HHS Public Access

Author manuscript

Am J Med. Author manuscript; available in PMC 2024 March 01.

Published in final edited form as:

Am J Med. 2023 March ; 136(3): 302–307. doi:10.1016/j.amjmed.2022.11.010.

Predicting Alzheimer's Disease and Related Dementias in Heart Failure and Atrial Fibrillation

Sheila M. Manemann, MPH[a], **Alanna M. Chamberlain, PhD**[a], **Suzette J. Bielinski, PhD**[a], **Ruoxiang Jiang, BS**[a], **Susan A. Weston, MS**[a], **Véronique L. Roger, MD, MPH**[a,b,c]

[a]Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota, 55905, USA;

[b]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, 55905, USA;

[c]Division of Intramural Research, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD, 20892, USA.

Abstract

Background: The Framingham Heart Study Dementia Risk Score (FDRS) was developed in a general population of older persons. It is unknown how the FDRS variables predict Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD) in heart failure and atrial fibrillation populations. We ailed to evaluate the predictive ability of the FDRS variables in population-based cohorts of heart failure and atrial fibrillation and to determine whether the addition of other comorbidities and risk factors improves risk prediction for Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD).

Methods: Residents aged ≥50 years from 7 southeastern Minnesota counties with a first diagnosis of heart failure or atrial fibrillation between 1/1/2013 and 12/31/2017 were identified. Patients with AD/ADRD before or within 6 months after index atrial fibrillation or heart failure, and patients who died within 6 months after index were excluded. For both cohorts, models were constructed to predict AD/ADRD after index including the variables in the FDRS. Additional comorbidities and risk factors were added to the models. For all models, c-statistics using 5-fold cross-validation were calculated.

Results: Among 3,052 patients with heart failure (mean age 75 years, 53% male), 626 developed AD/ADRD; among 4,107 patients with atrial fibrillation (mean age 74 years, 57% male), 736 developed AD/ADRD. Among heart failure patients, the FDRS variables predicted AD/ADRD with c-statistic=0.69. Adding comorbidities and risk factors improved the c-statistic slightly to 0.70. The FDRS variables also performed well (c-statistic=0.73) in atrial fibrillation patients; adding comorbidities and risk factors slightly improved performance (c-statistic=0.75).

Corresponding Author: Sheila M. Manemann, MPH, Department of Quantitative Health Sciences, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; Telephone: (507)-266-3204, Manemann.sheila@mayo.edu.
*All Authors had access to the data and a role in writing the manuscript

Potential Competing Interests: The authors report no competing interests.

Conclusions: The variables from the FDRS predict AD/ADRD well in both heart failure and atrial fibrillation populations. The addition of comorbidities and risk factors only modestly improved prediction, indicating that the FDRS variables are appropriate to predict AD/ADRD in patients with heart failure and atrial fibrillation.

Keywords

Heart failure; Atrial fibrillation; Alzheimer's disease; Alzheimer's disease related dementias

INTRODUCTION

Heart failure and atrial fibrillation are diseases of aging, with heart failure affecting approximately 10% of persons over age 80 and atrial fibrillation affecting approximately 1 in 6 persons over 85.[1, 2] Furthermore, heart failure is associated with an excess risk of Alzheimer's disease and Alzheimer's disease related dementias AD/ADRD,[3–8] and atrial fibrillation is also associated with an increased risk of AD/ADRD, independent of the occurrence of clinical stroke.[9, 10] AD/ADRD is an important cause of morbidity and mortality in older persons.[11] The prolonged course of cognitive decline that results from AD/ADRD can influence the diagnosis and treatment of comorbid conditions and generates complex management. Thus, identifying heart failure and atrial fibrillation patients who are at risk for AD/ADRD could have important implications for patient management and outcomes in these individuals. The Framingham Heart Study Dementia Risk Score (FDRS) was recently developed in a general population of older individuals, with good discrimination (c-statistic: 0.716).[12] It was developed to be a practical tool for general practitioners by using information that can be easily assessed and is commonly available in the EHR. However, it is unknown how the FDRS variables predict AD/ADRD in heart failure and atrial fibrillation populations. Thus, utilizing EHR data, we aimed to evaluate the predictive ability of the variables included in the FDRS and to determine whether the addition of other comorbidities and risk factors improves risk prediction for AD/ADRD in population-based cohorts of individuals with heart failure and atrial fibrillation.

