



The relationship between mean telomere length and blood pressure: results from the National Health and Nutrition Examination Surveys

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Background: Recent studies have shown that telomere length has significantly relationship with different age-related diseases. However, the relationship between mean telomere length (MTL) and elevated blood pressure (BP) has been unclear. Therefore, the aim of the recent study was tried to explore the association of MTL with BP.

Methods: There were 5,981 subjects from the National Health and Nutrition Examination Surveys (NHANES, 1999–2002) was included in analysis. The MTL was measured using the quantitative polymerase chain reaction (PCR) method and expressed in telomere-to-single copy gene (T/S) ratio and grouped into quartiles. Multivariate linear [expressed in beta and 95% confidence interval (CI)], logistic regression [odds ratios (ORs) and 95% CI] analyses and smooth curve fitting were performed to evaluate the relationship between MTL, BPs and the likelihood of hypertension.

Results: The mean age of the participants was 45.2±17.3 years, including 2,923 (48.9%) males. After adjusting for potential confounders, MTL was significantly related to the prevalence of hypertension (OR: 0.12, 95% CI: 0.02, 0.94; P=0.04). Smooth curve fitting found a non-linear relationship between MTL, the levels of systolic and diastolic blood pressure (SBP/DBP) and the prevalence of hypertension. The inflection points for the smooth curve of MTL were at 0.86, 1.02 and 0.80 (T/S ratio) respectively. The betas (95% CIs) for SBP [-12.58 (-20.07, -5.09), P<0.01 and 2.25 (0.07, 4.43), P=0.04] and DBP [4.88 (1.29, 8.47), P<0.01 and -3.30 (-5.54, -1.06), P<0.01], and ORs (95% CIs) for the prevalence of hypertension [0.02 (0.001, 9.71), P=0.15 and 0.26 (0.026, 2.60), P=0.25] on the left and right of the inflection point, respectively.

Conclusions: Our findings revealed that MTL was related with SBP, DBP and the odds of hypertension in a non-linear manner.

Keywords: Blood pressure (BP); telomere length; systolic blood pressure (SBP); diastolic blood pressure (DBP)

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Introduction

Hypertension has become a major public health problem in worldwide due to its close relationship with cardiovascular and cerebrovascular disease events (1,2). Blood pressure (BP) is a key indicator to reflect the function of cardiac output and systemic vascular resistance (3). The values of BP are normally distributed values in the general population (4). BP is considered to be a continuous, polygenic and heterogeneous trait (4), and an indicator for cardiovascular risk stratification because it is an easily measured and accessible parameter for routine data collection (5).

In recent years, emerging new biomarkers have been discovered and might play an important role in the development of hypertension. Telomere, a non-transcriptional region of repetitive nucleotide sequences at each end of a chromosome, protects chromosomes from degradation or from fusion with neighboring chromosomes (6). In addition, the length of telomere is a good gauge of cell aging and biological health, which significantly associates with longevity and the aging process (6,7). Mean telomere length (MTL) has significantly relationship with different age-related diseases, such as heart failure (8), diabetes mellitus (9), osteoporosis (10), atherosclerosis (11) and dementia (12). However, little research is available indicating if MTL is associated with the development of hypertension. The present study aimed to address the knowledge gap by examining the association of MTL with systolic/diastolic blood pressure (SBP/DBP) and the odds of hypertension in US adults.

Methods

Study design and study population

The National Health and Nutrition Examination Surveys (NHANES) is a cross-sectional and nationally representative survey of the civilian, non-institutionalized US population conducted by the Centers for Disease Control and Prevention (CDC). We used data from the 1999–2000 and 2001–2002 cycles of NHANES. Participants who aged ≥ 18 with test results of telomere length were included for analysis. After applying the exclusion criteria (Figure 1), 5,981 participants were available for analysis. The survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention (Protocol

