Relationship of mean arterial pressure with other cardiac and biological factors

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Abstract

Objective: The relationship of Mean Arterial Pressure (MAP) with the other cardiac and biological factors is very complicated, and is not well-known in the literature. The report focuses on the associations of MAP with other cardiac and biological factors for shock patients.

Material & Methods: A real data set of 113 shock patients with 20 study variables is considered in the report, which is available on the site http://www.umass.edu/statdata/statdata/data/shock.txt. The probabilistic model of MAP has been derived using statistical joint generalized linear models.

Results: The MAP is positively associated with age (P=0.0065), systolic blood pressure (SBP) (P<0.0001), diastolic blood pressure (DBP) (P<0.0001), cardiac index (CI) (P<0.0001), joint interaction effects of heart rate (HR) & mean central venous pressure (MCVP) (HR*MCVP) (P=0.0288), DBP*MCVP (P=0.0022), body surface index (BSI)*MCVP (P=0.0337), SBP*BSI (P=0.0472), while it is negatively associated with survival status (Survive) (P=0.0127), MCVP (P=0.0004), BSI (P=0.0048), appearance time (AT) (P=0.0379), hematocrit (HCT) (P=0.0988), SBP*HR (P=0.0039) and SBP*DBP (P<0.0001). Variance of MAP is negatively associated with sex (P=0.0279), shock type at level 2 (P=0.0367), at level 3 (P=0.0012), SBP (P=0.0342), DBP (P<0.0001), BSI (P<0.0001), DBP*MCVP (P=0.0482), while it is positively associated with SBP*DBP (P=0.0004), DBP*BSI (P<0.0001) and HCT (P=0.0703).

Conclusion: MAP is higher at older ages. It increases if SBP, or DBP, or CI, or HR*MCVP, or DBP*MCVP, or MCVP*BSI, or SBP*BSI increases. It decreases if MCVP, or BSI, or AT, or HCT, or SBP*HR, or SBP*DBP increases.

Keywords: body surface index, cardiac index, heart rate, mean arterial pressure, mean central venous pressure, joint gamma models

Introduction

Mean Arterial Pressure (MAP) is the measurement that interprets the average blood pressure in an individual's blood vessels during a single cardiac cycle. It is significant as it measures the blood pressure necessary for adequate perfusion of the organs of the human body. It is recognized as a better indication of perfusion than SBP by many medical practitioners [1,2]. It is necessary to have a MAP of at least 60 mmHg to supply sufficient blood to the coronary arteries, brain and kidneys. The normal range of MAP is between 70 and 100 mmHg. If MAP deviates from this range for a long time, it may have drastic negative effects on the body [1-3]. Therefore, MAP is considered as a critical hemodynamic factor. The lack of sufficient regulation of MAP may have important pathophysiological consequences. Low MAP can cause insufficient blood flow to organs, shock, and syncope, while high MAP contributes to increased oxygen demand by the heart, vascular injury, ventricular remodeling, stroke, and end organ damage [4-6].

MAP as calculated from the SBP and DBP (using empirical equation MAP= DBP + (SBP-DBP)/3; Wikipedia), varies among individuals [7,8]. Many empirical equations of MAP such as MAP= (CO×SVR) + CVP (where CO is Cardiac Output; SVR is Systemic Vascular Resistance; CVP is Central Venous Pressure); MAP = DBP + 0.01×exp (4.14- 40.74/HR) (SBP - DBP) have been suggested (see Wikipedia). A critical evaluation of many empirical equations for predicting MAP has been reported in [9]. The accurate measurement of MAP is necessary in calibrating pressure waveforms to calculate

central BPs [8,10]. The prognostic implication of the MAP in the epidemiological investigation may be underestimated as the outcome of its incorrect calculation. Generally, MAP is computed by adding 33% of the Pulse Pressure (PP) to the DBP. Recent research articles show that these outcomes in underestimation of the MAP in all subjects [7,11]. The recently suggested rule of adding 40% of the PP to the DBP shows better average outcomes but does not show the optimization of individual MAPs [7]. Theoretically, oscillometric assessment is the optimal technique for exactly determining MAP [8]. Maximal pressure oscillations in the instrument cuff on the individual's upper arm occur when the vessel wall is maximally unloaded, i.e. at the instant that the cuff pressure equals the MAP [12,13]. MAP can be measured exactly with oscillometric devices that are affirmed for measurements of SBP and DBP according to the British Hypertension Society protocol [8,14]. Accurate measurement of MAP is still under problem [8,15].