METHODS

Study Setting

Utilizing resources of the Rochester Epidemiology Project (REP), this study was conducted within seven counties (Dodge, Freeborn, Mower, Olmsted, Steele, Wabasha, and Waseca) in southeastern Minnesota.[13–15] The REP, which includes data from various health care institutions (Mayo Clinic Rochester, Mayo Clinic Health System clinics and hospitals, and Olmsted Medical Center and its affiliated clinics), is a records linkage system that enables retrieval of nearly all health care encounters and clinical events of residents living in southeastern Minnesota.[13–15]

Heart Failure Case Identification

Residents of the 7-county area in southeastern MN age 50 or older with a first-ever International Classification of Diseases, Ninth Revision (ICD-9) code 428 or ICD-10 code I50 for heart failure between January 1, 2013 and December 31, 2017 were identified. Those

with a heart failure diagnosis code prior to the study period, using a 3-year look back window, were excluded. A heart failure case was defined as having at least 2 heart failure codes (in- or outpatient) separated by at least 30 days. This algorithm has been shown to maximize positive predictive value (PPV) and sensitivity.[16] The date of the first diagnosis code was considered the heart failure index date.

Atrial Fibrillation Case Identification

Cases of new-onset atrial fibrillation between 2013 and 2017 who were residents within the 7-county area were identified. Diagnostic codes ICD-9 code 427.3 and ICD-10 code I48 for atrial fibrillation or atrial flutter from inpatient and outpatient encounters among adults ≥50 years were obtained. Electronic interpretations of electrocardiograms (ECG) and Holter monitor reports were available from Mayo Clinic and Mayo Clinic Health System but were not available from Olmsted Medical center. Medical records were reviewed by trained nurse abstractors for Olmsted Medical Center as well as any ECGs or Holter reports with missing or inconclusive interpretations from Mayo Clinic. A diagnostic code plus evidence of atrial fibrillation or atrial flutter on either an ECG or Holter monitor (within 30 days prior to 1 year after an atrial fibrillation diagnostic code) was required to confirm the diagnosis. The date of diagnosis code was used as the index atrial fibrillation date.

Framingham Dementia Risk Score Variables

The variables included in the FDRS score include age, marital status (married, single, divorced/separated/widowed), body mass index (BMI), stroke/transient ischemic attack (TIA), diabetes, and cancer.[12] Age and marital status were obtained through the electronic indices of the REP. BMI was calculated using an algorithm that has been previously described.[17, 18] Stroke/TIA, diabetes, and cancer were ascertained via the REP by electronically retrieving ICD-9 and ICD-10 codes from both inpatient and outpatient encounters. The code sets used were outlined by the U.S. Department of Health and Human Services.[19, 20] For cancer, non-melanoma skin cancers were excluded. The occurrence of one code occurring within 3 years prior to the incident heart failure or atrial fibrillation date were required to be classified as having the condition.

Other Patient Characteristics

Sex, smoking status (current, never, or ever), and educational attainment (8th grade or less, some high school, high school/GED, some college or 2 year degree, 4 year college degree and post graduate studies) were obtained through the electronic indices of the REP. Additional comorbidities identified as a public health priority by the US Department of Health and Human Services were identified and retrieved from the REP as outlined above.[19, 20] Very few individuals in our cohort had autism, hepatitis, and human immunodeficiency virus (HIV) so these conditions were excluded, leaving 13 chronic conditions (hypertension, coronary artery disease, arrhythmia (in the heart failure cohort), heart failure (in the atrial fibrillation cohort), hyperlipidemia, arthritis, asthma, chronic kidney disease, chronic pulmonary obstructive disease, osteoporosis, depression, schizophrenia, and substance abuse disorder) in the analysis.

