i. If no, how old were you when you last quit? _____ years old

c. What was the *most* you have smoked per day?

_____ packs per day or _____ cigarettes per day

In the past 6 months have you often had:

9. Heartburn, indigestion or pain in stomach, bad pain in your abdomen?

☐ YES ☐ NO

10. Trouble with digestion, or heartburn (burning from abdomen into the throat)?

☐ YES ☐ NO

11. In the right side of the belly?

☐ YES ☐ NO

12. In the left side of the belly?

☐ YES ☐ NO

13. That came on while or right after eating?

☐ YES ☐ NO

14. That came on 1 or 2 hours after eating?

☐ YES ☐ NO

15. That was worse on bending over or lying down?

☐ YES ☐ NO

16. That awakened you from sleep?

☐ YES ☐ NO

17. That was helped by baking soda, antacids, etc.?

☐ YES ☐ NO

18. That was not helped by medicines?

☐ YES ☐ NO

19. That was relieved or helped by eating?

☐ YES ☐ NO

20. Trouble with digestion (bad pain, burning, excessive gas, etc) caused by food?

☐ YES ☐ NO

21. That was relieved by a bowel movement?

☐ YES ☐ NO

Before one year ago had you ever had:

22. Trouble swallowing solid foods?

☐ YES ☐ NO

23. Trouble swallowing liquids?

☐ YES ☐ NO

Before one year ago had you often had:

24. Nausea (sick to stomach) or vomiting?

☐ YES ☐ NO

25. Heartburn, indigestion or stomach pain?

☐ YES ☐ NO

In the past 6 months have you often had:

26. A feeling of choking or a lump in your throat when not eating? ☐ YES ☐ NO

27. A hoarse voice which has not improved? ☐ YES ☐ NO

28. Trouble swallowing solid foods?

☐ YES

☐ NO

In the past year,

29. Have you often had trouble swallowing/feeling food getting stuck?

☐ YES

☐ NO

30. Trouble swallowing liquids?

☐ YES

☐ NO

In the past 6 months have you often:

31. Had nausea (sick to stomach) or vomiting?

☐ YES

☐ NO

32. Been bothered by excessive gas or bloating?

☐ YES

☐ NO

33. For the past month have you had a poor appetite?

☐ YES

☐ NO

In the past year or two has a doctor said you had:

34. Gallstones or gallbladder trouble?

☐ YES

☐ NO

35. Liver disease (such as hepatitis)?

☐ YES

☐ NO

36. Stomach or duodenal ulcer?

☐ YES

☐ NO

37. A hiatal (diaphragmatic) hernia?

☐ YES

☐ NO

38. In the past year did you smoke cigarettes?

☐ YES

☐ NO

a. If yes, did you smoke 2 packs a day or more?

☐

b. Or 1 to 2 packs a day?

☐

c. Or less than 1 pack a day?

☐

d. Do you usually inhale when you smoke?

☐ YES

☐ NO

e. Have you smoked altogether less than 10 years?

☐ YES

☐ NO

f. For 10 to 20 years?

☐ YES

☐ NO

g. Or for more than 20 years?

☐ YES

☐ NO

39. Have you smoked 2 packs of cigarettes a day for 20 years or more?

☐ YES

☐ NO