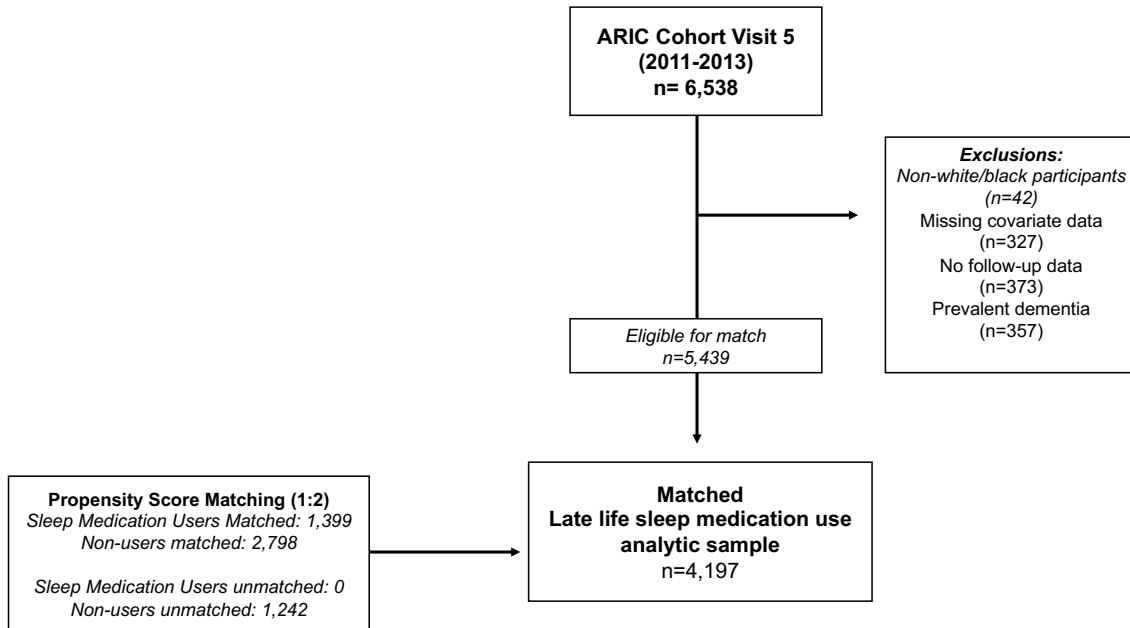**Associations of late-life sleep medication use with incident dementia in the Atherosclerosis Risk in Communities (ARIC) Study**

Supplemental Materials

Table of Contents:

Supplemental Figure 1. Atherosclerosis Risk in Communities (ARIC) Study: Late-life sleep medication use analytic sample flow chart

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                        ┌──────────────────────────┐
                        │   ARIC Cohort Visit 5    │
                        │       (2011-2013)        │
                        │       n= 6,538           │
                        └──────────────────────────┘
                                    │
                                    │              ┌──────────────────────────────┐
                                    │              │        Exclusions:           │
                                    │─────────────▶│  Non-white/black participants│
                                    │              │           (n=42)             │
                                    │              │    Missing covariate data    │
                                    │              │           (n=327)            │
                                    │              │      No follow-up data       │
                                    │              │           (n=373)            │
                                    │              │      Prevalent dementia       │
                        ┌──────────────────────┐   │           (n=357)            │
                        │  Eligible for match  │   └──────────────────────────────┘
                        │      n=5,439         │
                        └──────────────────────┘
                                    │
                                    ▼
┌──────────────────────────────┐   ┌──────────────────────────────┐
│ Propensity Score Matching    │   │          Matched             │
│          (1:2)               │   │  Late life sleep medication  │
│ Sleep Medication Users       │──▶│       use analytic sample    │
│   Matched: 1,399             │   │          n=4,197             │
│ Non-users matched: 2,798     │   └──────────────────────────────┘
│                              │
│ Sleep Medication Users       │
│   unmatched: 0               │
│ Non-users unmatched: 1,242   │
└──────────────────────────────┘
```

Supplemental Table 1. Medications included in sleep medication definition by medication class

Barbiturates (n=17)	N (%)*	Benzodiazepine Derivatives (n=448)	N (%)*	Antidepressants	N (%)*†	Hypnotics (n=242)	N (%)*	Non-benzodiazepine sedatives (Z-drugs) (n=149)	N (%)*