From the above empirical equations of MAP, it is observed that MAP has some associations with other cardiac factors (or parameters) such as SBP, DBP, HR, CO, SVR, CVP etc. Several associations of MAP have been reported in many articles [16-20]. A few of them are stated as follows. The relationship between MAP and Cardiovascular Disease (CVD) hospitalization is nonlinear (P <0.001 for linearity test) based on Logistic regression and odds ratio [16]. The Editorial letter by Ahn and Lim displays direct arterial BP data in a patient under anesthesia, focusing that variations in MAP may result from differences in pressure waveforms even in the presence of stable SBP and DBP readings. First-trimester MAP is highly associated with preeclampsia risk, and it poorly differentiates between women who will and will not reveal the disease [17,18]. The relationship between MAP and organ perfusion has been discussed in the review article [19]. Pulse pressure and MAP are both associated with ischemic stroke [20].

Some empirical equations of MAP have been suggested by earlier researchers [4]. Several associations of MAP have been noticed by earlier researchers and medical practitioners, which have been derived based on simple correlation, Logistic regression, odds ratio, which are not appropriate statistical approaches for many factors simultaneously [16-20]. These associations should be derived based on probabilistic modeling of MAP [21,22]. But there is a very little study regarding the probabilistic relationship of MAP. The present report derives the probabilistic model of MAP with many cardiac factors along with some biological and biochemical factors for shock patients. Based on the probabilistic model, associations of MAP with cardiac, biological and biochemical factors are focused in the report. The current report examines the following queries.

- Is there any association of MAP with cardiac, biological and biochemical factors? If it is affirmative, what is the most probable MAP association model?
- How do we derive the most probable MAP association model?
- What are the roles of the explanatory factors on the MAP?

The article inquires about the above three research problems considering the following sections such as materials & methods, statistical analysis & results, discussions, and conclusions. The probabilistic MAP model is displayed in Table 1 using the data set displayed in the materials section. The MAP mean and dispersion models are derived by Joint Generalized Linear Models (JGLMs) that are stated in the methods section. The derived outcomes are displayed in the results section and illustrated in the discussion section. Based on the derived MAP probabilistic model, the present article reaches some conclusions.

Material & Statistical Methods

■ Materials

The report derives the probabilistic model of MAP with a real data set of 113 shock patients including 20 explanatory factors/variables. The data set has been recorded twice (at the time of admission and before death or discharge). The data description, source, and data collection method are displayed in [23]. These are not redisplayed herein. For the immediate application of the covariates, they are restated as Age, Height, Sex (male=0, female =1), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Shock type (Shock) (non-shock=1, hypovolemic=2, cardiogenic, or bacterial, or neurogenic or other=3), Survival status (Survive) (survived=1, death=2), Mean Central Venous Pressure (MCVP), Mean Arterial Pressure (MAP), Heart Rate (HR), Appearance Time (AT), Body Surface Index (BSI), Mean Circulation Time (MCT), Cardiac Index (CI), Plasma Volume Index (PVI), Urinary Output (UO), Red Cell Index (RCI), Hematocrit (HCT), Hemoglobin (HG), and Card Sequence Record (initial=1, final=2) (CSR). This data set contains some cardiac

biological, and biochemical factors.

■ Statistical Methods

In the present study MAP is the interested response random variable, which is to be modeled with the remaining cardiac, biological and biochemical factors. Herein it is examined that the response MAP is non-constant variance and non-normally distributed random variable. This may be modeled by a suitable transformation if the variance of MAP is stabilized with the specific transformation. But the variance of MAP is not stabilized with any suitable transformation. Hence, MAP may be modeled by Joint Generalized Linear Models (JGLMs) with Gamma or Log-normal distribution, which has been clearly given in [24-27]. JGLMs are not explained herein explicitly. For detailed discussion about JGLMs, interested readers may consult with [24,25]. For MAP analysis, Gamma JGLMs fit shows better outcomes than Log-normal, so Gamma JGLMs are described herein shortly.

