Weekday sleep, total cholestrol and the modifying effect of age on systolic blood pressure: An analysis of the 2015-2018 non-obese NHANES population[*]

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Abstract

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Introduction

The clinical importance of systolic blood pressure (SBP) stands as a cornerstone extensively acknowledged and documented across the continuum of medical literature's data collection (Gurven et al. 2012; Su et al. 2022). Elevated SBP stands as a precursor linked with a spectrum of critical health conditions, encompassing cardiovascular diseases, stroke, and renal impairment, among others. This nexus between heightened SBP and these significant health adversities underscores the gravity of SBP as a predictive marker for adverse health outcomes. Noteworthy is the pivotal concern surrounding the trajectory of SBP in the natural aging process, a trajectory observed ubiquitously across diverse populations.

In western societies aged 40 years and above, a demonstrable pattern emerges, revealing an approximate elevation of 7 mmHg in SBP per decade among individuals above 40 years. This discernible and consistent increment in SBP with advancing age accentuates its profound impact within the broader context of aging-related health dynamics. Similarly, while diastolic blood pressure (DBP), demonstrates a concurrent rise correlating with age, presents a substantially lower rate of increase when juxtaposed against the ascending trajectory observed in SBP (Gurven et al. 2012; Su et al. 2022). Thus, in light of the significance attached to SBP dynamics within aging populations and the intricate interplay between age, sleep, cholestrol levels and blood pressure alterations, our investigative focus is oriented towards the exploration of variables that exert potential influence on systolic blood pressure (SBP). This deliberate focus aims to elucidate the multifaceted nature of factors contributing to SBP variability, enabling a more comprehensive understanding of its determinants within the framework of health and aging.

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[*]Replication files are available on the author's Github account (http://github.com/okutse/sleepBP). **Current version**: December 11, 2023

Methods

Study population

Data utilized in this paper is sourced from the National Health and Nutrition Examination Survey (NHANES), a comprehensive nationwide survey administered by the National Center for Health Statistics (NCHS) via the Centers for Disease Control and Prevention (CDC). The survey assesses the health and nutrition of the entire non-institutionalized US population, spanning all ages and residing in all 50 states as well as Washington D.C. As such, the survey provides a cross-sectional view of a representative sample of the US population. Further information about NHANES can be found at www.cdc.gov/nchs/nhanes.

Data

Our current analyses combine the 2015 - 2018 NHANES survey cycles to yield $n = 19225$ observations on 35 covariates. This sample size was comprised $n = 9971$ and $n = 9254$ observations from the 2015/2016 and 2017/2018 survey cycles, respectively. Analyses excluded individuals with missing data on sleep ($n = 6818$), blood pressure (BP) (n = 1055), and body mass index (BMI) or those with BMI > 25 kg/m^2 (overweight) (n = 5521). Individuals that reported being on anti-hypertensive medication were also excluded from further analyses (n = 2944). Our final analyses were based on a sample of n = 1977 observations on 28 covariates.

Outcome definition:

We defined our outcome as systolic and diastolic blood pressure. These variables are measured by trained examiners using standardized procedures. Given that systolic and diastolic blood pressure measurements are taken at least four times on an individual, our definition of these outcome is based on an average of the first three blood pressure measurements.

Exposures:

Sleep duration on workdays was evaluated by the questionnaire with the following questions: "Number of hours usually sleep on weekdays or workdays". We then categorized this variable into three groups, that is, < 6 h, 6–8 h, 8 h respectively, and used < 6 h as the reference group in our analysis. We also explored the association between total cholestrol (in mmol/L) level on systolic blood pressure including potential effect modification by other factors.

