Title: Short-term and Mid-term Blood Pressure Variability and long-term Mortality: evidence from the Third National Health and Nutrition Examination Study

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# Abstract (200 words, unstructured)

# Introduction

While the association between hypertension and mortality risk was first noted in actuarial studies in the first half of the twentieth century1,2 it was not until the 1960s that studies such as Framingham and the Seven Countries Study3,4 demonstrated the link between hypertension and CVD risk. These observational studies in turn led to trials that showed treatment of hypertension could reduce risk.5 In the United States, guidelines on the management of hypertension have been produced by the Joint National Commission since 1976 and are now in their eighth edition.6 Screening for hypertension among adults for the prevention of cardiovascular disease is the only action with the highest “A” level evidence based rating from the U.S. Preventative Services Task Force (USPSTF). Despite this, the USPSTF notes that there is still a substantial research gap in understanding “white coat hypertension” and “masked hypertension”, which describe the variability of measured blood pressure depending on context. A better understanding of the clinical course associated with these variations is not only important for understanding errors in our current attributions of blood pressure to long-term health outcomes, but also for potentially identifying new mechanisms by which blood pressure may impact cardiovascular outcomes.

While most studies to date of blood pressure and cardiovascular risk have focused on mean blood pressure, there is a growing literature investigating the impacts of variation in blood pressure on cardiovascular-related outcomes.7,8 This literature can be divided into studies that examine very short term (beat to beat), short term (within 24 hours), mid-term or visit-to-visit (day to day), long term (< 5 years) and very-long term (> 5 years) blood pressure variablity9. Work is still emerging on the clinical significance of these different types of blood pressure variation as they related to cardiovascular disease mortality. While these time windows of variation are sometimes framed as errors in measurement10, emerging evidence suggests that visit-to-visit and 24 hour variation may both predict cardiovascular outcomes. Prior work showed that the standard deviation of visit-to-visit systolic blood pressure was associated with all-cause mortality over a 14-year follow-up.11 Frattola and colleagues found that increased 24-hour blood pressure variability was related to end-organ damage in 73 hypertensive subjects followed for an average of 7.4 years.12 Findings relating 24-hour or awake blood pressure variability to end-organ damage or the risk of cardiovascular events have been found in samples of hypertensive subjects13, the elderly14,15, and in the general population.16 Visit-to-visit systolic blood pressure variability has likewise been associated with risk of stroke.17,18 Importantly, analysis of visit-to-visit variability is likely to be systematically different between individuals and not based solely on random variation.11

These studies have focused primarily on blood pressure variability measured beyond the course of a single office visit. For incorporation of blood pressure variability into routine practice, it may be useful to measure variation in the course of a patient’s visit for incorporation into risk stratification. However, the significance of the very short-term (VST) variations in blood pressure that might be recorded in one visit is unclear. Previous work by Muntner and colleagues using a quantile analysis did not find associations between within visit systolic and diastolic blood pressure variability and mortality.19 In this study, we consider the prognostic significance of the very short-term variations in blood pressure using the same large, U.S. nationally representative cohort of adults – but using a different analytic approach that better accounts for the randomness of individual variation to deal with regression dilution bias. In addition, we examine cardiovascular mortality specifically, and include a longer follow-up for mortality. We also take advantage of the availability of two sets of measurements (home and clinic) several months apart to estimate the effect of visit-to-visit variability, and explicitly compare the contribution of each of these different types of variability to cardiovascular mortality.

A key difficulty in using variability measures as covariates is that it takes a large number of measurements to accurately measure variability. Regression based on a small number of measurements per individual will be subject to bias in estimation of regression parameters. While corrections for so-called “regression deflation” are possible, they make it difficult to combine the results of individuals with different numbers of measurements, or to combine multiple predictors that are each measured with uncertainty. Thus we see that while Rothwell et al. (2010) carefully separated out individuals with different numbers of blood pressure observations in their analysis, they produced multiple inconsistent parameter estimates. We describe here a novel Bayesian methodology that correctly accounts for measurement error, and is fully flexible as regards the different covariates that can be combined.

