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Supplemental methods

Collection of data

The data from the UK Biobank consortium are available online (URL: <https://www.ukbiobank.ac.uk/data-showcase/>), and the information is identified by field IDs. We used the self-reported duration of sleep in hours to determine sleep exposure (Field ID 1160). Baseline eGFR values were calculated from the information of serum creatinine levels (Field ID 30700) and ethnicity (Field ID 21000). Age was determined by subtracting years of initial assessment center (Field ID 53) visit with years of birth (Field ID 34). Raw data for the following information provided by the UK Biobank were collected: sex (Field ID 31), smoking history (Field ID 20116, missing N = 1687), body mass index (Field ID 21,001, missing N = 1795), waist circumference (Field ID 48, missing N = 954), total cholesterol (Field ID 30690, missing N = 140), HDL cholesterol (Field ID 30760, missing N = 39,456), LDL cholesterol (Field ID 30780, missing N = 916), and self-reported frequency of moderate physical activity per week (Field ID 884, missing N = 23,196). A history of cardiovascular disease was identified by angina, stroke or heart attack diagnosed by a doctor (Field ID 6150, missing N = 1008). Hypertension was determined when people reported a history of treatment with hypertension medication (Field ID 6177 and 6153, missing N = 3342). A history of diabetes mellitus was collected by self-report (Field ID 2443, missing N = 1378). Systolic and diastolic BP were determined by the average of two automated measurements (Field ID 4080 and 4079, missing N = 40,097 and 40,085, respectively), and those with a single missing measurement were considered missing. Self-reported naps during the day (rarely/never, sometimes, usually; Field ID 1190, missing N = 681) and snoring (Field ID 1210, missing N = 32,915) were collected. Spot urine microalbumin-to-creatinine ratios were calculated by dividing the microalbumin level (Field ID 30,500) by the urine creatinine value (Field ID 30,510), scaled to a mg/g unit. Those with < 6.7 mg/L of urine microalbumin, the low detection limit, were considered to have 6.7 mg/L of urine microalbumin (missing N = 13,175).

Adjusted variables for the multivariable models

The first multivariable model was a less stringent model, and we aimed to adjust variables potentially directly associated with sleeping habits: age, sex, smoking history, napping, and snoring. When analyzing incident ESKD outcome, baseline eGFR and urine microalbumin-to-creatinine ratio values were additionally adjusted to reflect baseline kidney function. The second multivariable model was adjusted for all clinical covariates that might be confounders or potential mediators to examine a direct association between sleep duration and outcomes. When analyzing incident ESKD, the number of adjusted variables was reduced to ensure sufficient statistical power, as the outcome was relatively rarer than CKD. Adjustment variables were selected based on clinical importance; we adjusted for age, sex,

previous major cardiovascular disease history (angina, heart attack, or stroke), hypertension, diabetes mellitus, body mass index, smoking history, baseline eGFR, urine microalbumin-to-creatinine ratios, nap habits, and self-reported snoring.

Supplemental Table 1. Genetic instruments implemented in the study and their association with each short sleep duration or long sleep duration phenotype identified by Hassan S Dashti et al.