Covariates:

Our analyses included the following as covariates: Race divided into four groups as Mexican American, white, black and other race. Alcohol consumption was grouped into drinking, no drinking, not recorded. Smoking status as smoking, not smoking, not recorded. Diabetes was defined as yes, no, borderline, or not recorded. Hypertension was defined as yes, no, or not recorded. Snorting was defined as yes, no, and not recorded. US citizenship status was defined as citizen by birth or naturalization, don't know, not a citizen, or refused to answer. Education level was grouped into four categories including graduate studies, high school, less than grade 12 or some college. Additional covariates included marital status, gender, age, albumin, creatinine,hemoglobin, total cholesterol (TC), aspertate aminotransferase (AST), high-density lipoprotein (HDL), and body mass index (BMI). Details about these variables can be found at https://wwwn.cdc.gov/nchs/nhanes/search/default.aspx. Age, albumin, creatinine, hemoglobin, TC, AST, HDL, and BMI were analyzed as continuous variables whereas gender, alcohol consumption, diabetes, smoking, race, hypertension, and snorting were analyzed as categorical variables. Table @ref{tab:tabone} highlights the variable names and descriptions as utilized in this study.

Table 1: Variable descriptions

Variable	Name	Description
SEQN	sequence number	Respondent number
SDMVPSU	psu	Masked variance unit pseudo-PSU variable for variance estimation
WTINT2YR	weights	Full sample 2-year interview weights
SDMVSTRA	strata	Masked variance unit pseudo-stratum variable for variance estimation
RIAGENDR	gender	Respondent's number
RIDAGEYR	age (yrs)	Respondent's age in years
DMDMARTL	marital status	Marital status
INDFMIN2	income category	Total family income (reported as a range value in dollars)
RIDRETH3	race	Recode of reported race and Hispanic origin information, with Non-Hispanic Asian Category
DMDHHSZA	children <5	Number of children aged 5 years or younger in the household
DMDEDUC2	education level	What is the highest grade or level of school{you have/SP has} completed or the highest degree {you have/s/he has} received?
DMDCITZN	citizenship status	{Are you/Is SP} a citizen of the United States? [Information about citizenship is being collected by the U.S. Public Health Serv
SLD012	sleep	Number of hours usually sleep on weekdays or workdays
BMXBMI	bmi	Body mass index
ALQ121	alcohol use	In the past 12 months, how often did you drink any type of alcoholic beverage?
LBDHDDSI	hdl	High density lipoprotein
LBDSALSI	albumin	Albumin (g/L)
DIQ010	diabetes	Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?
BPQ020	hypertension	{Have you/Has SP} ever been told by a doctor or other health professional that {you/s/he} had hypertension, also called high blood pressure?
URXCRS	creatinine	Creatinine, urine (umol/L)
SLQ040	snort	In the past 12 months, how often did {you/SP} snort, gasp, or stop breathing while {you were/s/he was} asleep?
LBDTCSI	total cholestrol levels	Total cholesterol (mmol/L)
LBXHGB	hemoglobin	Hemoglobin (g/dL)
LBXSASSI	AST	Aspertate aminotransferase
SMQ040	smoke	Do you now smoke cigarettes?
BPXDI	blood pressure	Systolic and diastolic blood pressure taken as the average of the first three measurements

Statistical modeling

Variable selection based on univariate regression

Univariate regression analyses were performed on all potentially confounding covariates excluding hypertension. Model 1 was fitted to the data including the exposure variables as well as all potentially confounding covariates from univariate regression analysis. Model 2 was fitted to the same set of covariates including an interaction term between age and total cholesterol levels. Model 3 was fitted to the data including only covariates that had a statistically significant association with SBP in univariate analyses excluding HDL, hemoglobin, diabetes, survey cycle, and alcohol consumption. Model 4 included similar covariates as Model 3 but examined, in addition, all possible two-way interactions between the covariates. This model is essentially overfit to the data. Model 5 included the same set of covariates as Model 3 in addition to an interaction term between age and total cholesterol levels.