**METHODS**

## Study population. Data were from the Third National Health and Nutrition Examination Survey (NHANES III), a survey and examination of a sample of the civilian, non-institutionalized US population conducted by the National Center for Health Statistics from 1988-1994.20 We chose to focus on this older version of NHANES in order to have baseline blood pressure measurements with sufficient follow-up time to examine longer-term impacts on mortality. We used data from the National Death Index (NDI) mortality linkage through December of 2015.

Measurement of blood pressure**.** The examinations consisted of two parts: an in-home examination and a mobile clinic examination, which occurred on different days. The in-home measures were taken by trained interviewers, and the mobile clinic measures were taken by physicians who were specifically trained for measurement practices for the survey. In the home examination portion of this survey, blood pressure was measured antecubitally three times for each subject, with one minute between recordings.21 A second set of three measurements was taken at the mobile examination clinic, also with one minute between recordings. There were generally a few months between these sets of measurements. Physicians taking the measurements were instructed that subjects should sit still for a minimum of 5 minutes prior to the measurement being taken. All blood pressure measurements were recorded to the nearest even number. There were inconsistencies in the home data collection that became apparent on examination of the reported blood pressure measurements, several of which to our knowledge have not been reported in previous analyses of the NHANES III data. These were: 1) Last-digit preference 2) Pseudo-repetition, and 3) Missing or implausible measurements. In appendix 1 we describe how we dealt with these data errors in our analysis; in summary, the first two were not deemed sufficiently relevant to need accounting for, and the last was dealt with by excluding the questionable data. There were *n*=15295 individuals with two complete sets of usable blood-pressure, and these were all included in our primary analysis.

Measurement of other variables.Our primary focus was to determine whether variability of BP provides additional information for predicting future mortality beyond what is already embedded in standard measures of risk. As the standard measure of risk we use the 1998 version of the Framingham Risk Score (FRS). This reduces the sample size. Out of the overall NHANES population, for 9418 individuals we were able to calculate the FRS. The others were excluded for one of the following reasons: 1) Age below 30 or above 74, 2) Missing cholesterol values, 3) Pre-existing CHD. While we focus analyses on the healthier middle-aged population where the FRS could be calculated, we also include findings on the general population.

## Statistical models. The data allow us to examine two versions of very short term (VST) blood pressure variability – in the home and in the mobile examination clinic. We could also estimate a measure of longer term (LT) variability by the difference between the two sets of measurements. We denote the three variability parameters for each individual by

with each of these parameters calculated for systolic and diastolic blood pressure measurements. We also use in the model the variance (home and clinic), which is the square of the SD, and the precision τ, which is the reciprocal of the variance.

In our model we assume that each individual has an overall mean and a BP difference . These are assumed normally distributed in the population and independent. There is also an individual home and clinic variance parameter (SD2), which are assumed to have independent inverse gamma distributions, consistent with the observation that the empirical SDs of the three clinic and three home measurements have correlation of 0.02 for diastolic and 0.07 for systolic blood pressure. The overall means and the differences between the means are also nearly uncorrelated (Pearson’s r ∽ -0.006), the only minor exceptions being the correlations of 0.28 and 0.18 between overall mean systolic and the clinic and home systolic SDs respectively.

The main method we apply is a Bayesian hierarchical proportional hazards model, stratified by gender and race/ethnicity. This approach has the advantage of not suffering from regression-dilution bias, which occurs when there are random errors in the variable of interest. This is an issue in any analysis where the predictive covariate is observed only with uncertainty, and this noisy-covariate problem is particularly acute when using a measure of variability based on a small number of observations. The model-fitting has been carried out using Markov Chain Monte Carlo (MCMC) on the Stan platform22, whereby the exact algorithm used was the No-U-Turn Sampler (NUTS) Hamiltonian Monte Carlo (HMC). The code and the data are available at <https://github.com/hamishwp/Nhanes2021>. We originally proposed this approach23 and has since been applied to modeling of blood pressure variability.24

As the aim of this study is to estimate the effect of blood pressure variability on long-term survival, while accounting appropriately for covariate uncertainty, as variability is only very approximately ascertained by such a small number of measurements. It is more important to have a roughly accurate but stable estimate of the uncertainty in individual variance parameters. This inspires our empirical Bayesapproach25, where we first calculate a maximum likelihood estimate of the hyperparameters that define the distribution of individual BP parameters (means and variances) and then hold that fixed as a prior distribution for the Bayesian analysis of the survival data.