Phenotype of the genetic instrument	SNP	Chr:position	Effect allele	Other allele	Effect allele frequency	Info	OR [95% CI]	P
Short sleep	rs2863957	2:114089551	C	A	0.782	1.00	1.056 [1.041-1.071]	2.60E-18
	rs13107325	4:103188709	T	C	0.075	1.00	1.078 [1.055-1.101]	2.50E-13
	rs1229762	7:114218582	T	C	0.665	1.00	1.038 [1.025-1.051]	1.10E-12
	rs1380703	2:57941287	G	A	0.384	0.96	1.036 [1.024-1.049]	1.60E-11
	rs12963463	18:53099093	C	T	0.299	0.97	1.029 [1.016-1.042]	1.90E-11
	rs75539574	2:58871658	A	C	0.915	0.98	1.046 [1.024-1.068]	8.40E-11
	rs17388803	15:48027204	C	A	0.106	0.96	1.054 [1.034-1.074]	6.50E-10
	rs4585442	5:135508381	G	A	0.311	1.00	1.031 [1.019-1.044]	8.10E-10
	rs1607227	11:28808617	G	T	0.705	0.99	1.031 [1.018-1.045]	1.50E-09
	rs2820313	1:201870221	G	A	0.341	1.00	1.031 [1.019-1.043]	2.30E-09
	rs17005118	4:82288564	A	G	0.265	1.00	1.03 [1.017-1.044]	2.50E-09
	rs5757675	22:39838892	G	T	0.260	0.99	1.035 [1.021-1.048]	2.70E-09
	rs12567114	1:98527951	G	A	0.725	0.99	1.037 [1.024-1.051]	4.10E-09
	rs142180737	6:28344731	C	T	0.009	0.86	1.167 [1.097-1.242]	4.40E-09
	rs2186122	1:66470206	T	A	0.562	0.99	1.024 [1.012-1.036]	4.80E-09
	rs11763750	7:2080114	G	A	0.814	1.00	1.036 [1.02-1.051]	5.10E-09
	rs12518468	5:7249696	C	T	0.328	0.99	1.032 [1.019-1.044]	8.50E-09
	rs9367621	6:55040290	T	A	0.431	1.00	1.024 [1.013-1.036]	1.60E-08
	rs3776864	5:102327868	A	C	0.667	1.00	1.032 [1.019-1.045]	1.70E-08
	rs60882754	8:52886619	A	T	0.939	1.00	1.057 [1.032-1.083]	1.80E-08
	rs59779556	16:56227965	T	G	0.554	1.00	1.025 [1.013-1.037]	2.00E-08
	rs2014830	3:50172397	C	T	0.698	0.99	1.03 [1.017-1.043]	2.70E-08
	rs205024	17:11227352	C	T	0.617	1.00	1.031 [1.018-1.043]	2.70E-08
	rs12661667	6:41792545	T	C	0.263	1.00	1.028 [1.015-1.042]	2.80E-08
rs7939345	11:47980568	T	G	0.208	1.00	1.036 [1.021-1.05]	4.00E-08	
rs9321171	6:129848635	C	T	0.540	0.99	1.032 [1.02-1.044]	4.20E-08	
rs7524118	1:34736052	C	T	0.708	1.00	1.03 [1.017-1.043]	4.90E-08	
Long sleep	rs6737318	2:114083120	G	A	0.222	0.99	1.079 [1.056-1.103]	3.40E-13
	rs75458655	11:118115331	T	C	0.023	1.00	1.203 [1.136-1.275]	5.40E-12
	rs17688916	17:43778680	T	A	0.796	0.96467	1.074 [1.048-1.1]	1.10E-11
	rs17817288	16:53807764	A	G	0.518	1.00	1.04 [1.021-1.059]	8.90E-09
	rs549961083	5:58184093	T	C	0.001	0.868466	1.705 [1.357-2.143]	9.60E-09
	rs3751046	11:122828342	G	A	0.147	0.99	1.072 [1.044-1.099]	2.00E-08
	rs7534398	1:7767464	A	T	0.201	0.99	1.048 [1.024-1.072]	2.10E-08
	rs10899257	11:76415209	A	G	0.144	1.00	1.07 [1.043-1.098]	4.60E-08

Reference: Dashti HS, Jones SE, Wood AR, et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. Nat Commun. 2019;10:1100.

Supplemental Table 2. Clinical analysis results with the multivariable models constructed by the complete-case method.