Variable selection based on LASSO and best subsets

Furthermore, we conducted two distinct variable selection methodologies, similarly excluding hypertension. Model 6 was based on best subset selection with 10-fold cross-validation to ascertain the optimal number of subsets. Notably, for systolic blood pressure, the forward best subset selection method discerned 13 variables, whereas diastolic blood pressure exhibited 19 selected variables. However, a limitation inherent in forward best subset selection is its inability to eliminate previously selected features, potentially disregarding their relevance in light of newly added variables. Consequently, this methodology may yield sub-optimal variable selections due to its lack of adaptability.

In an effort to mitigate this limitation and introduce regularization, LASSO regularization was employed. This involved a 10-fold cross-validation process to determine the optimal penalty parameter, λ. For diastolic blood pressure, the λ value associated with the lowest mean squared error (MSE) led to the selection of 25 variables. Conversely, when considering systolic blood pressure, the λ value minimizing the MSE resulted in the exclusion of a sole variable. Subsequently, a λ value was strategically chosen to ensure a negligible increase of no more than 1% in MSE, ultimately leading to the inclusion of 29 variables in the model. Model 7 consisted in variables selected by the LASSO regression. In addition, our study incorporated an alternative model that not only incorporated the variables identified through LASSO but also introduced an interaction term involving age and cholesterol levels; Model 8. This extended model aimed to explore potential combined effects between age and cholesterol on the outcome variable.

Model performance evaluation

All models fitted to the data in this investigation were nested and evaluations were based on information criteria including Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC). The BIC is favored over the AIC due to its increasing penalty with larger sample sizes, resulting in more stringent significance levels (Vrieze 2012). Additionally, we also used performance measures including the mean squared error (MSE), r-squared, and adjusted r-squared. The likelihood ratio test (LRT) was used in competing model comparisons testing the null hypothesis that the nested models are equivalent, and the extra parameters in the larger model do not improve the fit significantly, that is, these terms have effect sizes equivalent to 0. 3 summarizes the model performance metrics compared for all models implemented in this investigation. The final model superiority was based on likelihood ratio tests.

Results

Descriptive statistics

Table 2 summarizes participant characteristics in the 2015 - 2018 NHANES survey cycles stratified by gender. The 2015-2016 survey cycle comprised 53.77% of the total analyzed sample whereas the 2017 - 2018 survey cycle comprised 46.23% of the total analyzed sample. Among the participants, the proportion of males and females were 53.76% (n = 1063) and 46.23% (n = 914), respectively. With race, the proportion of Mexican American, White and Black were 9.16%, 34.90% and 17.10%, respectively. Overall, the mean (SD) values

for age, albumin, SBP, DBP, hemoglobin, TC, AST, HDL, BMI were 43.79 (17.43) years, 43.04 (3.59) g/L, 118.61 (16.41) mmHg, 69.60 (11.18) mmHg, 13.94 (1.46)g/dL, 4.81 (1.02) mmol/L, 23.47 (13.17) IU/L, 1.60 (0.43) mmol/L, and 22.08 (2.03) kg/m2, respectively. Among the participants, 73.70% were alcohol drinkers, 5.06% were diabetic, 7.79% were hypertensive, 13.76% experienced snorting whereas 21.60% were smokers. Sleep duration was divided into three groups, which were < 6 h, 6–8 h, 8 h, each with a proportion of 7.89%, 40.06%, 52.05%, respectively. Male and female participants differed significantly on all characteristics except citizenship status, and the cycle of the survey.

Table 2: Unweighted summary characteristics of the participants in the NHANES 2015 - 2018 survey cycles stratified by gender. BMI = Body Mass Index; HDL = High Density Lipoprotein, TC = Total Cholestrol level; AST = aspertate aminotransferase. SBP = Systolic blood pressure, DBP = Diastolic blood pressure.