				non-SSRIs (n=367)					
Xanthines *Aminophylline, Dyphylline, Theophylline, Theophylline in Dextrose*	9 (53%)	**Benzodiazepines** *Alprazolam, Chlordiazepoxide, Clorazepate Dipotassium, Diazepam, Lorazepam, Oxazepam, Prazepam*	327 (73%)	**Monoamine Oxidase Inhibitors (MAOIs)** *Isocarboxazide, Phenelzine Sulfate, Selegiline, Tranylcypromine Sulfate*	1 (0.3%)	**Non-Barbiturate Hypnotics** *Chloral Hydrate, Paraldehyde*	0 (0%)	**Non-Benzodiazepine - GABA-Receptor Modulators** *Zolpidem Tartrate, Eszopiclone, Zaleplon*	149 (100%)
Xanthine-Expectorants *Dyphylline-Guaifenesin, Theophylline-Guaifenesin, Theophylline Sodium*	1 (5.9%)	**Benzodiazepine Hypnotics** *Estazolam, Flurazepam, Midazolam, Quazepam, Temazepam, Triazolam*	34 (7.6%)	**Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)** *Desvenlafaxine Succinate, Duloxetine HCl, Venlafaxine HCl*	98 (26.7%)	**Antihistamine Hypnotics** *Doxylamine Succinate, Diphenhydramine HCl*	46 (19.0%)	**Zolpidem & Dietary Management Product**	0 (0%)
Xanthine-Sympathomimetics-Expectorant *Theophylline-PSE-GG*	0 (0%)	**Anticonvulsants - Benzodiazepines** *Clonazepam, Diazepam (Anticonvulsant)*	86 (19.2%)	**Tricyclic Agents** *Amitriptyline HCl, Amoxapine, Clomipramine HCl, Desipramine HCl, Doxepin HCl, Imipramine HCl, Imipramine Pamoate, Nortriptyline HCl, Protriptyline HCl*	144 (39.2)	**Antihistamine Hypnotic Combinations** *Diphenhydramine – APAP, Ibuprofen Diphenhydramine Citrate, Ibuprofen-Diphenhydramine HCl*	196 (81.0%)		
Xanthine-Nutritional Supplement Combinations	0 (0%)	**Benzodiazepine-Nutritional Combination** *Alprazolam-Dietary, Diazepam-Dietary, Temazepam-Dietary*	0 (0%)	**Tricyclic Agents-Nutritional Combination** *Amitriptyline HCl - Dietary*	0 (0%)	**Hypnotic Tricyclic Agents Combinations** *Doxepin HCl (sleep)*	0 (0%)		
Barbiturate Hypnotics *Amobarbital Sodium, Butabarbital Sodium, Mephobarbital, Pentobarbital, Phenobarbital, Phenobarbital, Secobarbital Sodium*	7 (41.2%)	**Benzodiazepines & Tricyclic Agents** *Chlordiazepoxide-Amitriptyline*	1 (0.2%)	**Tetracyclics & Other Antidepressants** *Mirtazapine (25), Maprotiline HCl (0), Bupropion HCl (47), Bupropion Hydrobromide (0), Trazodone HCl (90)*	153 (41.7%)				
				Antidepressant-Nutritional Combinations *Trazodone- Dietary (4)*	4 (1.0%)				
				Selective Serotonin Reuptake Inhibitors (SSRIs) n=505	**N*†**				
				Citalopram Hydrobromide (158), Escitalopram Oxalate (61), Fluoxetine HCl (66), Fluvoxamine Maleate (0), Paroxetine HCl (66), Sertraline HCl (156)	506 (100%)				

*Percentages calculated within drug class.