(AD/ADRD) Ascertainment

Clinically diagnosed AD/ADRD after the heart failure or atrial fibrillation diagnosis was ascertained by the Centers for Medicare and Medicaid (CMS) Chronic Conditions Data Warehouse[21] ICD code set for AD/ADRD, which has been shown to have a sensitivity of 87%.[22] We used the criterion of the occurrence of at least 1 code for AD/ADRD. AD/ADRD was ascertained through 3/31/2021.

Statistical Methods

Subjects who developed AD/ADRD within 6 months after their index event were excluded because it is presumed that AD/ADRD was preexisting. In addition, patients who died within 6 months after index were excluded, along with those missing covariate data. Patients were followed through the first of either death, last clinical encounter, or 3/31/2021,with time to event calculated from the index date. Baseline clinical characteristics were summarized as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. The cumulative incidence of AD/ADRD after the index event was estimated, treating death as a competing risk. Cox proportional hazards regression was used to model the risk of AD/ADRD after index with the variables used to estimate the FDRS as predictors (age, marital status, body mass index, stroke/TIA, diabetes, and cancer). Additional predictors were then added to the models to assess whether model prediction improved; these included sex, smoking, education, hypertension, coronary artery disease, arrhythmia (in the heart failure model), heart failure (in the atrial fibrillation model), hyperlipidemia, arthritis, asthma, chronic kidney disease, chronic pulmonary disease, osteoporosis, depression, schizophrenia, and substance abuse disorder. Discrimination was assessed using the C-statistic, and calibration was assessed using a group-based measure of calibration that utilizes a model-based framework that provides a natural extension to survival data.[23] Five-fold cross-validation was used to assess model performance. The data were split into 5 equal, mutually exclusive datasets with analysis done on 4 of the folds and validation performed on the remaining ‘hold-out’ fold. This was repeated using each of the 5 folds as the hold-out fold. Results were averaged across the 5 hold-out folds. Data analyses were performed using SAS software, version 9.4 (SAS institute Inc, Cary, NC) and R version 4.03 (R Foundation for Statistical Computing, Vienna, Austria). This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

RESULTS

We identified 3,052 patients with heart failure (mean age 75 years, 53% male) and 4,107 patients with atrial fibrillation (mean age 74 years, 57% male; Table 1). During a mean (SD) follow-up of 3.5 (1.8) years, 626 cases of AD/ADRD occurred among the heart failure cohort. The 1- and 3-year cumulative incidence (95% confidence interval [CI]) after index of AD/ADRD among patients with heart failure was 3.3% (2.6%–3.9%) and 13.8% (12.5%–15.1%), respectively. During a mean (SD) follow-up of 3.7 (1.8) years, 736 cases of AD/ADRD occurred among the atrial fibrillation cohort; 1- and 3-year cumulative incidence (95% CI) of AD/ADRD was 3.0% (2.5%–3.6%) and 11.5% (10.5%–12.4%), respectively.

In patients with heart failure, the FDRS variables predicted AD/ADRD with a c-statistic of 0.69 (Table 2). Adding additional comorbidities and risk factors improved the c-statistic slightly to 0.72. The FDRS variables also performed well in patients with atrial fibrillation (c-statistic: 0.74; Table 2), and adding other comorbidities and risk factors improved the performance (c-statistic: 0.76). The cross-validation analysis for heart failure yielded a mean c-statistic of 0.69 for the model with the FDRS variables and a mean c-statistic of 0.70 after adding additional comorbidities and risk factors. The cross-validation analysis for atrial fibrillation yielded a mean c-statistic of 0.73 for the model with the FDRS variables and a mean c-statistic of 0.75 for the model with the additional comorbidities and risk factors. Furthermore, the models were well calibrated as indicated by a mean standardized incidence ratio of 0.988 for the heart failure cohort and 0.994 for the atrial fibrillation cohort (Table 3).