Variable	**Overall**, N = 1,977	**Female**, N = 1,063	**Male**, N = 914	**p-value**
BMI	22.08 (2.03)	21.83 (2.04)	22.37 (1.98)	<0.001
HDL	1.60 (0.45)	1.73 (0.45)	1.45 (0.40)	<0.001
TC	4.81 (1.02)	4.87 (1.05)	4.73 (0.99)	0.005
Hemoglobin	13.94 (1.46)	13.20 (1.18)	14.81 (1.28)	<0.001
Albumin	43.04 (3.59)	42.40 (3.36)	43.78 (3.70)	<0.001
AST	23.47 (13.17)	21.59 (9.78)	25.66 (15.98)	<0.001
Creatinine	10,132.60 (7,349.24)	8,715.09 (6,809.53)	11,781.19 (7,609.15)	<0.001
Hypertension				0.002
Don't know	4.00 (0.20%)	2.00 (0.19%)	2.00 (0.22%)	
No	1,819.00 (92.01%)	998.00 (93.89%)	821.00 (89.82%)	
Yes	154.00 (7.79%)	63.00 (5.93%)	91.00 (9.96%)	
Diabetes				0.010
Borderline	33.00 (1.67%)	15.00 (1.41%)	18.00 (1.97%)	
No	1,844.00 (93.27%)	1,008.00 (94.83%)	836.00 (91.47%)	
Yes	100.00 (5.06%)	40.00 (3.76%)	60.00 (6.56%)	
Citizenship				0.2
Citizen	1,616.00 (81.74%)	858.00 (80.71%)	758.00 (82.93%)	
Unknown	1.00 (0.05%)	1.00 (0.09%)	0.00 (0.00%)	
Non-citizen	357.00 (18.06%)	201.00 (18.91%)	156.00 (17.07%)	
Refused	3.00 (0.15%)	3.00 (0.28%)	0.00 (0.00%)	
Education				<0.001
GraduateStudies	646.00 (32.68%)	394.00 (37.06%)	252.00 (27.57%)	
Highschool	415.00 (20.99%)	192.00 (18.06%)	223.00 (24.40%)	
Less12grade	359.00 (18.16%)	143.00 (13.45%)	216.00 (23.63%)	
someCollege	557.00 (28.17%)	334.00 (31.42%)	223.00 (24.40%)	
Children > 5 yrs				0.002
0	1,547.00 (78.25%)	798.00 (75.07%)	749.00 (81.95%)	
1	274.00 (13.86%)	168.00 (15.80%)	106.00 (11.60%)	
2	123.00 (6.22%)	74.00 (6.96%)	49.00 (5.36%)	
3 or more	33.00 (1.67%)	23.00 (2.16%)	10.00 (1.09%)	
Age (yrs)	43.79 (17.43)	42.77 (16.65)	44.98 (18.24)	0.024
Marital status				0.003
Divorced	180.00 (9.10%)	111.00 (10.44%)	69.00 (7.55%)	
Living with partner	197.00 (9.96%)	93.00 (8.75%)	104.00 (11.38%)	
Married	961.00 (48.61%)	530.00 (49.86%)	431.00 (47.16%)	
Never married	504.00 (25.49%)	245.00 (23.05%)	259.00 (28.34%)	
Separated	54.00 (2.73%)	33.00 (3.10%)	21.00 (2.30%)	
Widowed	81.00 (4.10%)	51.00 (4.80%)	30.00 (3.28%)	

