NIGHTTIME BLOOD PRESSURE DIPPING IN YOUNG ADULTS AND CORONARY ARTERY CALCIUM 10-15 YEARS LATER: THE CARDIA STUDY

Short title: Nighttime BP and coronary artery calcium

ON-LINE SUPPLEMENT

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Methods Supplement

Measurement of Covariates

Education was determined by self-report of highest grade level achieved. Body mass index (BMI) was calculated based on measured height and weight at the baseline visit. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dl or use of hypoglycemic agents at baseline (CARDIA year 5). Family history of hypertension and family history of diabetes were determined by self-report. Current smoking, defined as regular cigarette smoking (at least five cigarettes a week almost every week for at least three months) was assessed by self-report. Additionally, serum cotinine, a biochemical marker of nicotine uptake, was measured at year 0.

High density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels were measured in a fasting serum sample at year 5. Physical activity was assessed by the CARDIA physical activity questionnaire, which measured the self-reported frequency of participation in 13 different categories of recreational sports and exercise in the past 12 months.[1] Physical activity scores were computed by multiplying the frequency of participation by the intensity of activity and reported as "exercise units."

[1] Jacobs DR, Hahn L, Haskell WL, Pirie P, Sidney S. Validity and reliability of short physical activity history: CARDIA Study and the Minnesota Heart Health Program. *J Cardiopulm Rehabil.* 1989;9:448-459.

Table S1. Participant Characteristics and their Association with Coronary Artery Calcification at Year 20 or Year 15

Characteristic	Year 20 (n=213)			Year 15 (n=26)		
	CAC	No CAC	p-value	CAC	No CAC	p-value
Age, mean (SD), y	31.9 (3.0)	30.0 (3.6)	<0.001	32.8 (2.6)	29.7 (3.6)	0.08
Male, %	59.2	39.0	0.01	100.0	52.4	0.05
Black, %	55.1	64.0	0.26	60.0	71.4	0.62
Education, mean (SD) years	13.3 (2.0)	13.7 (1.8)	0.15	14.2 (3.2)	13.3 (2.2)	0.45
BMI, mean (SD) kg/ m^2	27.9 (4.9)	26.3 (5.3)	0.07	25.2 (3.6)	26.1 (4.8)	0.71
Baseline smoker, %	53.1	18.3	<0.001	40.0	19.1	0.32
Serum cotinine level (ng/ml), mean (SD)	125.7 (153.7)	41.2 (107.5)	<0.001	198.4 (281.0)	55.7 (113.1)	0.32
High density lipoprotein (mg/dl), mean (SD)	49.0 (15.6)	51.2 (13.0)	0.32	39.6 (6.7)	53.0 (14.1)	0.05
Low density lipoprotein (mg/dl), mean (SD)	122.4 (31.3)	107.4 (28.1)	0.002	128.8 (31.3)	110.1 (24.3)	0.15
Known diabetes mellitus, %	6.1	0.6	0.01	20.0	0.0	0.04
Known hypertension, %	4.1	6.7	0.50	0.0	9.5	0.47
Glucose level (mg/dl) at year 7, mean (SD)	101.1 (41.7)	87.4 (9.0)	0.03	168.8 (180.3)	89.3 (6.8)	0.38
Baseline clinic SBP (mm Hg), mean (SD)	109.7 (10.0)	108.7 (10.0)	0.54	108.0 (6.7)	105.5 (11.3)	0.64
Baseline clinic DBP (mm Hg), mean (SD)	73.3 (9.2)	73.1 (9.6)	0.90	71.2 (5.9)	72.9 (9.3)	0.71
Clinic pulse pressure (mm Hg), mean (SD)	36.4 (8.1)	35.6 (7.7)	0.52	36.8 (7.5)	32.6 (7.6)	0.28

