Appendix for

Health-Oriented Sleep States: Making Sleep States Reflect Health Conditions

Haoqi Sun, PhD[1], Wolfgang Ganglberger, PhD[1], Samaneh Nasiri, PhD[1,2], Thijs E. Nassi, PhD[1], Erik-Jan Meulenbrugge, MSc[1], Alice D. Lam, MD, PhD[3], Sahar Zafar, MD[3], Aditya Gupta, MSc[3], Manohar Ghanta, MSc[3], Valdery F Moura Junior, PhD[3], Chol Shin[4], Rhoda Au, PhD[5], Sydney S. Cash, MD, PhD[3], Robert J. Thomas, MD[6†], M. Brandon Westover, MD, PhD[1*†]

[1] Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, USA

[2] Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, USA

[3] Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

[4] Biomedical Research Center, Korea University Ansan Hospital, Ansan, South Korea

[5] Chobanian & Avedisian School of Medicine, Boston University, Boston, MA, USA

[6] Division of Pulmonary, Critical Care and Sleep, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

[†]Co-senior authors

*Corresponding Author:

M. Brandon Westover, MD, PhD

Emily Fisher Landau Professor of Neurology

Department of Neurology,

Beth Israel Deaconess Medical Center

Harvard Medical School

KS-444, 330 Brookline Avenue, Boston, MA 02215, USA

bwestove@bidmc.harvard.edu

Sleep Staging Performance

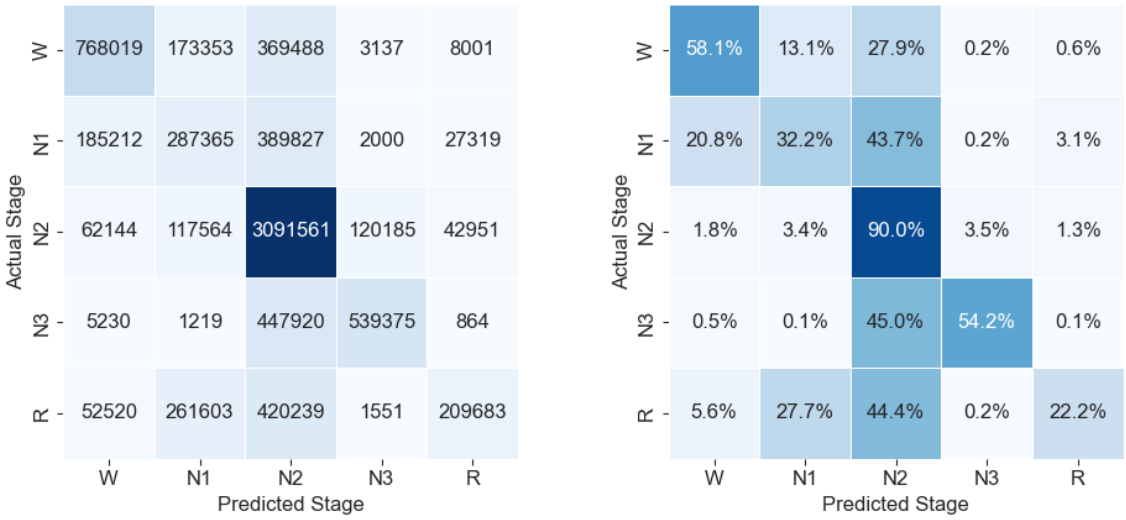


Figure S1. The confusion matrix for the actual vs. predicted sleep stages. The agreement between actual vs. predicted sleep stages, as measured by Cohen's kappa, is 0.466. (Left) the actual number of 30-second epochs). (Right) The normalized percentages where each row sums up to 100%.