■ Gamma JGLMs

Let us consider MAP=yi be a positive continuous response random variable with $E(y_i) = \mu_i$ and $Var(y_i) = \sigma_i^2 V(\mu_i)$, where μi's and σ_i^2's are mean & dispersion parameters, respectively. Here V (•) represents the variance function including two components such that σ_i^2 (free from mean changes) and $V(\mu_i)$ (dependent on the mean changes). Theoretically, GLM family distribution is known by $V(\mu_i)$. For instance, if V(μ) = μ, it is Poisson, and it is Normal or Gamma as V(μ)= 1, or V(μ) = μ^2, etc. Gamma JGLMs mean & variance models are $\eta_i = g(\mu_i) = x_i^t \beta$ and $\varepsilon_i = h(\sigma_i^2) = w_i^t \gamma$,

where $g(\cdot)$ & $h(\cdot)$ are the GLM link functions for the mean & variance linear predictors respectively, and x_i^t, w_i^t are the vectors of explanatory variables/ factors, related with the mean and variance parameters respectively. Maximum Likelihood (ML) method is adopted to estimate mean parameters, while the Restricted ML (REML) method is applied to estimate dispersion parameters [24].

Statistical Analysis & Results

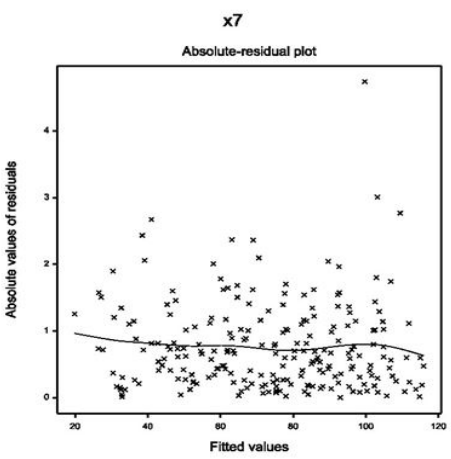
■ Statistical Analysis

The response MAP has been modeled by JGLMs with both Gamma & Log-normal distributions. Here MAP is considered as the dependent or response variable, and the remaining 19 variables are considered as the explanatory variables of MAP. Final model has been chosen based on the lowest Akaike Information Criterion (AIC) value (within each class), which minimizes both the squared error loss and predicted additive errors [28]. According to the AIC criterion, JGLMs Gamma fit (AIC= 1146.424) is better than Log-normal (AIC=1152). Two insignificant effects (here HR in the mean model & MCVP in the variance model) are retained in the mean & variance models due to the marginality rule, namely that if an interaction effect (here HR*MCVP in the mean model, and DBP*MCVP in the variance model) is significant all its related lower-order interactions (here nil) & main effects (here HR, MCVP & DBP) should be included in the model [29]. Partially significant effect HCT is included in both mean & variance models which is known as a confounder in Epidemiology. For better fit, some insignificant effects (here Survival status in the variance model) may be included in the model [28,30]. Only the final MAP Gamma JGLM analysis outcomes are displayed in Table 1.

The derived probabilistic model of MAP (Table 1) is a data generated model, which is to be verified by model checking tools. Note that valid interpretations are drawn from the data generated probabilistic model. For the joint Gamma fitted MAP models (Table 1), model checking graphical analysis is presented in Figure 1. In Figure 1(a), absolute residuals for the fitted MAP (Table 1) are plotted with respect to fitted values, which is exactly flat linear, indicating that variance is constant with the running means. Figure 1(b) reveals the normal probability plot for the fitted MAP mean model (Table 1), which does not indicate any lack of fit. Both the figures do not indicate any discrepancy in the fitted MAP models (Table 1). These figures confirm that the Gamm fitted MAP model is an approximate true model of MAP.

■ Results

Final Gamma fitted MAP analysis summarized outcomes are displayed in Table 1. Table 1 reveals that MAP is positively associated with age (P=0.0065), Systolic Blood Pressure (SBP) (P<0.0001), Diastolic Blood Pressure (DBP) (P<0.0001), Cardiac Index (CI) (P<0.0001), joint interaction effects of Heart Rate (HR) & Mean Central Venous Pressure (MCVP) (HR*MCVP) (P=0.0288), DBP*MCVP (P=0.0022), Body Surface Index (BSI)*MCVP (P=0.0337), SBP*BSI (P=0.0472), while it is negatively associated with survival status (Survive) (P=0.0127), MCVP (P=0.0004), BSI (P=0.0048), Appearance Time (AT) (P=0.0379),