DISCUSSION

The variables from the FDRS predict AD/ADRD well in a population-based cohort of heart failure and atrial fibrillation patients. The addition of comorbidities and other cardiovascular disease risk factors only modestly improved prediction, indicating that the FDRS variables are appropriate to predict Alzheimer's disease and Alzheimer's disease related dementias in patients with heart failure and atrial fibrillation.

Our results have important implications because the variables in the FDRS, as well as the additional comorbidities and risk factors, can be easily obtained from the EHR. Thus, using data that is easily accessible to clinicians may help predict who is at risk for AD/ADRD among patients with heart failure and atrial fibrillation. Both atrial fibrillation and heart failure are conditions that require effective self-management that in turn relies on cognitive function; thus, having the ability to identify patients at risk for AD/ADRD could have great implications for patient management and outcomes in these individuals. We recently reported that in a population of patients with heart failure, AD/ADRD both prior to and after a diagnosis was heart failure was associated with an increased risk of healthcare utilization and death.[24] Thus, by identifying heart failure and atrial fibrillation patients at risk for AD/ADRD, interventions could be targeted to these patients to potentially prevent or reduce the impact of AD/ADRD and in turn improve outcomes.

Some limitations should be considered to aid in the interpretation of our findings. We used diagnosis codes to ascertain heart failure; however, we used a validated EHR algorithm that maximizes PPV and sensitivity.[16] We also used diagnosis codes to define AD/ADRD, and as the onset of AD/ADRD is difficult to define in clinical practice, under-ascertainment during early stages is a concern.[25–27] However, the REP captures data from primary and specialty care, outpatient visits and hospitalizations, and the reliability of EHR ascertainment of AD/ADRD has been validated in the REP.[28] The generalizability of our study may be limited as our region is predominantly white; however, this region has similar age, sex, and racial/ethnic characteristics as the state of Minnesota and the Upper Midwest region of the US.[13, 15]

Our study has notable strengths. It was conducted in large, contemporary, community-based cohorts of patients with heart failure and atrial fibrillation. We have robust EHR data via the

resources of the REP, with nearly complete capture of comorbid conditions and outcomes in a large area of southeastern Minnesota.[13] Furthermore, five-fold cross-validation was used to assess model performance.

CONCLUSION

Using EHR data from a community population, the variables in the FDRS predict AD/ADRD well in both heart failure and atrial fibrillation populations. The addition of comorbidities and other cardiovascular disease risk factors only modestly improved prediction. These results indicate that the FDRS variables are appropriate to predict AD/ADRD in patients with heart failure and atrial fibrillation.

ACKNOWLEDGMENTS

We thank Deborah Strain for manuscript formatting and preparation.

Funding Source:

This work was supported by the National Institute on Aging (R21 AG064804) and used the resources of the Rochester Epidemiology Project (REP) medical records-linkage system, which is supported by the National Institute on Aging (NIA; AG058738), by the Mayo Clinic Research Committee, and by fees paid annually by REP users. The content of this article is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health (NIH) or the Mayo Clinic. The funding sources played no role in the design, conduct, or reporting of this study.

Abbreviations and Acronyms:

AD/ADRD	Alzheimer's disease and Alzheimer's disease related dementias
BMI	body mass index
CMS	Centers for Medicare and Medicaid
ECG	electronic interpretations of electrocardiograms
EHR	electronic health record
FDRS	Framingham Heart Study Dementia Risk Score
HIV	human immunodeficiency virus
PPV	positive predictive value
REP	Rochester Epidemiology Project
SD	standard deviation
TIA	transient ischemic attack

REFERENCES

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370–2375. [PubMed: 11343485]

2. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation. 2021;143(8):e254–e743. [PubMed: 33501848]
3. Witt LS, Rotter J, Stearns SC, et al. Heart Failure and Cognitive Impairment in the Atherosclerosis Risk in Communities (ARIC) Study. J Gen Intern Med. 2018;33(10):1721–1728. [PubMed: 30030736]
4. Qiu C, Winblad B, Marengoni A, et al. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. Arch Intern Med. 2006;166(9):1003–1008. [PubMed: 16682574]
5. Haring B, Leng X, Robinson J, et al. Cardiovascular disease and cognitive decline in postmenopausal women: results from the Women's Health Initiative Memory Study. J Am Heart Assoc. 2013;2(6):e000369. [PubMed: 24351701]
6. Noale M, Limongi F, Zambon S, et al. Incidence of dementia: evidence for an effect modification by gender. The ILSA Study. Int Psychogeriatr. 2013;25(11):1867–1876. [PubMed: 23905558]
7. Rusanen M, Kivipelto M, Levalahti E, et al. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. Journal of Alzheimer's disease : JAD. 2014;42(1):183–191. [PubMed: 24825565]
8. Adelborg K, Horvath-Puho E, Ording A, et al. Heart failure and risk of dementia: a Danish nationwide population-based cohort study. Eur J Heart Fail. 2017;19(2):253–260. [PubMed: 27612177]
9. Kalantarian S, Stern TA, Mansour M and Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med. 2013;158(5 Pt 1):338–346. [PubMed: 23460057]
10. Miyasaka Y, Barnes ME, Petersen RC, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a community-based cohort. Eur Heart J. 2007;28(16):1962–1967. [PubMed: 17459900]
11. Alzheimer's Association. 2022 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2022;18(4)700–789. [PubMed: 35289055]
12. Li J, Ogrodnik M, Devine S, et al. Practical risk score for 5-, 10-, and 20-year prediction of dementia in elderly persons: Framingham Heart Study. Alzheimers Dement. 2018;14(1):35–42. [PubMed: 28627378]
13. Rocca WA, Grossardt BR, Brue SM, et al. Data resource profile: expansion of the Rochester Epidemiology Project medical records-linkage system (E-REP). Int J Epidemiol. 2018;47(2):368–368j. [PubMed: 29346555]
14. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR and Melton LJ 3rd. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. Mayo Clin Proc. 2012;87(12):1202–1213. [PubMed: 23199802]
15. St Sauver JL, Grossardt BR, Leibson CL, et al. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. Mayo Clin Proc. 2012;87(2):151–160. [PubMed: 22305027]
16. Tison GH, Chamberlain AM, Pletcher MJ, et al. Identifying heart failure using EMR-based algorithms. Int J Med Inform. 2018 (120):1–7.
17. Manemann SM, St Sauver JL, Liu H, et al. Longitudinal cohorts for harnessing the electronic health record for disease prediction in a US population. BMJ Open. 2021;11(6):e044353.
18. Cheng FW, Gao X, Mitchell DC, et al. Body mass index and all-cause mortality among older adults. Obesity (Silver Spring). 2016;24(10):2232–2239. [PubMed: 27570944]
19. Goodman RA, Posner SF, Huang ES, Parekh AK and Koh HK. Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. Prev Chronic Dis. 2013;10E66.
20. US Department of Health and Human Services. Multiple chronic conditions - a strategic framework: optimum health and quality of life for individuals with multiple chronic conditions. Washington, DC, December, 2010. Accessed at: https://www.hhs.gov/sites/default/files/ash/initiatives/mcc/mcc_framework.pdf on 5/7/2021.
21. Centers for Medicare and Medicaid Chronic Conditions Data Warehouse (CCW), CCW Condition Algorithms. Accessed May 7, 2021 from https://www.ccwdata.org/web/guest/condition-categories.
22. Taylor DH Jr., Fillenbaum GG and Ezell ME. The accuracy of medicare claims data in identifying Alzheimer's disease. J Clin Epidemiol. 2002;55(9):929–937. [PubMed: 12393082]

23. Crowson CS, Atkinson EJ and Therneau TM. Assessing calibration of prognostic risk scores. Stat Methods Med Res. 2016;25(4):1692–1706. [PubMed: 23907781]

24. Manemann SM, Knopman DS, St Sauver J, et al. Alzheimer's disease and related dementias and heart failure: A community study. J Am Geriatr Soc. 2022 (In Press).