Survey cycle				0.3
0	1,063.00 (53.77%)	561.00 (52.78%)	502.00 (54.92%)	
1	914.00 (46.23%)	502.00 (47.22%)	412.00 (45.08%)	
DBP	69.60 (11.18)	68.79 (10.70)	70.55 (11.65)	<0.001
SBP	118.61 (16.41)	115.78 (16.64)	121.90 (15.52)	<0.001
Sleep				0.005
<6hrs	156.00 (7.89%)	73.00 (6.87%)	83.00 (9.08%)	
>8hrs	1,029.00 (52.05%)	588.00 (55.32%)	441.00 (48.25%)	
6-8hrs	792.00 (40.06%)	402.00 (37.82%)	390.00 (42.67%)	
Race				<0.001
Black	338.00 (17.10%)	143.00 (13.45%)	195.00 (21.33%)	
Mexican American	181.00 (9.16%)	96.00 (9.03%)	85.00 (9.30%)	
Other	768.00 (38.85%)	455.00 (42.80%)	313.00 (34.25%)	
White	690.00 (34.90%)	369.00 (34.71%)	321.00 (35.12%)	
Smoking status				<0.001
Not recorded	1,229.00 (62.16%)	763.00 (71.78%)	466.00 (50.98%)	
Not Smoking	321.00 (16.24%)	137.00 (12.89%)	184.00 (20.13%)	
Smoking	427.00 (21.60%)	163.00 (15.33%)	264.00 (28.88%)	
Snort				<0.001
No	1,590.00 (80.42%)	902.00 (84.85%)	688.00 (75.27%)	
Not recorded	115.00 (5.82%)	49.00 (4.61%)	66.00 (7.22%)	
Yes	272.00 (13.76%)	112.00 (10.54%)	160.00 (17.51%)	
Alcohol				<0.001
Drinking	1,457.00 (73.70%)	737.00 (69.33%)	720.00 (78.77%)	
No drinking	111.00 (5.61%)	52.00 (4.89%)	59.00 (6.46%)	
Not recorded	409.00 (20.69%)	274.00 (25.78%)	135.00 (14.77%)	
Income				<0.001
Low income	131.00 (6.63%)	64.00 (6.02%)	67.00 (7.33%)	
Lower-middle income	389.00 (19.68%)	187.00 (17.59%)	202.00 (22.10%)	
Middle income	550.00 (27.82%)	284.00 (26.72%)	266.00 (29.10%)	
Unknown/Refused	58.00 (2.93%)	27.00 (2.54%)	31.00 (3.39%)	
Upper-middle income	391.00 (19.78%)	210.00 (19.76%)	181.00 (19.80%)	
Varied/High income	458.00 (23.17%)	291.00 (27.38%)	167.00 (18.27%)	

[1] Mean (SD); n (%)

[2] Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

Univariate regression analysis

Univariate regression analysis results exploring the association between the exposures, selected potential confounding variables showed substantial associations between BMI ($\beta = 0.95$ mmHg; 95%CI [0.60 - 1.3]; $p<0.05$), TC ($\beta = 3.6$ mmHg; 95%CI [2.9 - 4.3]; $p<0.05$), albumin ($\beta = -0.48$ mmHg; 95% CI [-0.68mmHg - -0.27]; $p < 0.05$), AST ($\beta = 0.12$ mmHg; 95%CI [0.07 - 0.18]; $p <0.05$), and age (years) ($\beta = 0.49$ mmHg; 95% CI [0.45 - 0.52]; $p <0.05$) and systolic blood pressure. Weekday sleep duration between 6 and 8 hours was associated with a 4.0 mmHg (95% CI [-6.8 - -1.2]) decrease in the average systolic blood pressure compared to 6 hours of sleep. On the other hand, more than 8 hours of sleep was associated with a decrease of 3.1 mmHg in systolic blood compared to 6 hours of sleep. Substantial associations were noted between citizenship, education, number of children below five years, gender, marital status, race, smoking status, snorting, alcohol, and income.