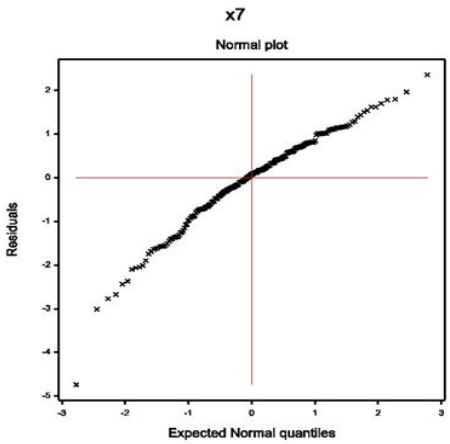


FIGURE 1. For the joint Gamma fitted models of MAP (Table 1), the (a) absolute residuals plot with the fitted values, and (b) the normal probability plot for the mean model

TABLE 1. Results for mean and dispersion models for mean arterial pressure from Gamma fit

Model	Covariate	Estimate	s.e.	t-value	P-value
	Constant	2.9353	0.14642	20.047	<0.0001
	Age	0.0006	0.00019	3.041	0.0065
	Survive status	-0.0166	0.00659	-2.513	0.0127
	Systolic blood pressure (SBP)	0.0089	0.00107	8.321	<0.0001
	Heart rate (HR)	0.0004	0.00043	0.989	0.3238
	SBP*HR	-0.0001	0.00001	-2.914	0.0039
Mean	Diastolic BP (DBP)	0.0228	0.00075	30.397	<0.0001
	SBP*DBP	-0.0001	0.00001	-17.524	<0.0001
Model	Mean central venous pressure (MCVP)	-0.0202	0.00571	-3.544	0.0004
	HR*MCVP (x8.x10)	0.0001	0.00002	2.201	0.0288
	DBP*MCVP (x9.x10)	0.0001	0.00003	3.099	0.0022
	Body surface index (BSI)	-0.2259	0.07933	-2.847	0.0048
	MCVP*BSI	0.0063	0.00296	2.137	0.0337
	SBP*BSI	0.0011	0.00056	1.996	0.0472
	Cardiac index (CI)	0.0126	0.00245	5.137	<0.0001
	Appearance time (AT)	-0.0015	0.00071	-2.089	0.0379
	Henatocrit (HCT)	-0.0008	0.00047	-1.658	0.0988
	Constant	11.094	3.1266	3.548	0.0005
	Sex	-0.581	0.2622	-2.214	0.0279
	Survive status	0.426	0.3235	1.316	0.1896
	Shock type	-0.75	0.3565	-2.102	0.0367
	Shock type	-1.035	0.3161	-3.276	0.0012
Dispersion Model	SBP	-0.025	0.0117	-2.131	0.0342
	DBP	-0.307	0.0542	-5.665	<0.0001
	SBP*DBP	0.001	0.0002	3.592	0.0004
	BSI	-8.455	1.9275	-4.387	<0.0001
	DBP*BSI	0.132	0.0307	4.314	<0.0001
	MCVP	0.077	0.0629	1.229	0.2204
	DBP*MCVP	-0.002	0.0011	-1.987	0.0482
	HCT	0.036	0.0197	1.821	0.0703

Hematocrit (HCT) (P=0.0988), SBP*HR (P=0.0039) and SBP*DBP (P<0.0001). Variance of MAP is negatively associated with sex (P=0.0279), shock type at level 2 (P=0.0367), shock type at level 3 (P=0.0012), SBP (P=0.0342), DBP (P<0.0001), BSI (P<0.0001), DBP*MCVP (P=0.0482), while it is positively associated with SBP*DBP (P=0.0004), DBP*BSI (P<0.0001) and HCT (P=0.0703).