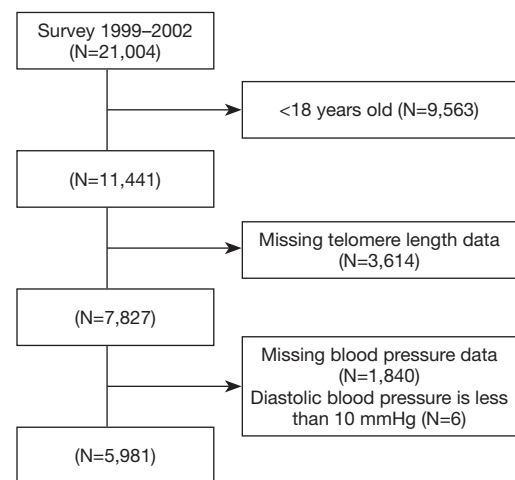


Figure 1 Study flow chart of participants.

#98-12). All participants have provided informed consent.

Measurement of BP

Three (or four for few participants) BP measurements (systolic and diastolic) were taken using a mercury sphygmomanometer in the mobile examination center (MEC) or during home examinations on all eligible individuals. For participants who were not able to complete examination in MEC (50 years and older, or less than 1 year of age) an abbreviated examination was conducted in their homes. BP measurements were taken by one of the MEC examiners. The procedures for BP measurement according to the latest recommendations of the American Heart Association Human Blood Pressure Determination by sphygmomanometers (13). Using diastolic reading as example, if all diastolic readings were zero, the average BP value would be zero. If there is one diastolic reading as zero and one (or more) non-zero values, the diastolic reading with zero was excluded from BP calculation. If two out of three diastolic readings are zero, the only non-zero diastolic reading was extracted for BP calculation. Two physicians (MEC setting) and two health technologists (Home Examination setting) were trained to collect NHANES BP data using a standardized protocol. Hypertension was defined as having a history of hypertension, a SBP ≥ 140 mmHg, a DPB ≥ 90 mmHg, and/or using

antihypertensive medications (14).

Measurement of telomere length

Each sample was assayed 3 times on 3 separate days. The samples were assayed on duplicate wells, resulting in 6 data points. Sample plates were assayed in groups of 3 plates, and no 2 plates were grouped together for more than once. Each assay plate contained 96 control wells with 8 control deoxyribonucleic acid (DNA) samples. Assay runs with 8 or more invalid control wells were excluded from further analysis (<1% of runs). Control DNA values were used to normalize between-run variability. Runs with more than 4 control DNA values that deviated beyond 2.5 standard deviations from the mean for all assay runs were excluded from further analysis (<6% of runs). For each sample, any potential outliers were identified and excluded from the calculations (<2% of samples). The mean and standard deviation of the T/S ratio were then calculated. The inter assay coefficient of variation was 6.5%. Five 96-well quality control plates which represented 5% of the complete set were provided. These duplicate samples were blinded to the investigators. If more than 5% of the duplicate samples on the quality control plates were discordant with their pair in the complete set, the variant failed quality control (i.e., >95% duplicate concordance required). The MTL assay was performed in the laboratory at the University of California, San Francisco, using the quantitative polymerase chain reaction (PCR) method to measure telomere length relative to standard reference DNA (T/S ratio), as described in detail previously (15,16). Mean T/S ratio was measured by the telomere length relative to standard reference DNA. The formula to convert T/S ratio to base pairs was $3,274 + 2,413 \times (T/S)$. The conversion from T/S ratio to bp was calculated based on a comparison of telomeric restriction fragment length from Southern blot analysis and T/S ratios using DNA samples from the human diploid fibroblast cell line IMR90 at different population doublings. The detailed information and methods are provided on the website (https://wwwn.cdc.gov/Nchs/Nhanes/1999-2000/TELO_A.htm).

Participants and clinical covariates

Demographics (including age, gender), previous medical history, smoking status, alcohol consumption and medication use (antihypertensive drugs, lipid lowering drugs and antidiuretic drugs) were collected from

interviews. Anthropometric measurements, BP readings, blood and urine specimens, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), fasting blood glucose (FBG), C-reactive protein (CRP) and routine biochemical indicators were also obtained using standardized approach. Detailed description of data collection methods have been provided on the official website (<https://www.cdc.gov/nchs/index.htm>).