We define *Yij*, where *i*=1,…,*N* for the number of individuals and *j*=1,2,3, for the number of blood pressure measurements for subject *i*. Then  , where and represent the mean and standard deviation respectively, for the *i*-th individual, and are independent standard normal random variables. Blood pressure interacts with mortality as in the standard Cox proportional hazards model, so that individual *i* has mortality rate at age *t* given by

or, in the case of applying the FRS-1998 score

Here the superscripts *H* and *C* indicate whether this is the individual parameter for *Home* or *Clinic* BP measurements, and *S* and *D* tell whether these are systolic or diastolic BP, and is the demographic group – one of six possible combinations of sex (male/female) and race-ethnicity (White/Black/Mexican-American – these being the ethnic categories of the NHANES dataset, except for a small “Other” category that we have excluded from the analysis). For each demographic group we estimate a separate Gompertz baseline mortality . In order to better understand the value of these variability covariates in augmenting the predictive power of more traditional covariates, we also consider a version of the model with an extra term , where is the Framingham Risk Score (1998 version) for individual *i*. As the mean systolic BP is a substantial component of the FRS, this version of the model drops the mean-BP terms and from the linear predictor.

It is important to recognize that the individual covariates – , etc. – that enter into the individual mortality rate above are not observed quantities. They influence the observed BP measurements, and in the course of our MCMC simulations posterior distributions are generated for each individual, representing an inference about the range of possible values that these unknown quantities might have, based on the totality of observations. In order to improve the numerical stability and interpretability of the results, these inferred covariates are centered and normalized. Each inferred covariate appears in the mortality formula as where is the posterior standard deviation for the covariate and is a centering parameter chosen to bring the average model mortality over the population – and averaged over the complete posterior distribution – as near as possible to the observed mortality at each age. Note that the choice of does not, in principle, affect the statistical analysis. The main purpose is to help the interpretability of the Gompertz mortality parameters, making the baseline mortality comparable to the average over the population. Such centering is also generally good practice for the numerical stability of the algorithm. Normalization by has the advantage of making all the parameters comparable in scale, so that means that an increase of 1 SD in an individual’s value of this covariate would correspond to a doubling of mortality risk.

Our statistical approach proceeded through the following steps (further details are provided in the supplemental appendix):

1. Estimate the population distribution of mean BP (*M*), medium-term BP variability (Δ, the absolute difference between home and clinic means), and short-term BP variability ( and , the home and clinic SD respectively), separately for systolic and diastolic BP. This is an empirical Bayes approach to determining the highest level prior distribution. Fixing these at the outset substantially accelerates the convergence of the algorithm, relative to a completely hierarchical approach that would be updating the top-level parameters at every round.
2. Treat each individual’s inherent value of these 8 quantities as unknown samples from the population distribution, modified by the evidence of their 6 BP measurements.
3. In the framework of a Markov-chain Monte Carlo (MCMC) algorithm these unknown quantities are multiply imputed, to infer parameter values (8 different 𝛽 parameters, corresponding to the 8 covariates) that take account of this individual-level uncertainty.
4. The resulting posterior parameters are rescaled to the SD of the posterior samples, and interpreted for their statistical significance and impact on mortality. Note that 𝛽 represents the impact on mortality risk of changes in an inherent covariate such as an individual’s SD for systolic BP, that is unknown from this data set (because of ineluctable measurement error in estimating, for example, SD from a sample of size 3, but which could in principle be measured to arbitrary precision, by increasing the sample size.