Gamma fitted MAP mean ($\hat{\mu}$) model (Table 1) is $\hat{\mu}$ = exp. (2.9353 + 0.0006 Age – 0.0166 Survive + 0.0089 SBP + 0.0004 HR – 0.0001 SBP*HR + 0.0228 DBP – 0.0001 SBP*DBP – 0.0202 MCVP + 0.0001 HR*MCVP + 0.0001 DBP*MCVP – 0.2259 BSI + 0.0063 MCVP*BSI + 0.0011 SBP*BSI + 0.0126 CI – 0.0015 AT – 0.0008 HCT), and the fitted MAP variance ($\hat{\sigma}^2$) model is $\hat{\sigma}^2$ = exp. (11.094–0.581 Sex +0.426 Survive –0.750 Shock type level 2–1.035 Shock type level 3 – 0.025 SBP – 0.307 DBP +

0.001 SBP*DBP – 8.455 BSI + 0.132 BDP*BSI + 0.077 MCVP – 0.002 DBP*MCVP + 0.036 HCT).

Note that mean MAP is explained by Age, Survival status, SBP, HR, SBP*HR, DBP, SBP*DBP, MCVP, HR*MCVP, DBP*MCVP, BSI, MCVP*BSI, SBP*BSI, CI, AT, and HCT, while the variance of MAP is explained by Sex, Survival status, Shock type level 2, Shock type level 3, SBP, DBP, SBP*DBP, BSI, DBP*BSI, MCVP, DBP*MCVP, and HCT.

Discussion

The summarized results of MAP analysis are displayed in Table 1. The above two equations show the MAP fitted mean & variance models (Table1). These two equations show the association of MAP with the other remaining factors/ variables. From the MAP mean model, it is derived herein that MAP is directly associated with age (P=0.0065), interpreting that MAP is higher at older ages than younger, which is observed in practice. Mean MAP is inversely associated with survival status (survived=1, death=2), (P=0.0127), concluding that MAP is higher for survived shock patients than patients close to death. Mean MAP is directly associated with SBP (P<0.0001) (highly significant, for large t-value), implying that MAP rises as SBP increases. It supports the earlier empirical MAP equations. Mean MAP is inversely associated with SBP*HR (P=0.0039), denoting that MAP increases as SBP*HR decreases, while HR is insignificant (P=0.3238). Therefore, inclusion of HR in the empirical MAP equation is not appropriate [4], which is not reported in earlier articles. Mean MAP is directly associated with DBP (P<0.0001) (highly significant, for large t-value), implying that MAP rises as DBP increases. It supports the earlier empirical MAP equations. Mean MAP is inversely associated with SBP*DBP (P<0.0001), denoting that MAP increases as SBP*DBP decreases. This shows that the two marginal effects SBP & DBP are positively associated with MAP, while their interaction effect is negatively associated with MAP. This indicates that even SBP & DBP are very high, but MAP may not be high, due to their inverse interaction effect. It is noted in many earlier articles, but could not explain [17]. Mean MAP is inversely associated with MCVP (P=0.0004), interpreting that MAP rises as MCVP decreases. It is not pointed out in earlier articles. Mean MAP is directly associated with HR*MCVP (P=0.0288), indicating that MAP rises as HR*MCVP increases, which is not pointed out in earlier articles. Mean MAP is directly associated with DBP*MCVP (P=0.0022), concluding that MAP rises as DBP*MCVP increases. This is not pointed out in earlier articles.

Also, from the mean MAP model, it is derived that mean MAP is inversely associated with BSI (P=0.0048), implying that MAP rises as BSI decreases, which is not pointed out in earlier articles. Mean MAP is directly associated with MCVP*BSI (P=0.0337), implying that MAP rises as MCVP*BSI increases. This is not pointed out in earlier articles. Mean MAP is directly associated with SBP*BSI (P=0.0472), implying that MAP rises as SBP*BSI increases. This is not pointed out in earlier articles. Mean MAP is directly associated with CI (P<0.0001), concluding that MAP increases as CI increases. Empirical MAP equations include CO but not CI. Note that CI=CO/BSA, where BSA is body surface area. It indirectly supports the empirical MAP equations. Mean MAP is inversely associated with AT (P=0.0379), interpreting that MAP rises as AT decreases. This is not pointed out in earlier articles. Mean MAP is inversely associated with HCT (P=0.0988), indicating that MAP rises as HCT decreases, which is not pointed out in earlier articles.