25. Barnes DE, Zhou J, Walker RL, et al. Development and Validation of eRADAR: A Tool Using EHR Data to Detect Unrecognized Dementia. J Am Geriatr Soc. 2020;68(1):103–111. [PubMed: 31612463]

26. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. Alzheimers Dement. 2019;15(3):321–387.

27. Bradford A, Kunik ME, Schulz P, Williams SP and Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer Dis Assoc Disord. 2009;23(4):306–314. [PubMed: 19568149]

28. Knopman DS, Petersen RC, Rocca WA, Larson EB and Ganguli M. Passive case-finding for Alzheimer's disease and dementia in two U.S. communities. Alzheimers Dement. 2011;7(1):53–60. [PubMed: 21255743]

Clinical Significance

- In community-based heart failure and atrial fibrillation populations, the addition of comorbidities and cardiovascular risk factors to the variables in the Framingham Heart Study Dementia Risk Score only modestly improved prediction of dementia.
- Using electronic health record data, the variables in the Framingham Heart Study Dementia Risk Score predict dementia well in both heart failure and atrial fibrillation populations.

Table 1.

Baseline Characteristics by Disease Status

	Heart failure (N=3052)	Atrial fibrillation (N=4107)
Age, years, mean (SD)	75.0 (11.1)	74.2 (10.9)
Male	1629 (53.4)	2323 (56.6)
Marital Status		
Married	1794 (58.8)	2609 (63.5)
Single	241 (7.9)	284 (6.9)
Divorced/separated/widowed	1017 (33.3)	1214 (29.6)
Education		
8th grade or less	139 (4.6)	136 (3.3)
Some high school	193 (6.3)	233 (5.7)
High school / GED	1209 (39.6)	1507 (36.7)
Some college or 2 year degree	811 (26.6)	1129 (27.5)
4 year college degree	265 (8.7)	429 (10.4)
Post graduate studies	435 (14.3)	673 (16.4)
Smoking status		
Never smoker	1141 (37.4)	1594 (38.8)
Current smoker	258 (8.5)	325 (7.9)
Former smoker	1653 (54.2)	2188 (53.3)
Body mass index, kg/m^2, mean (SD)	31.1 (7.7)	31.2 (7.2)
Ejection fraction (SD)	50.7 (14.4)	
Stroke/TIA	624 (20.4)	574 (14.0)
Diabetes	1753 (57.4)	1995 (48.6)
Cancer	903 (29.6)	1067 (26.0)
Hypertension	2675 (87.6)	3155 (76.8)
Coronary artery disease	1802 (59.0)	1521 (37.0)
Arrhythmia	2560 (83.9)	
Heart failure		762 (18.6)
Hyperlipidemia	2404 (78.8)	2867 (69.8)
Arthritis	1694 (55.5)	2061 (50.2)
Asthma	358 (11.7)	405 (9.9)
Chronic kidney disease	1299 (42.6)	1036 (25.2)
Chronic pulmonary disease	906 (29.7)	858 (20.9)
Osteoporosis	463 (15.2)	472 (11.5)
Depression	747 (24.5)	718 (17.5)
Schizophrenia	105 (3.4)	86 (2.1)
Substance abuse disorder	379 (12.4)	302 (7.4)

All results are N (%) unless otherwise indicated.

GED, general educational development; SD, standard deviation; TIA, transient ischemic attack

Table 2.