Pack-years of tobacco at year 5, mean (SD)	5.2 (7.0)	1.6 (4.1)	0.001	5.7 (7.8)	2.7 (5.2)	0.30
Alcohol intake (ML/day), mean (SD)	23.7 (30.0)	8.0 (15.1)	0.001	7.4 (14.0)	5.7 (11.0)	0.78
Physical activity (Kcal/d), mean (SD)	308.9 (274.9)	350.3 (283.8)	0.36	258.2 (156.8)	323.9 (222.8)	0.49
Family history of hypertension, %	69.4	60.4	0.26	20.0	42.9	0.35
Family history of diabetes, %	20.4	12.2	0.15	20.0	14.3	0.75
Poor sleep quality, %	10.2	20.1	0.11	20.0	9.5	0.51
Dipping quartile* at baseline, %						
Q1	36.7	22.6	0.004	60.0	9.5	0.07
Q2	16.3	29.3		20.0	28.6	
Q3	12.2	28.7		0.0	28.6	
Q4	34.7	19.5		20.0	33.3	

*Quartiles of mean nocturnal systolic BP/mean daytime systolic BP ratio: **Q1:** 0.7197-0.8454 (n=70); **Q2:** 0.8455-0.8809 (n=71); **Q3:** 0.8810-0.9203 (n=70); **Q4:** 0.9204-1.2358 (n=70)

SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitoring

Table S2. Characteristics of Participants at Time of CAC* Measurement by Dipping Ratio Quartiles (N=281)

Characteristic	Total	Q1: 0.72-0.85	Q2: 0.85 - 0.88	Q3: 0.88-0.92	Q4: 0.92-1.24	p-value
Age, mean (SD) years	45.0 (3.9)	45.8 (3.9)	44.2 (4.0)	44.8 (4.2)	45.2 (3.5)	0.17
BMI, mean (SD) kg/ m^2	30.3 (7.0)	29.2 (7.2)	30.5 (6.9)	30.4 (6.9)	31.2 (6.9)	0.47
Current smoker, %	17.8	15.7	15.5	10.0	30.0	0.01
Smoking cessation rate, %	12.5	17.1	9.9	10.0	12.9	0.52
Pack-years of tobacco, mean (SD)	4.5 (9.5)	5.9 (11.8)	4.1 (10.9)	2.9 (5.8)	5.0 (8.3)	0.28
High density lipoprotein cholesterol (mg/dl), mean (SD)	52.3 (16.6)	52.7 (20.3)	54.0 (16.7)	52.7 (13.5)	49.6 (15.0)	0.52
Low density lipoprotein cholesterol (mg/dl), mean (SD)	109.7 (28.9)	112.8 (28.7)	109.7 (29.0)	108.1 (28.3)	108.2 (30.2)	0.80
Known diabetes mellitus, %	7.8	2.9	8.5	8.6	11.4	0.29
Known hypertension, %	27.8	22.9	31.0	27.1	30.0	0.71
Glucose level (mg/dl), mean (SD)	99.8 (41.9)	92.8 (11.6)	96.7 (36.9)	105.8 (56.9)	104.0 (48.1)	0.27
Clinic SBP (mm Hg), mean (SD)	116.1 (16.6)	114.0 (13.7)	114.8 (13.3)	118.0 (21.3)	117.6 (16.9)	0.45
Clinic DBP (mm Hg), mean (SD)	73.8 (11.4)	71.4 (10.8)	74.7 (10.2)	75.0 (14.0)	74.2 (9.9)	0.29
Clinic pulse pressure (mm Hg), mean (SD)	42.3 (10.5)	42.6 (8.9)	40.1 (9.3)	43.2 (10.4)	43.4 (13.1)	0.28

*If CAC measurement not available, Year 20 data were used

Quartiles of mean nocturnal systolic BP/mean daytime systolic BP ratio: **Q1:** 0.7197-0.8454 (n=70); **Q2:** 0.8455-0.8809 (n=71); **Q3:** 0.8810-0.9203 (n=70); **Q4:** 0.9204-1.2358 (n=70)

Table S3. Association of Blood Pressure Dipping Quartile with Future Coronary Artery Calcification (CAC), Stratified by Baseline Smoking Status