Sleep States Ordered by Stage Probability

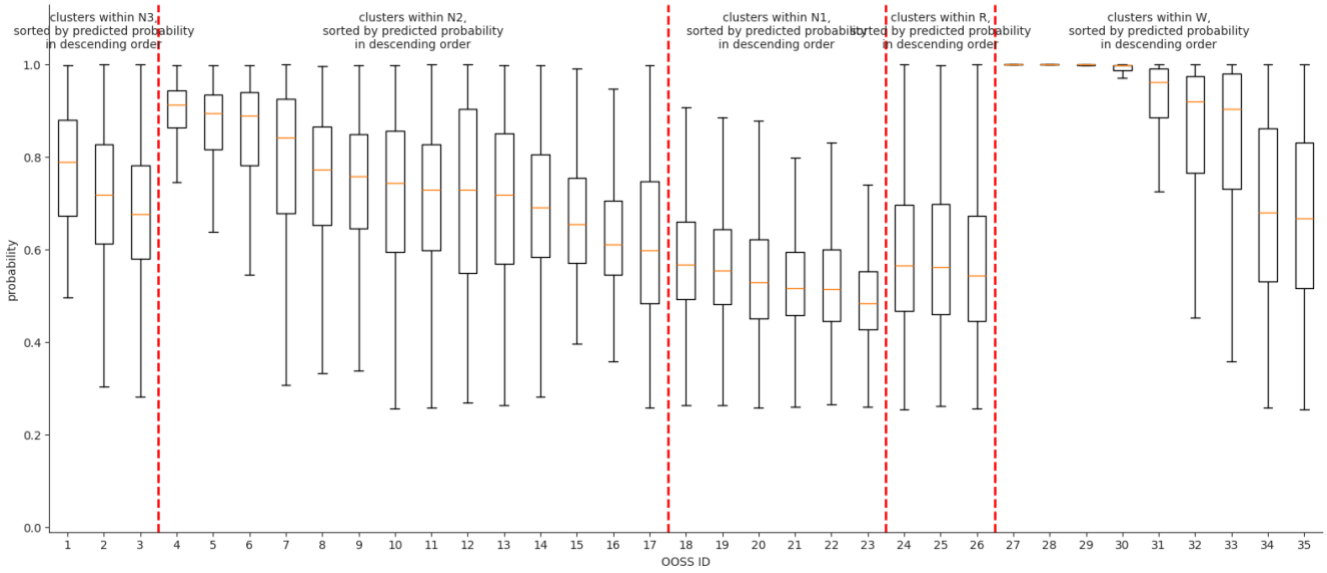


Figure S2. The probability of being in the confined sleep stage for each health-oriented sleep state (HOSS). The HOSSs are sorted in descending order within their confined sleep stage, hence the ones with smaller IDs are more "typical" of that sleep stage.