†numbers do not sum to total N for medication class due to individuals taking more than 1 medication

Supplemental Table 2. ARIC Participant characteristics of pre-match and matched samples

	Pre-matched Sample (n=5439)		Matched Sample (n=4197)	
	Non-users (n=4040)	Sleep Medication users (n=1399)	Non-users (n=2798)	Sleep Medication users (n=1399)
Demographics				
Baseline age, years	75.3 ± 5.0	75.2 ± 5.0	75.3 ± 5.0	75.2 ± 5.0
Female, n (%)	2234 (55.3)	990 (70.8)	1972 (70.5)	990 (70.8)
White, n (%)	3073 (76.1)	1190 (85.1)	2325 (83.1)	1190 (85.1)
Education Level, n (%)				
< high school	528 (13.1)	180 (12.9)	400 (14.3)	180 (12.9)
high school graduate	1672 (41.4)	631 (45.1)	1179 (42.1)	631 (45.1)
> high school graduate	1840 (45.5)	588 (42.0)	1219 (43.6)	588 (42.0)
APOE ε4, n (%)	1106 (27.4)	349 (24.9)	734 (26.2)	349 (24.9)
Lifestyle + Health Status Characteristics				
Current Smoker, n (%)	232 (5.7)	99 (7.1)	160 (5.7)	99 (7.1)
Current Alcohol consumption, n (%)	2036 (50.4)	670 (47.9)	1432 (51.2)	670 (47.9)
Depression (CES-D Score ≥9), n (%)	186 (4.6)	157 (11.2)	131 (4.7)	157 (11.2)
BMI, kg/m^2	28.8 ± 5.6	28.9 ± 5.9	28.6 ± 5.7	28.9 ± 5.9
Cardiovascular Risk Factors				
Systolic BP, mmHg	130.0 ± 17.9	129 ± 18.0	130.0 ± 18.1	129 ± 18.0
Prevalent Diabetes, n (%)	1094 (27.1)	415 (29.7)	715 (25.6)	415 (29.7)
Prevalent CHD, n (%)	619 (15.3)	230 (16.4)	370 (13.2)	230 (16.4)
Anti-hypertensive Medication use, n (%)	2975 (73.6)	1084 (77.5)	1990 (71.1)	1084 (77.5)

Presented as mean ± SD unless otherwise noted

Supplemental Table 3. Late-life sleep medication use and risk of dementia, excluding individuals with dementia within 1 year (N=4,162)*

	Matched Non-Users (n=2,783)	Sleep Medication Users (n=1,379)
Incident Dementia, n	352	245
Model[†]	Hazard Ratio (95% Confidence Intervals)	
Model 1	(reference)	**1.48 (1.26, 1.74)**
Model 2	(reference)	**1.54 (1.31, 1.81)**
Model 3	(reference)	**1.45 (1.23, 1.71)**
Model 4	(reference)	**1.44 (1.22, 1.70)**

* Matched sample 2:1
[†] Model Adjustments: Model 1: Crude unadjusted; Model 2: Adjusted for age, sex, race-center, education, and APOE; Model 3: Model 2 + adjustment for smoking status, alcohol consumption, depression, and BMI; Model 4: Model 3 + adjustment for systolic blood pressure, anti-hypertensive medications, prevalent diabetes and prevalent CHD

Supplemental Table 4. Late-life sleep medication use and risk of dementia in sample matched on all covariates

	Matched Non-Users (n=2,798)	Sleep Medication Users (n=1,399)
Incident Dementia, n	388	265
Cumulative Incidence	*13.9%*	*18.9%*
Incidence Rate, per 100 person-yrs	*2.25*	*3.17*
Model[†]	Hazard Ratio (95% Confidence Intervals)	
Model 1	(reference)	**1.43 (1.22, 1.67)**
Model 2	(reference)	**1.59 (1.36, 1.86)**
Model 3	(reference)	**1.47 (1.25, 1.72)**
Model 4	(reference)	**1.45 (1.24, 1.70)**

*Matched sample 2:1

Model Adjustments: Model 1: Crude unadjusted; Model 2: Adjusted for age, sex, race-center, education and APOE; Model 3: Model 2 + adjustment for smoking status, alcohol consumption, depression, and BMI; Model 4: Model 3 + adjustment for systolic blood pressure, anti-hypertensive medications, prevalent diabetes, and prevalent CHD