Subjects, outcomes and exposures	Multivariable model 1 ^b		Multivariable model 2 ^c	
	OR or HR (95% CI)	P	Adjusted OR or HR (95% CI)	P
Total participants^a				
CKD stage 3-5				
Short sleep (< 6 hrs)	1.25 (1.15-1.36)	< 0.001	1.05 (0.94-1.16)	0.42
Long sleep (≥ 9 hrs)	1.51 (1.42-1.60)	< 0.001	1.33 (1.24-1.44)	< 0.001
CKD with eGFR ≥ 45				
Short sleep (< 6 hrs)	1.18 (1.07-1.30)	0.001	1.01 (0.90-1.13)	0.88
Long sleep (≥ 9 hrs)	1.42 (1.33-1.52)	< 0.001	1.27 (1.17-1.37)	< 0.001
Incident ESKD				
Short sleep (< 6 hrs)	1.58 (0.94-2.63)	0.08	1.51 (0.90-2.53)	0.12
Long sleep (≥ 9 hrs)	1.42 (0.98-2.07)	0.07	1.29 (0.89-1.89)	0.18
Male participants^a				
CKD stage 3-5				
Short sleep (< 6 hrs)	1.35 (1.19-1.53)	< 0.001	1.21 (1.04-1.40)	0.01
Long sleep (≥ 9 hrs)	1.52 (1.39-1.65)	< 0.001	1.32 (1.19-1.46)	< 0.001
CKD with eGFR ≥ 45				
Short sleep (< 6 hrs)	1.27 (1.11-1.47)	0.001	1.17 (0.99-1.38)	0.07
Long sleep (≥ 9 hrs)	1.43 (1.30-1.57)	< 0.001	1.28 (1.14-1.44)	< 0.001
Incident ESKD				
Short sleep (< 6 hrs)	2.10 (1.18-3.73)	0.01	2.02 (1.13-3.62)	0.02
Long sleep (≥ 9 hrs)	1.66 (1.06-2.62)	0.03	1.50 (0.95-2.37)	0.08
Female participants^a				
CKD stage 3-5				
Short sleep (< 6 hrs)	1.18 (1.05-1.32)	0.004	0.97 (0.85-1.12)	0.71
Long sleep (≥ 9 hrs)	1.49 (1.38-1.62)	< 0.001	1.32 (1.19-1.46)	< 0.001
CKD with eGFR ≥ 45				
Short sleep (< 6 hrs)	1.12 (0.99-1.26)	0.08	0.93 (0.80-1.09)	0.37
Long sleep (≥ 9 hrs)	1.40 (1.28-1.54)	< 0.001	1.23 (1.10-1.38)	< 0.001
Incident ESKD				
Short sleep (< 6 hrs)	0.86 (0.27-2.75)	0.80	0.81 (0.25-2.60)	0.72
Long sleep (≥ 9 hrs)	1.17 (0.58-2.32)	0.66	1.09 (0.54-2.18)	0.81

OR = odds ratio, HR = hazard ratio, CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESKD = end-stage kidney disease

^aAs the analysis was performed by the complete-case method, those with missing covariates were not included. The number of subjects (cases) was 430,998 (10,140 CKD stage 3-5 cases), including 200,232 (5318 CKD stage 3-5 cases) males and 230,766 (4822 CKD stage 3-5 cases) females for multivariable model 1. The number of subjects (cases) was 321,493 (7211 CKD stage 3-5 cases), including 152,370 (3539 CKD stage 3-5 cases) males and 169,123 (3672 CKD stage 3-5 cases) females for multivariable model 2. A total of 530 and 378 subjects with baseline eGFR < 15 mL/min/1.73 m² or prevalent ESKD history were not included when analyzing incident ESKD outcome by multivariable models 1 and 2, respectively.

^bMultivariable model 1 for CKD outcome was adjusted for age, sex, smoking history (nonsmoker, ex-smoker, current-smoker), habitual naps (never/rarely, sometimes, usually), or snoring. When analyzing incident ESKD outcome, baseline eGFR and the urine microalbumin-to-creatinine ratio were added to the model.

^cMultivariable model 2 for CKD outcome was adjusted for age, sex, body mass index, waist circumference, smoking history (nonsmoker, ex-smoker, current-smoker), frequency of moderate physical activity per week (days), previous history of cardiovascular disease (angina, heart attack or stroke), hypertension, systolic BP, diastolic BP, diabetes mellitus, hemoglobin A1c, total cholesterol, low-density lipoprotein, and high-density lipoprotein levels, as well as self-reported habitual naps (never/rarely, sometimes, usually) or snoring. When analyzing incident ESKD outcome, age, sex, baseline eGFR, urine microalbumin-creatinine ratio, body mass index, smoking history, history of cardiovascular disease, hypertension, diabetes mellitus, and habitual naps or snoring were adjusted for the multivariable model.

Supplemental Table 3. Association between the SNPs included in the genetic instruments and possible major confounders.

