



# A Novel Predictive Model for Agitation in Alzheimer's Dementia Using Administrative Claims Data

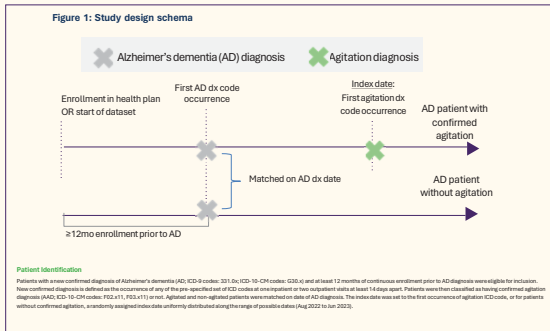
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## Introduction

•Agitation in Alzheimer's dementia (AAD) is a set of debilitating symptoms and behavioral disturbances for which little real-world evidence exists.<sup>1</sup> AAD ICD diagnosis codes were introduced in Aug 2022, where only a non-exhaustive set of behaviors and symptoms existed prior.<sup>2</sup>

## Methods

•A case-control study was conducted using Merative MarketScan claims data from 2015-2023 among n=968 cases newly diagnosed with agitation with existing Alzheimer's dementia diagnosis and n=968 non-agitated controls with Alzheimer's dementia who were matched on Alzheimer's diagnosis date.



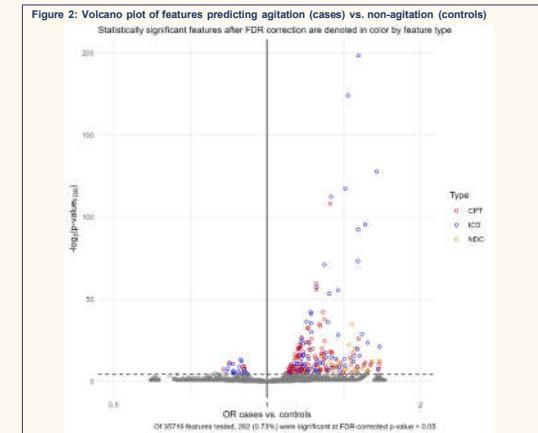
•Health service and treatment history was characterized using binary indicators for presence/absence of all possible diagnoses (ICD-9/10), procedures (CPT) and drug treatments (NDC) received by each patient prior to the index date, defined as AAD diagnosis date or, for those without confirmed agitation, a randomly index date uniformly distributed along the range of possible diagnosis dates.

•Bivariate analyses (i.e., chi-squared tests) identified potential predictors of agitation. Subsequently, features that were statistically significantly associated with agitation status at false discovery rate (FDR) corrected  $p < 0.05$  were entered into a LASSO regression to build a final prediction model.<sup>4</sup>

•Model fit and performance were examined using mean squared error and sensitivity/specificity, respectively.

•This study developed a model to predict agitation among Alzheimer's patients using prior health service and treatment history data. This approach can potentially improve RWE generation by enabling the use of historical data for outcomes research in AAD (and novel diseases more broadly) and provide utility as a claims-based screening tool for clinical practice.

## Results: Feature identification



•A total of 35,719 features were tested (14,266 NDC codes, 14,332 ICD codes, and 7,121 CPT codes), of which 262 were associated with agitation status, after controlling for age, sex and comorbidities. Fig 2 shows the distribution of features after FDR correction by effect size (OR) vs. log p-value.

•Significant features were further narrowed by LASSO regression models that optimized model fit via lowest MSE (model 1) or balanced model fit and parameter regularization via 5-fold cross-validation (model 2).<sup>2</sup> The final models included 148 and 110 features, respectively.

•The strongest predictors in the final model were exposure to/vaccine uptake for COVID-19 and diagnoses of and antidepressant/antipsychotic treatment for depression/anxiety.

•The final best fit model (model 1) achieved 83.5% sensitivity and 90.3% specificity in predicting actual agitation.