Statistical analysis

All continuous variables were presented as mean \pm standard deviation, and categorical variables were presented in frequency or as a percentage according to baseline MTL in quartiles. The one-way ANOVA, Kruskal Wallis H test and Chi-square tests were used to determine any statistical differences between subgroups. Pearson correlation analysis was used to assess the relationship between MTL and clinical parameters. The association of MTL with continuous (SBP, DBP) and binary (the prevalence of hypertension) outcomes were examined using multivariate linear or logistic regression analysis. Results were presented in coefficients (betas), odds ratio (OR) with the corresponding 95% confidence intervals (CIs). To test the robustness of our results, we have built several regression models. In model I, we only included MTL. In model II we additionally adjusted for age, gender and body mass index (BMI). In model III, age, gender, BMI, FBG, SBP, TC, HDL-C, TG, LDL-C, CRP, estimated glomerular filtration rate (eGFR), alcohol consumption, smoking and antihypertensive drugs were adjusted. We also used generalized additive model (GAM) to identify the non-linear relationship between MTL and SBP, DBP and the odds of hypertension, then performed the likelihood ratio test. To address the nonlinearity of MTL and BP, a using multivariate linear or logistic regression analysis with cubic spline functions model and smooth curve fitting (penalized spline method) were conducted (17). If a nonlinearity was detected, we calculated the inflection point using a recursive algorithm, then a two-piecewise linear regression model was performed to calculate the threshold effect of the MTL on BP in terms of the smoothing plot (18). Recursive method was performed to calculate automatically the inflection point, where the maximum model likelihood would be used. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Baseline characteristics of participants

Groups	Total	Q1: <0.90 T/S	Q2: 1.00–1.09 T/S	Q3: 1.10–1.19 T/S	Q4: ≥1.20 T/S	P value
Number	5,981	1,495	1,495	1,495	1,496	
Age (years)	45.2±17.3	55.3±17.7	47.4±16.7	41.1±15.0	36.9±13.9	<0.01
BMI (kg/m ²)	28.1±6.1	28.6±6.0	28.2±6.1	28.1±6.1	27.7±6.1	<0.01
SBP (mmHg)	119.1±15.3	122.5±15.7	119.4±15.7	117.8±14.8	116.7±14.5	<0.01
DBP (mmHg)	70.9±12.3	70.9±13.1	71.1±12.1	71.2±11.6	70.2±12.3	0.12
FBG (mmol/L)	101.6±31.9	106.4±34.1	102.4±31.2	100.6±35.6	96.5±24.1	<0.01
TC (mg/dL)	202.4±42.0	205.7±42.8	204.0±40.9	202.0±41.6	197.8±42.2	<0.01
HDL-C (mg/dL)	51.3±15.3	50.3±14.9	50.9±15.4	51.7±15.4	52.4±15.3	<0.01
TG (mg/dL)	148.3±127.9	157.0±107.8	154.8±168.5	149.1±129.6	130.5±90.4	<0.01
LDL-C (mg/dL)	122.9±34.9	124.1±33.1	126.3±34.9	120.5±33.8	120.8±37.4	<0.01
CRP (mg/dL)	1.4±0.7	1.5±0.8	1.4±0.6	1.3±0.7	1.4±0.6	0.02
Alcohol consumption (g/day)	10.1±34.9	8.3±35.8	9.3±29.6	10.6±34.9	12.4±38.7	0.01
eGFR (mL/min/1.73 m ²)	101.3±38.5	93.6±37.2	99.4±37.0	104.0±39.9	108.4±38.1	<0.01
MLT (T/S)	1.1±0.3	0.8±0.1	0.9±0.0	1.1±0.1	1.4±0.2	<0.01
Male, n (%)	2923 (48.9)	845 (56.5)	731 (48.9)	682 (45.6)	665 (44.5)	<0.01
Non-smoking, n (%)	3,089 (51.7)	690 (46.2)	743 (49.8)	828 (55.5)	828 (55.4)	<0.01
Antihypertensive drugs, n (%)	888 (14.8)	354 (23.7)	237 (15.9)	173 (11.6)	124 (8.3)	<0.01
Hypertension, n (%)	1,103 (18.4)	427 (28.6)	287 (19.2)	221 (14.8)	168 (11.2)	<0.01

Values are means (SD) except for qualitative variables, expressed as n (%). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate, MLT, mean telomere length; Q, quartiles.