Phenotype of the genetic instrument	SNP	Effect allele	Diabetes mellitus			Hypertension			Obesity			Current smoking			Lowest P
			Beta	Standard error	P	Beta	Standard error	P	Beta	Standard error	P	Beta	Standard error	P	
Short sleep	rs13107325	T	0.085	0.021	5.751E-05	-0.064	0.012	1.327E-07	0.090	0.011	4.289E-17	-0.046	0.016	3.399E-03	4.289E-17
	rs2820313	G	0.024	0.012	4.945E-02	0.023	0.007	5.143E-04	0.050	0.006	1.314E-16	0.026	0.009	2.478E-03	1.314E-16
	rs2014830	T	-0.073	0.013	9.305E-09	-0.026	0.007	1.343E-04	-0.043	0.006	9.324E-12	-0.013	0.009	1.536E-01	9.324E-12
	rs11763750	A	-0.060	0.015	6.444E-05	-0.048	0.008	5.374E-09	-0.045	0.007	1.500E-09	0.001	0.011	8.941E-01	1.500E-09
	rs142180737	C	0.126	0.061	3.795E-02	-0.007	0.035	8.316E-01	0.157	0.031	2.720E-07	0.081	0.043	6.245E-02	2.720E-07
	rs7939345	T	-0.009	0.014	5.363E-01	0.038	0.008	1.040E-06	-0.008	0.007	2.799E-01	0.028	0.010	4.757E-03	1.040E-06
	rs3776864	C	0.052	0.012	1.941E-05	0.002	0.007	7.161E-01	0.015	0.006	1.329E-02	0.013	0.009	1.293E-01	1.941E-05
	rs1229762	C	-0.022	0.012	7.028E-02	-0.012	0.007	7.869E-02	0.000	0.006	9.612E-01	-0.036	0.009	2.933E-05	2.933E-05
	rs2186122	A	-0.019	0.012	9.501E-02	-0.011	0.006	9.275E-02	-0.023	0.006	7.033E-05	-0.019	0.008	2.100E-02	7.033E-05
	rs1607227	T	-0.010	0.013	4.526E-01	-0.014	0.007	3.858E-02	-0.023	0.006	2.716E-04	-0.012	0.009	1.977E-01	2.716E-04
	rs1380703	G	-0.005	0.012	6.626E-01	0.015	0.007	2.159E-02	0.019	0.006	1.161E-03	-0.006	0.009	4.627E-01	1.161E-03
	rs2863957	A	0.011	0.014	4.134E-01	-0.024	0.008	1.540E-03	0.001	0.007	8.763E-01	0.001	0.010	9.104E-01	1.540E-03
	rs75539574	C	0.029	0.020	1.572E-01	0.018	0.011	1.161E-01	0.022	0.010	3.266E-02	0.017	0.015	2.438E-01	3.266E-02
	rs12518468	C	-0.025	0.012	4.235E-02	-0.005	0.007	4.708E-01	-0.006	0.006	3.131E-01	0.017	0.009	4.591E-02	4.235E-02
	rs12661667	T	-0.027	0.013	4.297E-02	0.000	0.007	9.764E-01	-0.001	0.006	8.295E-01	-0.018	0.009	5.134E-02	4.297E-02
	rs5757675	G	0.008	0.013	5.276E-01	0.014	0.007	4.551E-02	0.001	0.007	8.760E-01	0.013	0.009	1.743E-01	4.551E-02
	rs59779556	G	-0.019	0.012	1.002E-01	0.001	0.006	8.487E-01	-0.010	0.006	6.928E-02	0.012	0.008	1.282E-01	6.928E-02
	rs7524118	T	-0.023	0.013	7.480E-02	-0.003	0.007	6.944E-01	-0.007	0.006	2.655E-01	-0.011	0.009	1.996E-01	7.480E-02
	rs12963463	C	-0.023	0.013	7.679E-02	0.008	0.007	2.339E-01	0.006	0.006	3.375E-01	0.009	0.009	3.093E-01	7.679E-02
	rs12567114	A	-0.022	0.013	8.955E-02	-0.001	0.007	9.085E-01	-0.003	0.006	6.534E-01	-0.009	0.009	3.514E-01	8.955E-02
	rs60882754	T	0.008	0.024	7.503E-01	-0.005	0.013	6.872E-01	0.019	0.012	1.168E-01	-0.005	0.017	7.748E-01	1.168E-01
	rs17388803	C	0.005	0.019	8.019E-01	-0.016	0.010	1.311E-01	0.001	0.010	8.765E-01	0.011	0.014	4.149E-01	1.311E-01
	rs9367621	T	-0.016	0.012	1.630E-01	0.004	0.006	4.956E-01	-0.007	0.006	2.031E-01	0.001	0.008	8.943E-01	1.630E-01
	rs205024	T	-0.015	0.012	1.958E-01	0.003	0.006	6.203E-01	-0.002	0.006	6.764E-01	0.011	0.008	1.805E-01	1.805E-01
	rs4585442	G	0.009	0.012	4.917E-01	0.009	0.007	2.076E-01	-0.007	0.006	2.713E-01	-0.001	0.009	8.825E-01	2.076E-01
	rs9321171	T	0.010	0.012	3.725E-01	-0.005	0.006	4.504E-01	-0.002	0.006	6.658E-01	-0.004	0.008	6.101E-01	3.725E-01
rs17005118	A	0.002	0.013	9.065E-01	-0.002	0.007	8.125E-01	0.000	0.006	9.392E-01	0.007	0.009	4.447E-01	4.447E-01	
Long sleep	rs17817288	G	0.090	0.011	6.869E-15	0.040	0.006	2.145E-10	0.117	0.006	1.109E-93	0.005	0.008	5.213E-01	1.109E-93
	rs17688916	A	-0.005	0.014	7.549E-01	-0.035	0.008	1.076E-05	0.009	0.007	2.318E-01	-0.023	0.010	2.806E-02	1.076E-05
	rs6737318	G	0.012	0.014	3.816E-01	-0.024	0.008	1.534E-03	0.001	0.007	8.760E-01	0.001	0.010	9.096E-01	1.534E-03
	rs10899257	A	-0.044	0.017	8.623E-03	0.011	0.009	2.334E-01	-0.004	0.008	5.885E-01	-0.004	0.012	7.550E-01	8.623E-03
	rs75458655	T	0.020	0.038	6.109E-01	0.026	0.021	2.199E-01	0.006	0.019	7.368E-01	0.042	0.027	1.199E-01	1.199E-01
	rs549961083	T	0.145	0.152	3.413E-01	0.106	0.086	2.182E-01	-0.070	0.081	3.910E-01	0.032	0.111	7.763E-01	2.182E-01
	rs7534398	A	0.000	0.014	9.966E-01	0.004	0.008	5.738E-01	0.008	0.007	2.560E-01	-0.001	0.010	8.888E-01	2.560E-01
rs3751046	G	0.017	0.016	2.896E-01	0.001	0.009	8.865E-01	0.000	0.008	9.614E-01	0.012	0.012	2.776E-01	2.776E-01	