When presenting the outputs of our Bayesian model, we adapt standard Bayesian terminology to something closer to the nomenclature customary in epidemiology. We give for each parameter estimate a central 90% credible interval, by which we mean that the stated parameter has a 5% chance of being below the interval and a 5% chance of being above (given the data, and assuming the accuracy of the model). If the interval does not include 0, that may be understood to indicate that there is evidence that the parameter is nonzero. The posterior probability that a given parameter is on the side of zero given by the alternative – for us, generally the positive side – is a standard scale for the strength of evidence, called the “Bayes factor”. It is conventional to say that strong evidence for the research hypothesis is provided by a Bayes factor >20 and decisive evidence by a Bayes factor >150.26 We present instead a quantity more comparable to the usual one-tailed p-values, which is p=max(1,BF)/(1+BF), which may be understood as an estimate of the probability that the parameter is not on the side of the median estimate; thus P<0.10 (BF>19) may be seen as significant evidence that the covariate demonstrates a real effect, and P<0.013 (BF>150) as strong evidence. Because of the limits of precision in these simulation-based computations we cannot discriminate among results below 0.001, and these are reported simply as <0.001.

**RESULTS**

Table 6 presents the results of the association between mean, inter-visit precision, home precision and clinic precision for both systolic and diastolic blood pressure with cardiovascular mortality and all-cause mortality in the subset of the NHANES population with the 1998 Framingham Risk Scores. We first describe the findings for cardiovascular mortality, our primary outcome of interest. Both systolic mean BP (M) and systolic inter-visit difference (ΔS) had highly significant effects, with the coefficient for the mean being about three times as large. No other coefficient was found to be statistically relevant, though diastolic inter-visit difference (ΔD) had a comparable-sized coefficient estimate, and a Bayesian p-value 0.053. The mean (normalized) parameter estimate for systolic mean is 0.348, and for systolic Delta is 0.116. To appreciate the influence of these parameters, we note that the population mean of mean SBP is 125.9, and the SD is 18.2; thus individuals with mean SBP around 144 – approximately one-sixth of the population will be above this level – would be expected to have 42% higher CV mortality than others of the same age, sex, and ethnic category (risk ratio 1.42). The corresponding mortality increase for individuals whose intervisit SBP difference (delta) is around 7 points above the population mean of 1.35 is 12%. The former is consistent with expectations based on known links between systolic BP and CV mortality27, while the latter appears to be a new discovery; it is consistent with the results of prior work based on the ARIC (Atherosclerosis Risk in Communities) study, finding a significant connection between long-term SBP variability (five measurements over more than a decade) and cardiovascular disease.24

Applying the same model to all-cause mortality we find, unsurprisingly, that the coefficients that were statistically significant for predicting CV mortality have been reduced somewhat. In some cases, though, because of the increased power due to the much larger number of events forming the basis for the analysis, the statistical significance has increased. This is most notable for diastolic inter-visit difference, where the Bayesian p-value has gone down from 0.053 to 0.001.

When we look to the results for the whole population in Table 5 we see very similar coefficients, with an increase in significance for the systolic mean and Delta, and the diastolic Delta, due to the larger population size. There are two notable differences: an unexpected strongly negative coefficient for the effect of diastolic mean on cardiovascular and all-cause mortality, and a marginally significant negative influence of clinic diastolic SD on cardiovascular mortality. This could be seen as consistent with the known “paradoxical” effect of diastolic blood pressure in older populations28, combined with little or no influence in the younger population. This interpretation is consistent with the already noted fact that these effects disappear when we confine our analysis to the FRS population, excluding individuals over age 74 at baseline.