Results

Baseline of participants

The characteristics of all the subjects in this study stratified by the quartiles of MTL were presented in *Table 1*. The distributions of BP and MTL were showed in *Figure 2*. A total of 5,981 participants [2,923 (48.9%) men] were included with average age as 45.2 years. There were 1,103 (18.4%) people with hypertension. In addition, there were significant subgroup differences in age, gender, BMI, SBP, DBP, FBG, TC, TG, LDL-C, HDL-C, CRP, eGFR, alcohol consumption, smoking status, hypertension and the use of antihypertensive drugs (all $P < 0.05$).

The relationship between telomere length and BP

In Pearson correlation analysis (*Table 2*), MTL was

significantly correlated with age, BMI, SBP, FBG, TC, TG, LDL-C, HDL-C, CRP, alcohol consumption and eGFR (all $P < 0.05$). In order to further explore the association between MTL and SBP, DBP and the odds of hypertension, multivariate regression analysis were performed. As shown in *Table 3*, when treating MTL as a continuous variable (per 1 T/S increment), in the minimally adjusted model (model I), MTL was significantly associated with SBP ($\beta = -8.11$, 95% CI: $-9.58, -6.64$; $P < 0.01$), DBP ($\beta = -1.14$, 95% CI: $-2.32, 0.05$; $P = 0.06$) and the odds of hypertension (OR: 0.16, 95% CI: 0.12, 0.21; $P < 0.01$). However, in the model III, there was no association between MTL and SBP ($\beta = 0.25$, 95% CI: $-1.59, 2.10$, $P = 0.79$), DBP ($\beta = -0.58$, 95% CI: $-2.11, 0.95$, $P = 0.45$) but the association remained for the odds of hypertension (OR: 0.12, 95% CI: 0.02, 0.94; $P = 0.04$). When using the lowest quartiles of MTL as the referent, multivariate linear (SBP, DBP)/logistic

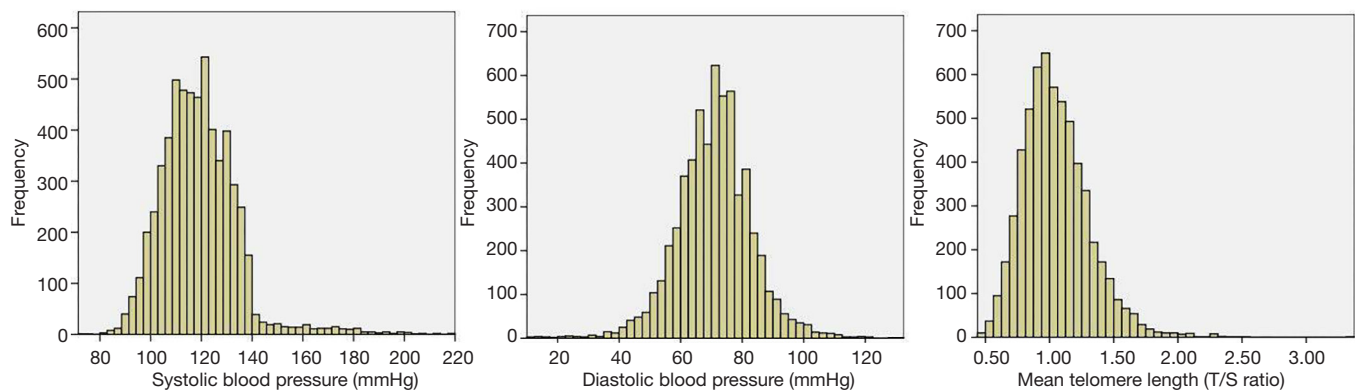


Figure 2 The distributions of BP and MTL. BP, blood pressure; MTL, mean telomere length.