## Results: Final predictive model

Table 1: Full predictive model characteristics

	Model 1	Model 2
No. features	148	110
Penalization parameter ( $\lambda$ )	0.0054	0.0126
Predicted probabilities (%)		
Cases	76.3%	72.0%
Controls	23.7%	28.0%
Mean difference	52.6%	44.0%
Fit statistics		
Mean squared error	0.1740	0.1834
Deviance ratio (pseudo- $r^2$ )	0.535	0.464

\*Model 1 is "best" model with lowest MSE. Model 2 is "recommended" model which has smallest feature set among models with  $\lambda$  within 1 SD of "best" model (SD( $\lambda$ )=0.0072)

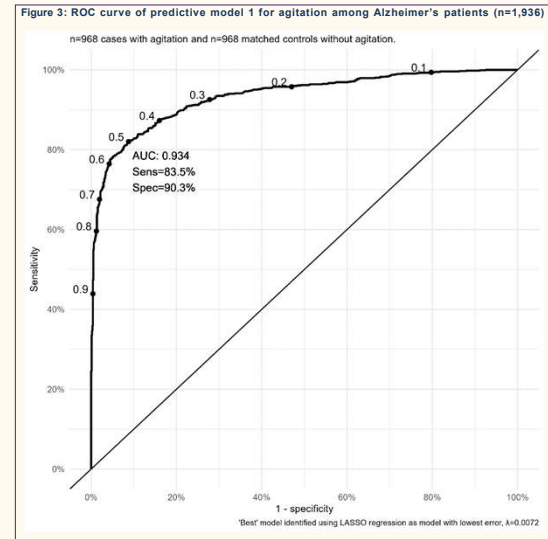


Table 2: Top features selected by LASSO full prediction model using best fit approach (model 1)

	Type	Beta coefficient
Fluad quadrivalent vaccine	Drug (NDC)	2.360
Acute cough (R05.1)	Diagnosis (ICD)	1.984
Fluzone quadrivalent vaccine	Drug (NDC)	1.888
Depression, unspecified (F32.A)	Diagnosis (ICD)	1.643
Risperidone (atypical antipsychotic)	Drug (NDC)	1.609
Care coordination and physician-patient interaction	Procedure (CPT)	1.601
Atorvastatin (lipid lowering medication)	Drug (NDC)	1.497
Latanoprost solution (glaucoma medication)	Drug (NDC)	1.436
Personal history of COVID-19 (Z86.16)	Diagnosis (ICD)	1.393
Cough, unspecified (R05.9)	Diagnosis (ICD)	1.346
Low back pain, unspecified (M54.50)	Diagnosis (ICD)	1.321
Mirtazapine (antidepressant)	Drug (NDC)	1.304
Potassium Cl (mineral supplement)	Drug (NDC)	1.286
20min non-complex chronic care management	Procedure (CPT)	1.226

## CONCLUSION

This analysis demonstrated the use of routinely available historical claims data on health service utilization and treatment to develop a prediction model for classifying likely agitation in an Alzheimer's patient population. The model achieved high sensitivity and specificity and can enable RWE generation using claims data in this population.

The modeling approach can be easily adapted to other patient populations and has notable applications for novel diseases like AAD for which diagnostic and treatment procedures are evolving.

Due to the routine availability and simple binary coding of patient history, the prediction model may also have utility as a claims-based screening tool or adapted to structured electronic health records.

Findings show that COVID-19-related exposure and health care services were strong predictors of agitation. These and other features will need to be validated in future work.

For any questions or comments, please reach out to anton.palma@otsuka-us.com

## References

- Cummings J, Mintzer J, Brodaty H, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *Int Psychogeriatr*. 2015 Jan; 27(1): 7-17.
- Hwang S, Teigland C, Pulungan Z, Parente A, DePalma R. (2020). Development of a claims-based algorithm to identify patients with agitation in Alzheimer's dementia. *Innov Aging*. 2020; 4(Suppl 1): 172.
- Lee D, Skomkowski M, Hertling N, et al. (2023). Brexpiprazole for the treatment of agitation in Alzheimer dementia. *JAMA Neurol*. 2023 Dec; 80(12): 1307-1316.
- Tibshirani R. (1996). Regression shrinkage and selection via the lasso. *Journal of the Royal Statistical Society. Series B*. 58 (1), 267-88.
- Friedman J, Hastie T, Tibshirani R. (2008). Regularization paths for generalized linear models via coordinate descent. *Journal of Statistical Software*. Vol 33(1), 1-22.

## Disclosures

Anton M. Palma, Ranjeeth K. Valandas and Zhen Zhang are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc.

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