Non-Smokers

	% with CAC	OR	95% confidence interval	p-value	Test for nonlinearity p-value
Crude (n/N)*					0.006
Q1 (10/43)	23.3	3.49	1.01-12.1	0.049	
Q2 (6/49)	12.2	1.61	0.42-6.08	0.49	
Q3 (4/50)	8.0	1.00 (ref)			
Q4 (6/35)	17.1	2.38	0.62-9.16	0.21	
Adjusted for age, sex, race, BMI, and HDL-C					0.13
Q1		3.68	0.92-14.6	0.065	
Q2		1.66	0.38-7.27	0.50	
Q3		1.00 (ref)			
Q4		1.71	0.39-7.54	0.48	
Adjusted for Year 5 ASBP, ADBP, SDBP					0.007
Q1		2.19	0.56-8.56	0.26	
Q2		1.02	0.25-4.20	0.97	
Q3		1.00 (ref)			
Q4		3.10	0.73-13.3	0.13	
Adjusted for additional year 5 covariates[†] and CAC exam year					0.12
Q1		1.14	0.17-7.84	0.90	
Q2		0.88	0.12-6.64	0.90	
Q3		1.00 (ref)			
Q4		2.14	0.22-21.2	0.51	

Smokers

	% with CAC	OR	95% confidence interval	p-value	Test for nonlinearity p-value
Crude (n/N)*					0.18
Q1 (11/17)	64.7	6.42	1.00-41.2	0.05	
Q2 (3/14)	21.4	0.96	0.13-7.23	0.96	
Q3 (2/9)	22.2	1.00 (ref)			
Q4 (12/22)	54.6	4.20	0.71-24.9	0.11	
Adjusted for age, sex, race, BMI, and HDL-C					0.22
Q1		7.75	1.04-57.5	0.045	
Q2		1.47	0.16-13.8	0.74	
Q3		1.00 (ref)			
Q4		5.03	0.72-35.3	0.10	
Adjusted for Year 5 ASBP, ADBP, SDBP					0.19
Q1		7.81	1.13-53.9	0.037	
Q2		1.03	0.13-7.94	0.98	
Q3		1.00 (ref)			
Q4		2.78	0.36-21.7	0.33	
Adjusted for additional year 5 covariates[†] and CAC exam year					0.077
Q1		24.0	1.26-459.6	0.034	
Q2		1.32	0.06-27.8	0.86	
Q3		1.00 (ref)			
Q4		11.7	0.47-295.2	0.13	

OR, odds ratio; ref, referent; ASBP, awake systolic blood pressure average; ADBP, awake diastolic blood pressure average; SDBP, sleep diastolic blood pressure average; CAC, coronary artery calcium.

* n/N: No. of cases/Total number of subjects with known non-zero Agatston score

Table S4. Presence of Coronary Artery Calcification (CARDIA Year 20 or Year 15) by Quartile of Baseline Mean Nighttime to Daytime Systolic BP Difference (N=239)

Quartile	% with CAC	OR	95% confidence interval	p-value
Crude (n/N)*				
Q1 (18/64)	28.1	4.30	(1.48-12.5)	0.007
Q2 (15/66)	22.7	3.24	(1.10-9.54)	0.03
Q3 (5/60)	8.3	1.00 (ref)		
Q4 (16/49)	32.7	5.33	(1.79-15.9)	0.003
Adjusted for additional Year 5-covariates† and CAC exam year				
Q1		4.46	(0.98-20.3)	0.053
Q2		5.12	(1.24-21.2)	0.024
Q3		1.00 (ref)		
Q4		8.00	(1.74-36.8)	0.008
Additionally-adjusted for smoking in CAC exam year				
Q1		4.05	(0.90-18.4)	0.07
Q2		4.40	(1.06-18.2)	0.04
Q3		1.00 (ref)		
Q4		6.90	(1.51-31.4)	0.013

CAC, coronary artery calcium; OR, odds ratio; ref, referent
* n/N: No. of cases/Total number of subjects with known non-zero Agatston score
† Adjusted for age, sex, race, education, BMI, baseline smoker, ASBP, ADBP, SDBP, serum cotinine level, LDL, HDL, known diabetes, known hypertension, baseline clinic systolic BP, baseline clinic diastolic BP, pack-years of tobacco, alcohol intake, physical

activity, family history of hypertension, family history of diabetes, poor sleep quality during ABPM, and CAC exam year.

Quartiles of mean nocturnal systolic BP minus mean daytime systolic BP ratio: **Q1:** -37 to -19 (n=75); **Q2:** -18 to -14 (n=74); **Q3:** -13 to -9 (n=71); **Q4:** -8 to 27 (n=61)