Table 2 The relationship between MTL (per 1 T/S ratio change) and clinical parameters

Variables	r	95% CI low	95% CI up	P value
Age	-0.40	-0.42	-0.38	<0.01
BMI	-0.06	-0.08	-0.03	<0.01
SBP	-0.14	-0.16	-0.11	<0.01
DBP	-0.02	-0.04	0.001	0.06
FBG	-0.11	-0.14	-0.08	<0.01
TC	-0.08	-0.10	-0.05	<0.01
HDL-C	0.05	0.02	0.07	<0.01
TG	-0.08	-0.11	-0.04	<0.01
LDL-C	-0.05	-0.09	-0.02	<0.01
CRP	-0.03	-0.05	-0.002	0.04
Alcohol consumption	0.03	0.008	0.06	<0.01
eGFR	0.13	0.11	0.15	<0.01

Data are expressed as mean (95% CI) and correlation coefficient. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; CI, confidence interval; MTL, mean telomere length.

(hypertension) regression analyses demonstrated that the betas for SBP (β s were -1.29, -0.80, and 0.22 from the second to the fourth quartiles, respectively, $P=0.66$ for trend), DBP (β s were 0.92, 1.26, and -0.36 from the second to the fourth quartiles, respectively, $P=0.75$ for trend) and the odds of hypertension (ORs were 0.52, 0.44, and 0.31 from the second to the fourth quartiles, respectively, $P<0.01$ for trend) in model III.

The analyses of non-linear relationship

Using a two-piecewise linear regression model, we calculated that the inflection point in T/S ratio for the association with SBP, DBP and hypertension to be 0.86, 1.02 and 0.80 respectively. On the left of the inflection point, the betas for SBP, DBP and the OR of hypertension prevalence were -12.58 (95% CI: -20.07, -5.09, $P<0.01$), 4.88 (95%

Table 3 Relationship between MTL and SBP, DBP, hypertension in different models

Exposure variables	Model I	Model II	Model III ^{abc}
SBP (mmHg)*			
MTL (per 1T/S increment)	-8.11 (-9.58, -6.64), <0.01	1.74 (0.28, 3.20), 0.02	0.25 (-1.59, 2.10), 0.79
MTL (quartiles)			
Q1	Ref	Ref	Ref
Q2	-3.09 (-4.18, -2.00), <0.01	0.06 (-0.95, 1.07), 0.91	-1.29 (-2.54, -0.04), 0.04
Q3	-4.67 (-5.76, -3.58), <0.01	0.68 (-0.37, 1.72), 0.20	-0.80 (-2.08, 0.48), 0.22
Q4	-5.75 (-6.84, -4.66), <0.01	1.16 (0.08, 2.23), 0.04	0.22 (-1.12, 1.57), 0.74
P for trend	<0.01	0.02	0.66
DBP (mmHg)*			
MTL (per 1T/S increment)	-1.14 (-2.32, 0.05), 0.06	1.15 (-0.12, 2.41), 0.08	-0.58 (-2.11, 0.95), 0.45
MTL (quartiles)			
Q1	Ref	Ref	Ref
Q2	0.15 (-0.73, 1.03), 0.73	0.99 (0.11, 1.86), 0.03	0.92 (-0.12, 1.96), 0.08
Q3	0.22 (-0.66, 1.10), 0.62	1.58 (0.67, 2.48), <0.01	1.26 (0.19, 2.32), 0.02
Q4	-0.74 (-1.62, 0.13), 0.09	0.96 (0.03, 1.89), 0.04	-0.36 (-1.47, 0.76), 0.53
P for trend	0.13	0.03	0.75
Hypertension[#]			
MTL (per 1T/S increment)	0.16 (0.12, 0.21), <0.01	1.41 (1.01, 1.98), 0.05	0.12 (0.02, 0.94), 0.04
MTL (quartiles)			
Q1	Ref	Ref	Ref
Q2	0.59 (0.50, 0.70), <0.01	0.99 (0.81, 1.21), 0.92	0.52 (0.15, 1.85), 0.31
Q3	0.43 (0.36, 0.52), <0.01	1.18 (0.95, 1.47), 0.14	0.44 (0.11, 1.76), 0.25
Q4	0.32 (0.26, 0.38), <0.01	1.16 (0.91, 1.48), 0.23	0.31 (0.07, 1.31), 0.11
P for trend	<0.01	0.11	<0.01