GWAS was performed with the SNPs included in the genetic instrument for diabetes, hypertension, obesity, and current smoking by logistic regression analysis adjusted for age, sex, and the first 20 principal components of the genetic information. The SNPs that reached genome-wide significance ($P < 5 \times 10^{-8}$) were excluded from the genetic instrument in the sensitivity analysis, and the SNPs are highlighted in color.

Supplemental Table 4. Association between CKD stages 3-5 and SNPs included in the genetic instruments.

Phenotype of the genetic instrument	SNP	Effect allele	Other allele	Beta	Standard error	P
Short sleep	rs7524118	T	C	-0.022	0.018	0.218
	rs2186122	A	T	-0.014	0.017	0.399
	rs12567114	A	G	-0.014	0.019	0.455
	rs2820313	G	A	-0.002	0.017	0.887
	rs1380703	G	A	0.010	0.017	0.568
	rs75539574	C	A	-0.007	0.030	0.826
	rs2863957	A	C	-0.002	0.020	0.929
	rs2014830	T	C	-0.035	0.018	0.052
	rs17005118	A	G	-0.034	0.019	0.072
	rs13107325	T	C	0.024	0.031	0.434
	rs12518468	C	T	-0.019	0.018	0.280
	rs3776864	C	A	-0.019	0.018	0.289
	rs4585442	G	A	0.018	0.018	0.318
	rs142180737	C	T	0.058	0.090	0.522
	rs12661667	T	C	0.007	0.019	0.719
	rs9367621	T	A	0.025	0.017	0.131
	rs9321171	T	C	0.024	0.017	0.142
	rs11763750	A	G	0.013	0.021	0.550
	rs1229762	C	T	-0.013	0.017	0.453
	rs60882754	T	A	-0.026	0.035	0.461
	rs1607227	T	G	-0.024	0.018	0.182
	rs7939345	T	G	0.036	0.020	0.076
	rs17388803	C	A	0.052	0.027	0.052
	rs59779556	G	T	-0.034	0.017	0.040
	rs205024	T	C	-0.031	0.017	0.068
	rs12963463	C	T	0.011	0.018	0.539
	rs5757675	G	T	0.001	0.019	0.963
	Long sleep	rs10899257	A	G	0.051	0.023
rs17688916		A	T	0.011	0.021	0.593
rs17817288		G	A	0.006	0.016	0.720
rs3751046		G	A	0.003	0.023	0.895
rs549961083		T	C	-0.053	0.236	0.823
rs6737318		G	A	-0.004	0.020	0.836
rs7534398		A	T	0.012	0.021	0.565
rs75458655		T	C	0.015	0.055	0.783