From the MAP variance model (Table 1), it is derived that MAP variance is negatively associated with sex (male =0, female =1) (P =0.0279), concluding that MAP levels are scattered more for male than female shock patients. MAP variance is negatively associated with shock type (non-shock =1, hypovolemic =2, cardiogenic, or bacterial, or neurogenic or other=3) at level 2 (P=0.0367) and at level 3 (P=0.0012), interpreting that MAP levels are scattered more for non-shock patients than shock patients. MAP variance is negatively associated with SBP (P=0.0342), indicating that scatteredness of MAP levels increases as SBP level decreases. MAP variance is negatively associated with DBP (P<0.0001), concluding that scatteredness of MAP levels increases as DBP level decreases. MAP variance is positively associated with SBP*DBP (P=0.0004), interpreting that MAP variance increases as SBP*DBP increases. MAP variance is negatively associated with BSI (P<0.0001), implying that scatteredness of MAP levels increases as BSI decreases. MAP variance is positively associated with DBP*BSI (P<0.0001), interpreting that MAP variance increases as DBP*BSI increases. MAP variance is negatively associated with DBP*MCVP (P=0.0482), interpreting that MAP variance increases as DBP*MCVP decreases. MAP variance is positively associated with HCT (P=0.0703), interpreting that scatteredness of

MAP levels increases as HCT increases.

Interpretations of the current outcomes of MAP modeling have been presented above. Mean and variance MAP models have suggested the above conclusions. The mean & variance of MAP can be estimated from the respective equation. The report supports that MAP is directly associated with SBP & DBP but it contradicts that MAP is negatively associated with MCVP, and it has no association with HR (empirical equations of MAP in Introduction Section). Earlier research articles and also practitioners could not estimate MAP exactly as the relationship of MAP with other cardiac, biological, and biochemical parameters is very complex. Here it is shown that MAP is associated with many marginal & joint interaction effects. Earlier reports could not identify any interaction effect which is associated with MAP. The report has explained the fact that even though both SBP & DBP are very high, MAP is not so high [17]. Adding 1/3 of the Pulse Pressure (PP) to the DBP is the most frequently used method for calculating MAP which does not yield the true MAP. In practice, it underestimated the real MAP value of all of the subjects. The discrepancy in the measurements cannot be explained [8]. Best of our knowledge, the report first focuses on the complex relationship of MAP. Most of the present outcomes are completely new in medical literature, so the present results are little compared with the earlier published outcomes.

The report has focused on the relationship of MAP with other cardiac and biological factors through its fitted mean & variance probabilistic models. The fitted MAP models have been accepted based on the smallest AIC value, on comparison of both the joint Gamma (AIC=1146.424) & Log-normal (AIC=1152) models, small standard error of the estimates (Table 1) and model diagnostic plots (Figure 1). It has been derived that MAP increases at older ages, or SBP, or DBP, or HR*MCVP, or DBP*MCVP, or MCVP*BSI, or SBP*BSI, or CI increases. It also increases if SBP*HR, or SBP*DBP, or MCVP, or BSI, or AT, or HCT decreases. Variance of MAP increases for male, or SBP, or DBP, or BSI, DBP*MCVP decreases. It also increases if SBP*DBP, or DBP*BSI, or HCT increases. The report has two purposes. The first is to compare the present outcomes to those of previous research.

It has supported and also contradicted some of the previous results (empirical equations of MAP). The second purpose is to evaluate the appropriate probabilistic model of MAP using suitable statistical methods. The present outcomes, though not completely conclusive, are revealing. Research should have greater faith in these outcomes than those emanating from the Logistic and odds ratio analysis.

The derived MAP models (Table 1), are related to the data set given in [23]. For different data sets, MAP models may be little different, but the associations of MAP with other cardiac and biological factors may remain same, which has not been verified herein, as similar data sets are not available. The report does not include many other cardiac factors such as basal HR, maximum HR, peak HR, ejection fraction, basal BP, maximum BP, etc., as these are not included in the given data set [23]. Future researchers may consider these additional cardiac factors to derive many influencing factors of MAP measurement.

Conclusion

The report presents a very complex relationship of MAP which gives the clear idea about the influencing factors of MAP to the medical practitioners. This report may help the researchers to explain the discrepancy of MAP measurement based on empirical equations. Medical practitioners can predict the MAP value from this relationship. Internal complex mechanism of the human body can only be predicted through appropriate probabilistic modeling. Medical research should be based on probabilistic modeling. Every individual should care for MAP at older ages along with SBP, DBP, CI, MCVP, HR, HCT and BSI.

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Conflict of interest

The authors confirm that this article content has no conflict of interest.

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