*, Data are expressed as β (95% CI), P value; [#], data are expressed as OR (95% CI), P value. Model I adjust for: None; Model II adjust for: age, gender and BMI; Model III adjust for: ^a, (SBP) age, gender, BMI, FBG, DBP, TC, HDL-C, TG, LDL-C, CRP, eGFR, alcohol consumption, smoking and antihypertensive drugs; ^b, (DBP) age, gender, BMI, FBG, SBP, TC, HDL-C, TG, LDL-C, CRP, eGFR, alcohol consumption, smoking and antihypertensive drugs; ^c, (hypertension) age, gender, BMI, FBG, SBP, TC, TG, HDL-C, CRP, eGFR, alcohol consumption, smoking and antihypertensive drugs. MTL, mean telomere length; SBP, systolic blood pressure; DBP, diastolic blood pressure; Q, quartiles; CI, confidence interval; OR, odds ratio; BMI, body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

CI: 1.29, 8.47, $P < 0.01$) and 0.02 (95% CI: 0.001, 9.71, $P = 0.15$) respectively. The corresponding effect estimates at the right of inflection point were 2.25 (95% CI: 0.07, 4.43, $P = 0.04$), -3.30 (95% CI: -5.54, -1.06, $P < 0.01$) and 0.26 (95% CI: 0.026, 2.60, $P = 0.25$), respectively. *Table 4*, suggesting an inverse relationship between MTL and

SBP on the left side of the inflection point, and an inverse relationship with DBP was on the right side with inflection point. As shown in *Figure 3*, the association between MTL and SBP (*Figure 3A*), DBP (*Figure 3B*) and the prevalence of hypertension (*Figure 3C*) were both non-linear after adjusting for potential confounding variables.

Table 4 The results of two-piecewise linear regression model between MTL and SBP, DBP, hypertension

Exposure variables	SBP (mmHg) ^{a*}	DBP (mmHg) ^{b*}	Hypertension ^{c#}
Cut off point of MTL	0.86	1.02	0.80
< Cut off point of MTL	-12.58 (-20.07, -5.09), <0.01	4.88 (1.29, 8.47), <0.01	0.02 (0.001, 9.71), 0.15
≥ Cut off point of MTL	2.25 (0.07, 4.43), 0.04	-3.30 (-5.54, -1.06), <0.01	0.26 (0.026, 2.60), 0.25
Log likelihood ratio test	<0.01	<0.01	0.32

^{*}, Data are expressed as β (95% CI), P value; [#], data are expressed as OR (95% CI), P value. Effect: SBP, DBP and hypertension; Cause: MTL; ^a, age, gender, BMI, FBG, DBP, TC, HDL-C, TG, LDL-C, CRP, eGFR, alcohol consumption, smoking and antihypertensive drugs; ^b, age, gender, BMI, FBG, SBP, TC, HDL-C, TG, LDL-C, CRP, eGFR, alcohol consumption, smoking and antihypertensive drugs; ^c, age, gender, BMI, FBG, SBP, TC, HDL-C, TG, LDL-C, CRP, eGFR, alcohol consumption, smoking and antihypertensive drugs. MTL, mean telomere length; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval; OR, odds ratio; BMI, body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