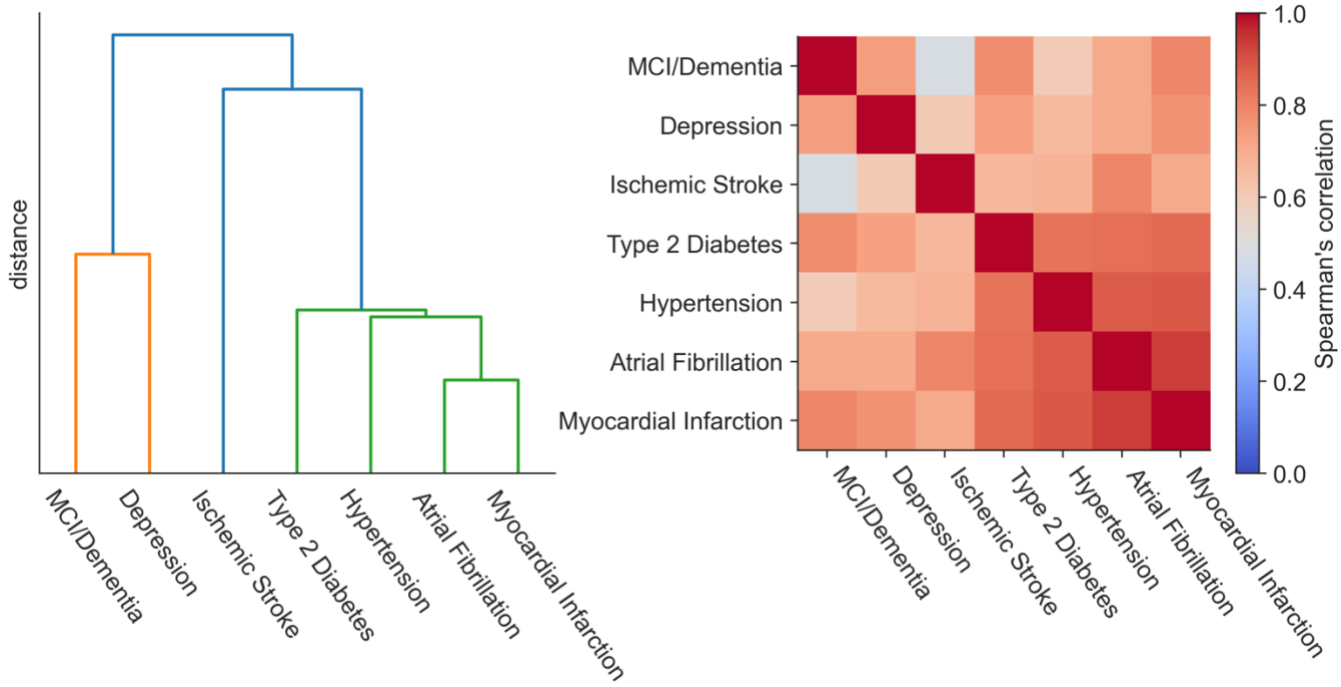


Figure S3. (Left) The hierarchical clustering of health outcomes based on the similarity of the HOSS signature in Figure 3. (Right) The pairwise similarity among the health outcomes, measured by Spearman's correlation.

Sleep State Interpretation: EEG Spectra

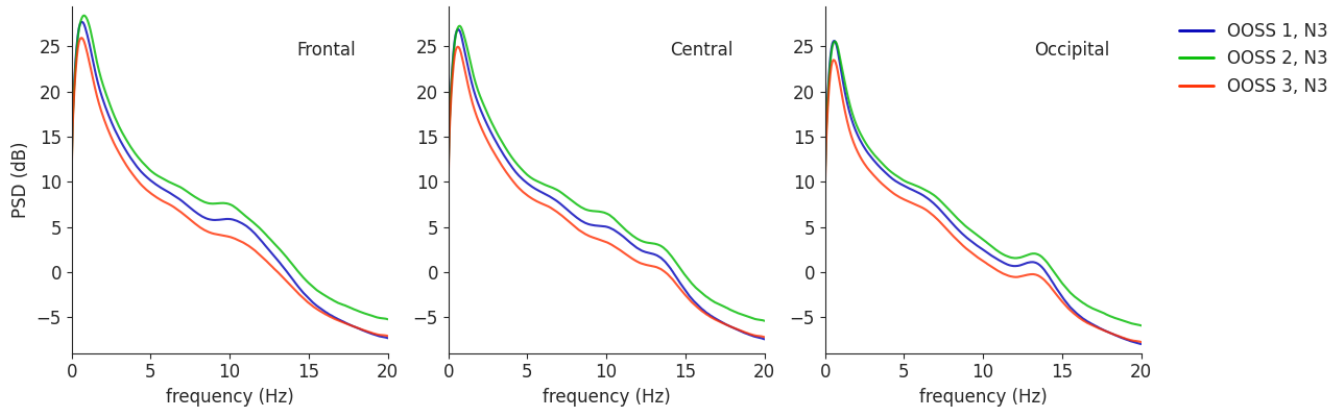


Figure S4. The average EEG spectrum for the health-oriented sleep states (HOSSs) in N3 separated into frontal, central, and occipital channels. Within each channel, the left and right signals were averaged. Different colors represent different HOSSs. The x-axis is frequency in Hz. The y-axis is power spectral density in decibels.

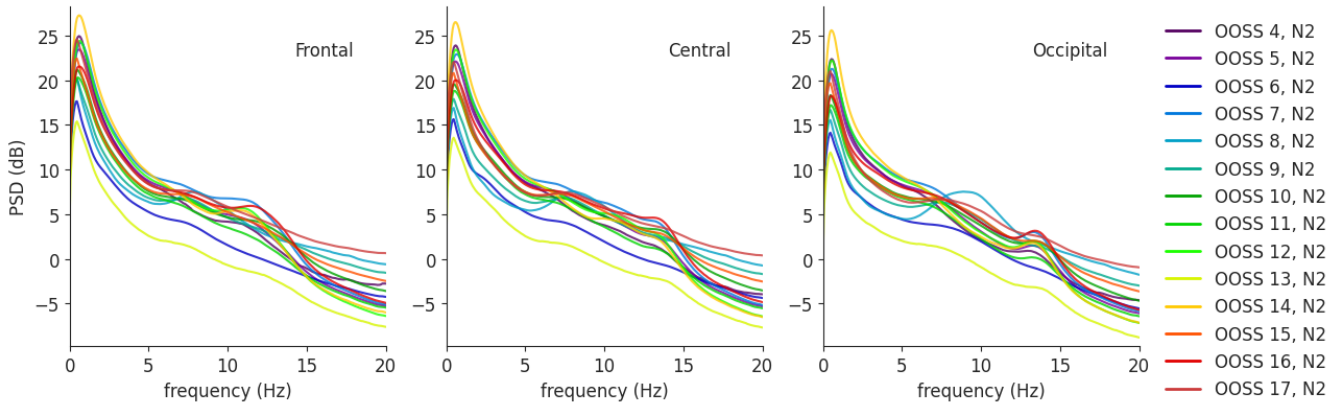


Figure S5. The average EEG spectrum for the health-oriented sleep states (HOSSs) in N2 separated into frontal, central, and occipital channels.