Model performance evaluation

Table 3 presents an overview of the performance measures of the various models applied to our data set. Model 6, utilizing best subset selection, revealed notably high MSE, suggesting limited predictive efficacy. Models 1 and 2, not including variable selection techniques, highlight the impact of incorporating the age-cholesterol interaction term with notable reduction in MSE. Models 3, 4, and 5 included solely significant univariate regression variables. Model 5, with the lowest AIC and second lowest BIC, demonstrates an acceptable MSE. Model 4, with the lowest MSE and highest R^2, demonstrated a high predictive power, although its extensive number of terms raise concerns of potential overfitting. Model 3, based solely on significant univariate covariates, performed well but exhibited a higher MSE than Models 4 and 5, suggesting the probable influence of interaction terms. Models 7 and 8, employing LASSO, exhibited comparable performance metrics, with Model 8 displaying reduced BIC and MSE, attributed chiefly to the significant inclusion of an age-cholesterol interaction term.

Table 3: Summary model performance measures.

	df[a]	AIC[b]	BIC[c]	MSE[d]	R^2	Adjusted R^2
Model 1	44	15888.48	16134.41	173.17	0.36	0.34
Model 2	45	15849.26	16100.78	169.60	0.37	0.36
Model 3	39	15883.76	16101.74	173.63	0.36	0.34
Model 4	600	16156.48	19510.09	113.00	0.58	0.40
Model 5	40	15848.93	16072.50	170.43	0.37	0.35
Model 6	25	15877.41	16017.15	2657.01	0.35	0.34
Model 7	41	15888.38	16117.55	173.69	0.36	0.34
Model 8	42	15849.19	16083.94	170.11	0.37	0.36

[a] df = degrees of freedom
[b] AIC = Akaike Information Criteria
[c] BIC = Bayesian Information Criteria
[d] MSE = Mean Squared Error

Likelihood ratio tests showed a statistically significant difference between Model 1 and 2 with evidence of in favor of the latter ($\chi^2_{(1)} = 7064; p > 0.05$). Model 2 which adjusted for all potentially confounding covariates in **??** including an interaction between cholestrol level and age was then compared to Model 3 which adjusted for only covariates we found significant in univariate analyses. Results here similarly showed evidence in favor of Model 2 ($\chi^2_{(1)} = 7979; p > 0.05$). Comparing Model 2 to Model 3 revealed a non-statistically difference in model fit suggesting that Model 3, even though smaller performed comparably well. Model 3 was thus selected and compared to Model 4, 5, 6, and 7 with evidence based on the LRT favoring its choice as the best model ($p > 0.05$). Additional regression diagnostics for Model 3 including residual versus fitted value plots, Q-Q plots for checking the normality of residuals, Cook's distance for outliers, residual and high leverage point plots did not reveal substantial deviations from linear regression assumptions. Model 3 was thus selected as the best model. Reported results are thus based on this model.

Multivariable Regression Analysis

Table 4 shows the coefficients of sleep, age, total cholesterol and the interaction between total cholesterol and age

Table 4: Sleep, Age and Cholesterol Coefficients for Model 5

Variable	Estimate	95% CI	p-value
Intercept	102.55	(88.42,116.69)	< 0.001
Sleep	0.75	(0.50, 1.00)	0.002
< 6hrs			
> 8hrs	-1.4	(-3.7,0.92)	0.2
$6 - 8$hrs	-3.0	(-5.3,-0.67)	0.012
Age	-0.04	(-0.22, 0.13)	0.6
TC	-3.5	(-5.2, -1.8)	<0.001
TC*Age	0.11	(0.07, 0.14)	<0.001

Discussion and conclusion

Study limitations

Our study encountered a significant challenge with missing data, resulting in a notable reduction in our sample size. Despite initially having a sample of $n=19,225$, the final analysis was conducted on a considerably smaller sample of $n=1,977$ observations. This substantial reduction in the sample size raises concerns about the robustness and reliability of our findings. Addressing this issue becomes crucial to ensure the validity of our study outcomes.

In response to this challenge, we propose the implementation of multiple imputation techniques. This approach involves generating multiple plausible sets of missing values based on observed data patterns. By imputing missing values using this method, we aim to enhance the completeness of our data set. This strategy is intended to mitigate potential biases resulting from missing data and fortify the reliability and accuracy of our analytical outcomes.

References

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