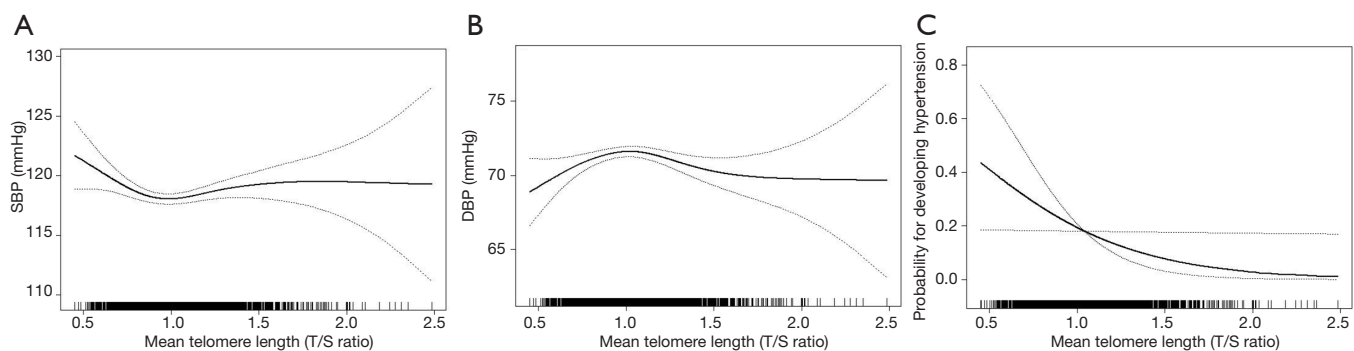


Figure 3 The relationship between MTL and BP: (A) SBP, (B) DBP and (C) hypertension. Data are expressed as mean (95% CI). MTL, mean telomere length; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.

Discussion

In the present study, a non-linear relationship was found between MTL, SBP/DBP and the odds of hypertension. The optimal cutoff point of the association of MTL with SBP, DBP and hypertension were 0.86, 1.02 and 0.80 T/S respectively. On each side of the optimal MTL value, the magnitude of correlation between MTL and SBP, DBP and the prevalence of hypertension were different.

During recent years, a large number of studies have shown that MTL was significantly linked to cardiovascular risk factors, such as alcohol consumption (19), smoking (20), BMI (21) and blood lipids (22). Our results agreed with those previous studies, while demonstrating a saturation threshold for the relationship between MTL and elevated BP. Meanwhile, Aydos and his team members found no relationship between SBP, DBP, BMI, and telomere length by using of Spearman's correlation coefficient (23). Demissie *et al.* (24) suggested that when comparing with

normotensive peers, subjects with hypertension had a shorter age-adjusted telomere length in 327 men from the Framingham Heart study. However, the mechanism behind was still unclear. Our finding may provide a useful guide to future study.

It is possible that the longer the MTL, the lower risk for the hypertension development. The possible reasons can be as follows: on the one hand, telomere length was inversely related to aging, and which BP increases with age (25); on the other hand, telomere length was closely related to inflammation and oxidative stress, which played an important role in monitoring BP (26). In addition, shorter MTL may relate to the dysfunction of endothelial cells and vascular smooth muscle cells, insulin resistance hence the development of high BP (27).

However, some limitations should be taken into consideration for the present study. First, this study is cross-sectional in nature, therefore causality is not confirmed.

Second, we did not examine markers related to inflammation and oxidative stress, which may also associate with hypertension (28,29). Third, the study population is limited to American population, the findings cannot be extrapolated to other populations. Despite these shortcomings, we have adjusted multiple confounding factors related to BP, and found a potential non-linear association between MTL and elevated BP. Finally, because this study only analyzed the relationship between BP and MLT, but not with telomere activity, the relationship between telomere activity and BP should be explored in the future.

In conclusion, a nonlinear association between MTL and elevated BP was found among US adults. Well-designed prospective studies are needed to clarify the causal relationship between them in the future.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm.2020.03.205>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention (Protocol #98-12). All participants gave written informed consent.

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