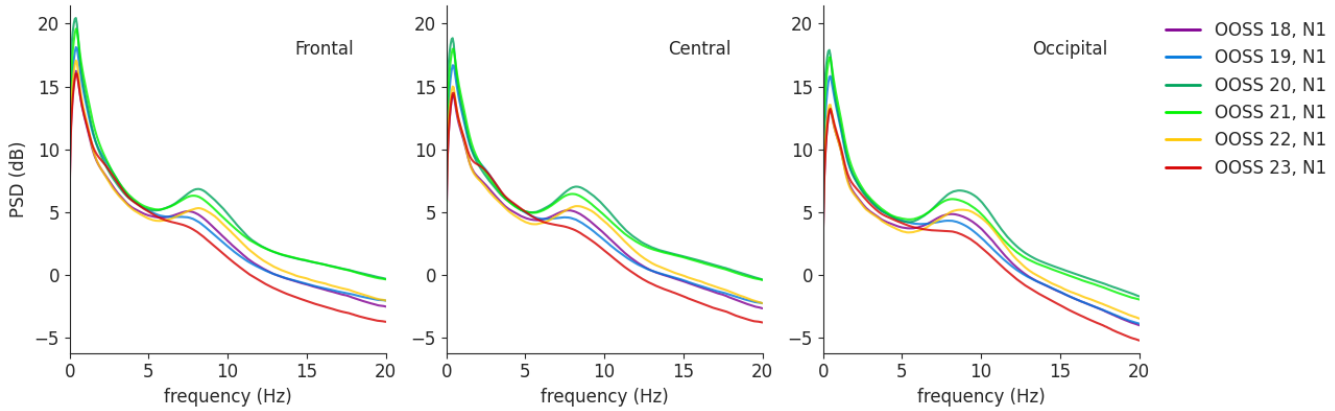


Figure S6. The average EEG spectrum for the health-oriented sleep states (HOSSs) in N1 separated into frontal, central, and occipital channels.

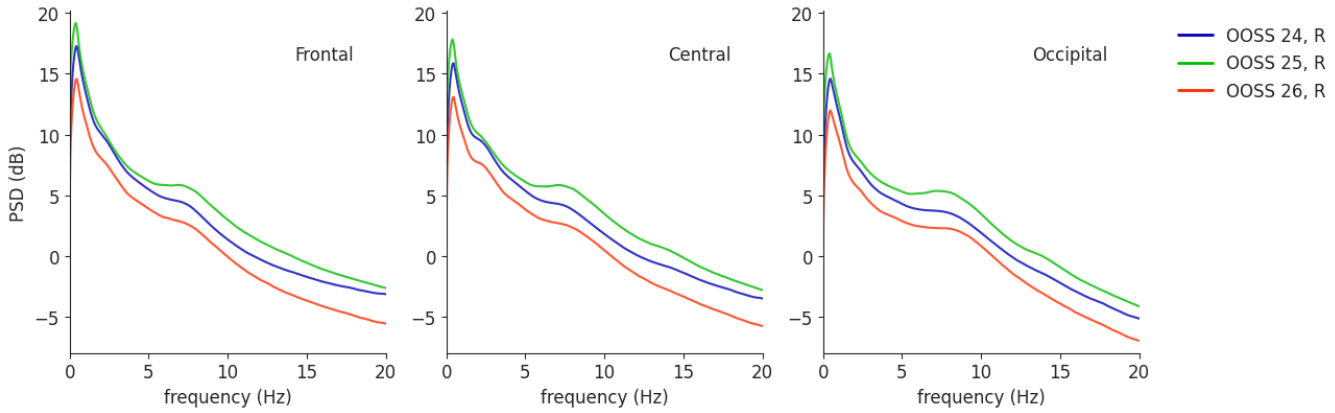


Figure S7. The average EEG spectrum for the health-oriented sleep states (HOSSs) in REM separated into frontal, central, and occipital channels.