When mean blood pressures were removed from the model and replaced by FRS we obtained the results tabulated in Table 7. We see that the coefficients for systolic and diastolic Delta are both strongly positive, and larger than they were in the model that included only the BP means without the FRS. This shows that the inter-visit difference is giving information that is not included in the FRS. We also see in this model a marginally significant effect of short-term variation in systolic BP as measured at home. For predicting CV mortality the Bayesian p-value is 0.047, and for all-cause mortality it is 0.033. As this is an isolated non-null result among multiple hypothesis tests, it must be viewed with some skepticism, but it does suggest that more targeted exploration of a link between short-term SBP variability and mortality may be warranted.

Part of our statistical procedure is an estimate of the distribution of individual means and SDs for systolic and diastolic BP. Based on this distribution, we may normalize the coefficients by multiplying them by the SD of the relevant covariate. These normalized coefficients should be approximately comparable to one another, with +1 meaning a fixed increase in mortality (factor of 2.718, the base of the natural logarithms) for an individual 1 SD above the population mean relative to the average population mortality (for someone of the same age, sex, and ethnic group).

Rather than considering a single percentile, we may choose to look at the whole risk distribution implied by the model, by plotting receiver-operator characteristic (ROC) curves, shown in figure 1. Within the context of a proportional hazards model, the plot shows how concentrated relative risk is. Within a population of a fixed age, the model predicts deaths to arise in proportion to the relative risk, so this may be thought of as a plot of true positive rate against false positive rate.29 The ROC curves measure the overall performance of the model to predict, based on the corresponding blood pressure measurements, which individuals (of the same sex, race, and age) will be the next to die. (A perfect oracle would appear in this plot as a right-angled bracket, with area 1 and AUC=1, which would imply no false-positives).

**Discussion**

Our primary findings were that discrepancy between home and clinic measurements – our proxy here for medium-term blood pressure variability – were associated with a meaningful amount of increased long-term risk of mortality, and particularly of mortality due to cardiovascular and cerebrovascular causes (CVD), and that this increased risk remained after controlling for mean blood pressure or for Framingham risk score. There was suggestive evidence that very short-term (1 minute apart) variability in measurements taken at home were also associated with increased long-term risk. While our results are from an observational study and are associational in nature, they suggest that variability of blood pressure readings over several months, and possibly very-short-terms variability as well, should receive increased attention as a potential predictor of increased CVD mortality risk. We also note that mean diastolic BP is found to have a highly significant negative link to all-cause mortality and to CVD mortality. This effect disappears in the primary analytic sample that has Framingham risk scores, perhaps because this subpopulation excludes the oldest subjects, which would be consistent with the effect that higher diastolic BP is associated with increased survival in the elderly.30,31

When the coefficients of the fitted models, the effect sizes, are scaled by the covariate standard deviation, we see the effect of systolic mean is about three times as large as that of the intervisit difference – about 0.33 vs 0.12 for CVD mortality, and 0.20 vs 0.07 for all-cause mortality. The association between mortality and intervisit variability is of very similar strength between systolic and diastolic blood pressure.

Some of our findings appear to disagree with prior work that also examined blood pressure variability using NHANES data11. In this case, the prior study looked largely at different parts of the data, and thus interpreting these findings in light of the current analysis can help to inform a better understanding of the relationships between different types of blood pressure variability and cardiovascular mortality. The disagreements are only secondarily due to the differences in statistical methodology. One difference in our findings is that we find a highly significant positive effect of inter-visit variability, both systolic and diastolic, on both CVD and all-cause mortality. They found no significant effect of diastolic inter-visit variability. The most likely explanation for this is that this prior work used a different measure of inter-visit variability, based on multiple clinic measurements. This creates a less noisy proxy for LT variability, but drastically reduces the sample size. Instead of the nearly 16,000 subjects included in our analysis (and included in subsequent analysis of within-visit variability19), there were fewer than 1000 subjects who had three sets of clinic measurements.

NHANES has a complex sampling design, including oversampling of various population groups. Thus, the effect sizes estimated here cannot be expected to reflect exactly the effect sizes that prevail in the whole population. Correction of Bayesian hierarchical models for study design is a still underexplored problem in statistics, and we hope to improve our estimates in this direction in a future work.

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