GWAS was performed with the SNPs included in the genetic instrument for CKD stage 3-5 outcome, adjusted for age, sex, and the first 20 principal components of the genetic information.

Supplemental Table 5. Leave-one-out analysis results of the two-sample MR analysis.

Phenotype of the genetic instrument	SNP	Inverse variance weighted			MR-Egger		
		Beta	Standard error	P	Beta	Standard error	P
Short sleep	rs11763750	0.093	0.045	0.037	0.550	0.219	0.020
	rs1229762	0.101	0.045	0.025	0.558	0.219	0.018
	rs12518468	0.118	0.045	0.009	0.530	0.206	0.017
	rs12567114	0.094	0.045	0.037	0.549	0.219	0.020
	rs12661667	0.114	0.044	0.010	0.506	0.212	0.026
	rs12963463	0.097	0.045	0.029	0.560	0.220	0.018
	rs13107325	0.083	0.045	0.064	0.530	0.244	0.041
	rs1380703	0.097	0.045	0.032	0.551	0.219	0.020
	rs142180737	0.073	0.045	0.102	0.365	0.243	0.147
	rs1607227	0.093	0.045	0.036	0.562	0.218	0.017
	rs17005118	0.095	0.045	0.033	0.562	0.219	0.018
	rs17388803	0.099	0.045	0.028	0.604	0.226	0.014
	rs2014830	0.119	0.045	0.008	0.510	0.205	0.021
	rs205024	0.105	0.045	0.019	0.544	0.219	0.021
	rs2820313	0.094	0.045	0.035	0.561	0.218	0.018
	rs2863957	0.091	0.046	0.049	0.622	0.244	0.018
	rs3776864	0.080	0.045	0.074	0.574	0.204	0.010
	rs4585442	0.092	0.045	0.040	0.565	0.217	0.016
	rs5757675	0.097	0.045	0.029	0.552	0.219	0.020
	rs59779556	0.095	0.044	0.032	0.593	0.222	0.014
	rs60882754	0.099	0.044	0.026	0.592	0.223	0.015
	rs7524118	0.103	0.045	0.021	0.546	0.220	0.021
	rs75539574	0.105	0.044	0.018	0.591	0.215	0.012
	rs7939345	0.070	0.045	0.115	0.537	0.187	0.009
rs9321171	0.102	0.045	0.024	0.550	0.219	0.020	
Long sleep	rs10899257	-0.058	0.055	0.287	-0.028	0.154	0.864
	rs17688916	-0.053	0.055	0.333	-0.019	0.155	0.906
	rs17817288	-0.054	0.053	0.313	-0.093	0.193	0.654
	rs3751046	-0.064	0.055	0.241	-0.033	0.154	0.840
	rs6737318	-0.046	0.059	0.431	0.000	0.162	0.999
	rs7534398	-0.081	0.053	0.122	0.034	0.159	0.840
	rs75458655	-0.076	0.054	0.160	-0.154	0.220	0.523

SNP = single nucleotide polymorphism.

The two-sample MR analysis was repeated by omitting each SNP from the genetic instrument for exposure by the fixed-effects inverse variance weighted method or by MR-Egger regression.

Supplemental Figure 1. General additive model plotting the U-shaped association between self-reported sleep duration and age-sex probabilities of prevalent CKD stages 3-5.