C-statistics (95% CI) for Predicting AD/ADRD by Disease Status

	Heart Failure N=3025 626 events		Atrial Fibrillation N=4107 736 events	
	Model 1[a]	**Model 2[b]**	**Model 1[a]**	**Model 2[c]**
Original dataset	0.69 (0.66–0.72)	0.72 (0.69–0.74)	0.74 (0.72–0.76)	0.76 (0.74– 0.78)
Cross-validation fold 1	0.68 (0.63–0.73)	0.69 (0.64–0.74)	0.74 (0.70–0.78)	0.75 (0.71–0.79)
Cross-validation fold 2	0.67 (0.61–0.72)	0.68 (0.63–0.73)	0.72 (0.67–0.76)	0.75 (0.71–0.79)
Cross-validation fold 3	0.69 (0.65–0.74)	0.72 (0.67–0.76)	0.76 (0.72–0.80)	0.78 (0.74–0.82)
Cross-validation fold 4	0.70 (0.65–0.75)	0.70 (0.65–0.75)	0.73 (0.69–0.77)	0.75 (0.71–0.79)
Cross-validation fold 5	0.70 (0.65–0.74)	0.71 (0.67–0.76)	0.71 (0.66–0.75)	0.73 (0.69–0.77)
Mean c-statistic from cross-validation	0.69	0.70	0.73	0.75

[a] age, marital status, body mass index, prior stroke/transient ischemic attack, prior diabetes, prior cancer

[b] Model 1 + hypertension, coronary artery disease, arrhythmia, hyperlipidemia, arthritis, asthma, chronic kidney disease, chronic pulmonary disease, depression, osteoporosis, schizophrenia, and substance abuse disorder, sex, ejection fraction, smoking, education

[c] Model 1 + hypertension, coronary artery disease, heart failure, hyperlipidemia, arthritis, asthma, chronic kidney disease, chronic pulmonary disease, depression, osteoporosis, schizophrenia, and substance abuse disorder, sex, smoking, education

Table 3.

Standardized Incidence Ratios (95% CI) for Predicting AD/ADRD by Disease Status

	Cross-validation fold	Observed number of events	Expected number of events	Standardized incidence ratio
		Heart failure		
Model 1[a]	1	109	124.24	0.88 (0.72–1.06)
	2	108	108.57	0.99 (0.82–1.20)
	3	113	116.88	0.97 (0.80–1.16)
	4	117	118.05	0.99 (0.82–1.19)
	5	126	108.74	1.16 (0.97–1.38)
	Mean SIR			0.998
Model 2[b]	1	109	128.67.	0.85 (0.70–1.02)
	2	108	109.76.	0.98 (0.81–1.19)
	3	113	114.58.	0.99 (0.81–1.19)
	4	117	121.65	0.96 (0.80–1.15)
	5	126	108.44	1.16 (0.97–1.38)
	Mean SIR			0.988
		Atrial fibrillation		
Model 1[a]	1	131	130.92	1.00 (0.84–1.19)
	2	120	145.05	0.83 (0.69–0.99)
	3	136	122.66	1.11 (0.93–1.31)
	4	140	137.10	1.02 (0.86–1.20)
	5	135	129.28	1.04 (0.88–1.24)
	Mean SIR			1.000
Model 2[c]	1	131	133.02	0.98 (0.82–1.17)
	2	120	141.07	0.85 (0.71–1.02)
	3	136	125.65	1.08 (0.91–1.28)
	4	140	135.42	1.03 (0.87–1.22)
	5	135	131.67	1.03 (0.86–1.21)
	Mean SIR			0.994

SIR, standardized incidence ratio

[a] age, marital status, body mass index, prior stroke/transient ischemic attack, prior diabetes, prior cancer

[b] Model 1 + hypertension, coronary artery disease, arrhythmia, hyperlipidemia, arthritis, asthma, chronic kidney disease, chronic pulmonary disease, depression, osteoporosis, schizophrenia, and substance abuse disorder, sex, ejection fraction, smoking, education

[c] Model 1 + hypertension, coronary artery disease, heart failure, hyperlipidemia, arthritis, asthma, chronic kidney disease, chronic pulmonary disease, depression, osteoporosis, schizophrenia, and substance abuse disorder, sex, smoking, education