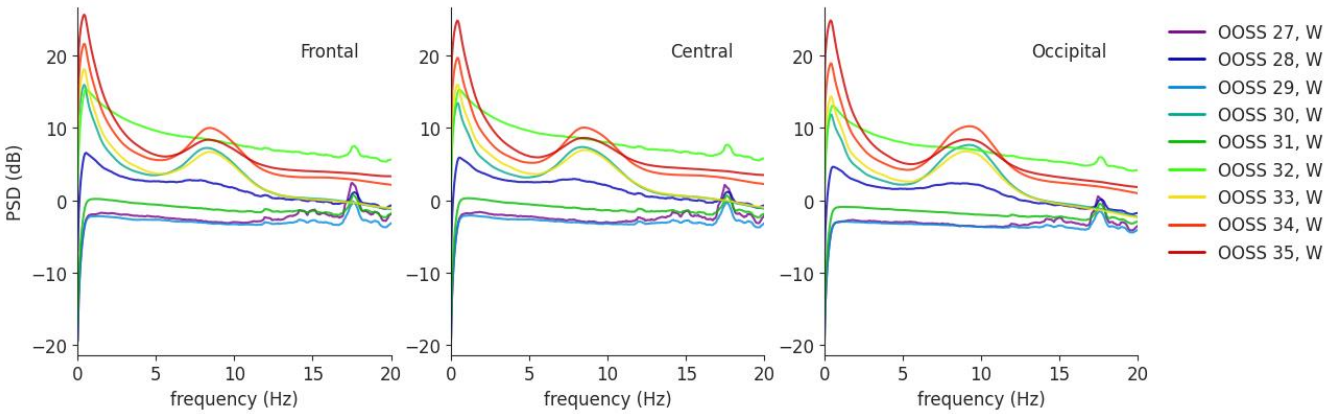


Figure S8. The average EEG spectrum for the health-oriented sleep states (HOSSs) in W separated into frontal, central, and occipital channels.

Sleep State Interpretation: Embedding into 2-dimensional space

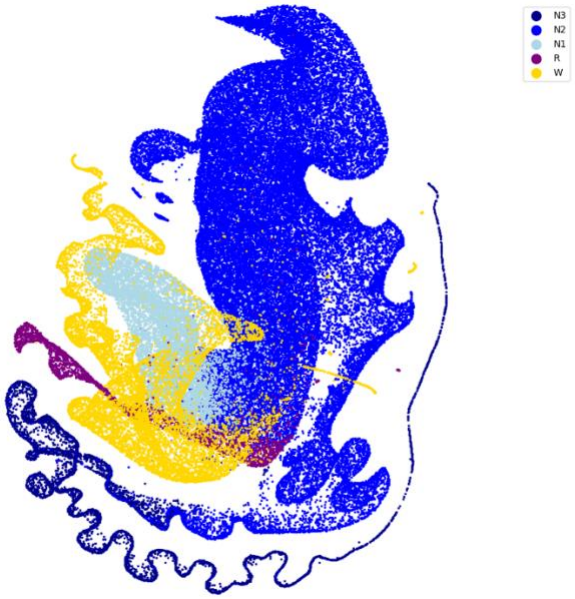


Figure S9. A 2-dimensional UMAP representation of the hidden layer of the ProductGraphSleepNet deep learning network for sleep staging. Different colors represent different sleep stages.

Table S1. ICD codes and medications used to ascertain the outcomes.

