

SUPPLEMENTAL MATERIAL

Table S1. ICD-9 codes or procedure code used to define cardiovascular diseases.

cardiovascular disease	2015 ICD-9-CM Diagnosis Codes
Myocardial infarction	410
Angina	411, 413
Other forms of chronic ischemic heart disease	414.0, 414.8, 414.9
Coronary artery bypass grafting	36.1 (2015 ICD-9-CM Procedure Codes)
Percutaneous coronary intervention	36.0 (2015 ICD-9-CM Procedure Codes)
Atrial fibrillation	427.3
Heart failure	428
Ischemic stroke	433, 434, 436
Hemorrhagic stroke	431,432
Subarachnoid hemorrhage	430
Other or unspecified stroke	435

Table S2. Restless legs syndrome treatment.

DRUG NAME	GROUP
Acetaminophen/codeine Phosphate	Opiates
Acetaminophen/hydrocodone Bitartrate	Opiates
Acetaminophen/oxycodone Hydrochloride	Opiates
Aspirin/oxycodone Hydrochloride	Opiates
Codeine Phos/dexbrompheniramine Maleate/pse Hcl	Opiates
Codeine Phos/dexchlorpheniramine Mal/phenyleph Hcl	Opiates
Codeine Phos/gg/pse Hcl	Opiates
Codeine Phos/phenyleph Hcl/promethazine Hcl	Opiates
Codeine Phos/phenyleph Hcl/pyril Mal	Opiates
Codeine Phosphate/guaifenesin	Opiates
Codeine Phosphate/phenylephrine Hydrochloride	Opiates
Codeine Phosphate/promethazine Hydrochloride	Opiates
Codeine Phosphate/pseudoephedrine Hydrochloride	Opiates
Codeine Sulfate	Opiates
Hydrocodone Bitartrate	Opiates
Hydrocodone Bitartrate/ibuprofen	Opiates
Hydrocodone Bitartrate/phenylephrine Hydrochloride	Opiates
Hydrocodone Bitartrate/potassium Guaiacolsulfonate	Opiates
Hydrocodone Tannate/pseudoephedrine Tannate	Opiates
Methadone Hydrochloride	Opiates
Oxycodone Hydrochloride	Opiates
Clonazepam	Benzodiazepines
Diazepam; lubricant	Benzodiazepines
Gabapentin	Anticonvulsants

Gabapentin Enacarbil	Anticonvulsants
Gabapentin; gabapentin	Anticonvulsants
Pregabalin	Anticonvulsants
Pramipexole Dihydrochloride	Dopaminergic
Ropinirole Hcl; ropinirole Hcl; ropinirole HclPregabalin	Dopaminergic
Ropinirole Hydrochloride Ropinirole Hcl; ropinirole Hcl; ropinirole Hcl	Dopaminergic
RotigotineRopinirole Hydrochloride	Dopaminergic
Rotigotine	Dopaminergic
Pergolide (Permax)	Ergot-dopamine
bromocriptine (Parlodel)	Ergot-dopamine
cabergoline (Dostinex)	Ergot-dopamine

Table S3. Hazard ratios (HRs) for the future development of different cardiovascular diseases (CVDs) when the RLS with treatment group and the RLS without treatment group were each individually compared to the group with no RLS.

Individual cardiovascular disease	No RLS	RLS with treatment	RLS without treatment
Myocardial infarction	1 (Ref.)	1.25(1.05, 1.50)*	1.32(0.97, 1.79)
Angina	1 (Ref.)	1.43(1.30, 1.58)***	1.45(1.23, 1.71)***
Other forms of chronic ischemic heart disease	1 (Ref.)	1.35(1.25, 1.46) ***	1.57(1.38, 1.77) ***
Coronary artery bypass grafting	1 (Ref.)	1.25(1.06, 1.48)**	1.45(1.11, 1.89)**
Coronary Artery disease	1 (Ref.)	1.35(1.25, 1.46) ***	1.57(1.38, 1.77) ***
Percutaneous coronary intervention	1 (Ref.)	1.17(0.86, 1.60)	0.56 (0.28, 1.15)
Atrial fibrillation	1 (Ref.)	1.17(1.03, 1.32)*	1.88(1.58, 2.25)***
Heart failure	1 (Ref.)	1.46(1.29, 1.65) ***	1.90(1.57, 2.31) ***
Ischemic stroke	1 (Ref.)	1.26(1.14, 1.38) ***	1.39(1.19, 1.62) ***
Hemorrhagic stroke	1 (Ref.)	0.98(0.69, 1.38)	1.10(0.63, 1.91)
Subarachnoid hemorrhage	1 (Ref.)	1.48(0.92, 2.38)	1.74(0.83, 3.67)
Other or unspecified stroke	1 (Ref.)	1.51(1.32, 1.72) ***	1.77(1.44, 2.18) ***

adjusted for age, sex, residence (rural vs Urban), region (east, south, Midwest, and unknown), alcohol consumption, presence of obesity, COPD, diabetes, hypertension, hyperlipidemia, sleep Apnea, depression, insomnia, peripheral neuropathy, Rheumatic arthritics, Osteoarthritis, CKD, Iron deficiency anemia, or Parkinson disease (each, yes/no), and use of antiplatelets, anticoagulants, statins, antihypertensives and hypoglycemic treatment (each, yes/no).

* P<0.05 ** P<0.01 *** P<0.001, relative to No RLS

Restless legs syndrome, RLS; Chronic kidney disease, CKD; Chronic obstructive pulmonary disease, COPD; cardiovascular disease, CVD

Table S4. HRs for the development of future CVD when the RLS with treatment group and the RLS without treatment group were each individually compared to the group with no RLS stratified by sex.

	No RLS	RLS with treatment	RLS without treatment	P-interaction
Sex				0.04
Men	1(ref)	1.22 (1.12, 1.32)*	1.37 (1.21, 1.55)*	
Women	1(ref)	1.29 (1.21, 1.36)*	1.64 (1.50, 1.80)*	

adjusted for age (y), residence (rural vs Urban), region (east, south, Midwest, and unknown), alcohol consumption, presence of obesity, COPD, diabetes, hypertension, hyperlipidemia, sleep Apnea, depression, insomnia, peripheral neuropathy, Rheumatic arthritics, Osteoarthritis, CKD, Iron deficiency anemia, or Parkinson disease (each, yes/no), and use of antiplatelets, anticoagulants, statins, antihypertensives and hypoglycemic treatment (each, yes/no).

* P<0.001, relative to the No RLS group

Restless legs syndrome, RLS; Chronic kidney disease, CKD; Chronic obstructive pulmonary disease, COPD; cardiovascular disease, CVD