Outcome[%]	**ICD-10 Code**[^]	**Medication**
Hypertension	I10, I11, I11.9, I11.0, I13.10, I15, I15.0, I15.1, I15.2, I15.8, I15.9, I16, I16.0, I16.1, I16.9	hydrochlorothiazide (Microzide, Oretic), chlorthalidone (Thalitone), losartan (Cozaar), valsartan (Diovan), prazosin (Minipress), amlodipine (Norvasc), nicardipine (Cardene), verapamil (Calan, Covera HS, Isoptin, Verelan), propranolol (Inderal), metoprolol (Lopressor), atenolol (Tenormin), metoprolol (Toprol XL), carvedilol (Coreg), lisinopril (Zestril, Prinivil), enalapril (Vasotec), captopril (Capoten), clonidine (Catapres), combination of drugs (Diovan HCT, Exforge, Exforge HCT, Hyzaar, Lotrel, Tarka, Tribenzor, Vaseretic)
Type 2 Diabetes	E11*	metformin (Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet), repaglinide (Prandin), miglitol (Glyset), pioglitazone (Actos), rosiglitazone (Avandia), sitagliptin (Januvia), glimepiride (Amaryl), glyburide (Diabeta, Glynase), glipizide (Glucotrol Glucotrol XL), dapagliflozin (Farxiga), canagliflozin (Invokana), insulin (NovoLIN, HumuLIN, HumaLOG Mix, NovoLOG, HumaLOG, Admelog, Fiasp, HumuLIN R, NovoLIN R, LEVEMIR, LANTUS, Basaglar), combination of drugs (Glucovance, ActoPlus Met, Avandamet, Avandaryl, Duetact, Invokamet, Janumet, Jentadueto, Kazano, Kombiglyze, Metaglip, PrandiMet, Xigduo XR)
Ischemic Stroke	I63.02, I63.6, I63.49, I63.00, I63.29, I63.19, I63.30, I63.40, I63.59, I63.12, I63.39, I63.9, I63.50, I63.8, I63.22, I63.20, I63.10, I63.09	aspirin, dipyridamole, clopidogrel, rivaroxaban, apixaban, atorvastatin (Lipitor), fluvastatin (Lescol, Lescol XL), lovastatin (Mevacor, Altoprev), pravastatin (Pravachol), rosuvastatin (Crestor), simvastatin (Zocor), pitavastatin (Livalo)
Atrial Fibrillation	I48*	metoprolol (Toprol XL, Lopressor), atenolol (Tenormin), diltiazem (Cartia XT, Tiazac, DILT-XR), verapamil (Verelan, Verelan PM, Calan SR), sotalol (Sotalol AF, Betapace, Sotylize), amiodarone (Pacerone, Nexterone), apixaban (Eliquis), rivaroxaban (Xarelto), warfarin (Jantoven, Coumadin), heparin, aspirin
Myocardial Infarction	I21*, I22*	morphine (Arymo ER, MorphaBond ER, MS Contin), nitroglycerin (Rectiv, Nitro-Time, Nitrolingual), isosorbide dinitrate (Isordil, Sorbitrate), isosorbide mononitrate (Imdur, Monoket, ISMO), clopidogrel (Plavix), eptifibatide (Integrilin), bivalirudin (Angiomax), carvedilol (Coreg), bisoprolol (Monocor, Zebeta), metoprolol (Toprol XL, Lopressor), nifediopine (Procardia XL, Adalat CC, Afeditab CR), atorvastatin (Lipitor), rosuvastatin (Crestor), lisinopril (Qbrelis, Prinivil, Zestril), captopril (Capoten), tPA, alteplase (Activase, Cathflo Activase), heparin, aspirin
Depression	F32*, F33*	fluoxatine (Prozac Weekly, Sarafem, Prozac), escitalopram (Lexapro), citalopram (Celexa), fluvoxamine (Luvox, Fevarin), paroxetine (Paxil,

		Pexeva, Paxil CR), sertraline (Zoloft), duloxetine (Irenka, Cymbalta), desvenlafaxine (Khedezla, Pristiq), venlafaxine (Effexor XR), trazodone (Desyrel, Desyrel Dividose, Oleptro, Trazodone D), bupropion (Wellbutrin XL, Wellbutrin SR, Forfivo XL), amitriptyline (Elavil), nortriptyline (Pamelor), imipramine (Tofranil), mirtazapine (Remeronsoltab, Remeron)
[%] The ascertainment of MCI or dementia is already described in the main text. [^] ICD-9 code was also included into the search, which was converted from ICD-10 code. [*] means followed by any sub-code. For example, E11* can be E11.0 or E11.00, etc.		

Table S2. Regular expressions used to ascertain ischemic stroke from imaging reports.

Pattern	**Regular expression (case insensitive)**
Is a brain-related report?	((MRI|MRA|MR ANGIO|CT|CTA|CT ANGIO)\s*(of)*\s*(the)*\s*(brw|brain|brn|neck|head|hed)|(brw|brain|brn|neck|head|hed)\s*(of)*\s*(the)*\s*(MRI|MRA|MR ANGIO|CT|CTA|CT ANGIO))
Ischemic stroke	(cereb\S*vasc\S*\sacciden\S*|CVA) | (cerebral\s*arter\S*|.CA)\s*(infact\S*|territ\S*|distribut\S*|strok\S*) | (cereb\S*|ischem\S*|chron\S*|acut\S*|emboli\S*|lacun\S*|remot\S*|territ\S*|smal\S*|punct\S*|capsul\S*)\s*(infarct\S*|strok\S*) | encephalomalac\S* | (hyper|hypo)(int|d)ensit\S*
Negation	(no|not|without|negative)(\s+[^\s.;]*){0,8} before the regular expression of ischemic stroke