Identification of distinct arterial waveform clusters and a longitudinal evaluation of their clinical usefulness

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Abstract

Clustering of arterial blood pressure (BP) waveform parameters could summarize complex information into distinct elements, which could be used to investigate cumulative (non-redundant) associations. We investigated this hypothesis in a large, adult population-based study (Vitamin D Assessment (ViDA) trial). To interpret the clusters and evaluate their usefulness, we examined their predictors and associations with cardiovascular events. In 4253 adults (mean age 65 years; 55% male) without a prior cardiovascular event, suprasystolic oscillometry was performed, yielding aortic pressure waveforms and several hemodynamic parameters. Participants were followed up for 4.6 years (median), accruing 300 cardiovascular events. Principal component analysis (PCA) reduced 14 arterial waveform parameters to 3 uncorrelated factors that together explained 90% of the variability of the original data. Factors 1, 2 and 3 appeared to represent BP pulsatility, mean BP and wave reflection, respectively. Across six antihypertensive drug classes, there were no differences in brachial systolic (P=0.23) and diastolic (P=0.13) BP; but there were significant variations in factor 3 (P<0.0001), especially for beta-blocker use. The first and third factors were positively associated with cardiovascular events (multivariable-adjusted standardized hazard ratio (95% confidence interval) = 1.33 (1.18-1.50) and 1.15 (1.02-1.30), respectively); while the second factor had a J-shaped relationship, with a nadir corresponding to a brachial diastolic BP of ~75 mmHg. In conclusion, BP pulsatility, mean BP and wave reflection are prognostically meaningful, distinct aspects of arterial function that can be used to summarize physiological variations in multiple arterial waveform parameters and identify truly cumulative associations when used as cardiovascular-risk outcomes.

Keywords: Blood pressure, wave reflection, arterial stiffness, hypertension, principal component analysis, cluster analysis

In the primary prevention of cardiovascular disease (CVD), brachial blood pressure (BP) is routinely used in cardiovascular risk assessment. But other measures of arterial function may be clinically important. Some of these include aortic, as opposed to brachial, systolic BP (SBP), augmentation index (AIx), excess pressure integral and backward pressure amplitude – arterial waveform parameters which have been shown to predict cardiovascular events independently of brachial BP.[1-3] While the prognostic significance of these parameters has been studied individually or collectively,[1-6] strong correlations amongst them complicate interpretations of results. Another problem is that, given they are numerous, several models are required to study their associations with different variables, which increases the probability of type I statistical errors (false positives).

Principal component analysis (PCA) is a statistical technique that reduces several correlated variables to fewer factors which represent distinct attributes that explain a high fraction of the variability in the original variables. Combining arterial waveform parameters into factors by this method quantifies common pathways by which they may vary. This could help to provide additional insight into the aetiology of CVD; but these analyses have not been previously published.

We used PCA to examine how arterial waveform parameters cluster in a large, population-based study of apparently healthy adults (without established CVD). To interpret the derived factors and evaluate their usefulness, we investigated how they varied with age, physiological parameters, antihypertensive medications and cardiovascular events.

Methods

The authors declare that all supporting data are available within the article and its online-only Data Supplement.

Participants

The present study is an analysis of data collected in the ViDA (Vitamin D Assessment) study, a randomized controlled trial of the health effects of vitamin D supplementation. Men and women aged 50-84 years and resident in Auckland were recruited. Exclusion criteria comprised: 1) diagnosis of a terminal illness and/or hospice care, 2) intending to leave New Zealand during the follow-up period, 3) taking vitamin D supplements (including cod liver oil) of >600 IU/day if aged 50-70 years or >800 IU/day if aged 71-84 years, 4) history of renal stones, hypercalcaemia, or medical conditions that can cause hypercalcaemia and 5) baseline serum calcium >2.50 mmol/L. Since the objective of the current study relates to apparently healthy people without established CVD, we excluded people (n=670) with a prior CVD history (determined from questionnaire responses and Ministry of Health databases; mentioned below). All baseline data were collected between 2011 and 2012. Ethics approval was provided by the Ministry of Health Multi-region Ethics committee. Written, informed consent was obtained from each participant. Full details have been published elsewhere.[7]

Non-BP measures

All measurements were performed by trained staff using a standardized protocol. Questionnaires were used to collect data on age, sex, ethnicity (self-identified), smoking and medical history. Medical history was also captured from hospitalisations prior to the baseline evaluation (April 2011 to November 2012). We used each participant's place of residence to calculate the 2013 New Zealand Deprivation Index (NZDep13), a proxy measure of social

deprivation created from the 2013 census data.[8] Without shoes and in light clothing, height was measured with a stadiometer (±0.1 cm) and weight with digital scales (±0.1 kg). Body mass index (BMI) was calculated as body weight (kg)/height $(m)^2$. A blood sample was taken and measured for serum total cholesterol and high-density lipoprotein (HDL) cholesterol on an Advia 2400 analyzer (Siemens Healthcare Diagnostics, Germany).

Medications dispensed, cardiovascular morbidity and mortality data were collected from the Ministry of Health databases. All New Zealand residents are allocated a unique National Health Index number, which was used to track drugs dispensed, hospital admissions and deaths. We assumed that measured arterial waveform parameters would only be influenced by prescribed antihypertensive medicines taken shortly before the measurements. Therefore, for the analyses of the association of antihypertensive medications with arterial waveform parameters, we focused on prescriptions with days of supply that encompassed the interview date. These drugs were categorised into six major antihypertensive classes – alpha(α)-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta(β)-blockers, calcium channel blockers and diuretics – and we focused on monotherapies only to make comparisons between different classes simpler. As variables adjusted for in CVD models, we focused on drugs (antihypertensive, lipid-lowering, antithrombotic) that had been dispensed in the 6 months prior to baseline assessment, as defined in nationally representative CVD models.[9] To capture outcomes recommended in national CVD risk assessment guidelines,[10] the primary cardiovascular endpoint was hospitalizations for or deaths from: heart failure, myocardial infarction, angina, chronic ischemic heart disease, cardiac arrest, cardiomyopathy, ischemic/hemorrhagic stroke, transient ischemic attack, other cerebrovascular disease, peripheral vascular disease, aneurysm or dissection of aorta. Secondary endpoints were cardiac events only and cerebrovascular events only (Table S1 in the online-only Data Supplement).

BP measures

After 15 minutes rest while sitting, brachial BP (±1 mmHg) was measured three times with an Omron T9P oscillometric device (Omron Healthcare, Kyoto, Japan) with an appropriately-sized cuff placed above the cubital fossa of the left arm. The mean of the two closest measurements were used for analyses. Suprasystolic oscillometry was performed with a BP+ device (Uscom, Sydney, Australia) (formerly known as a R6.5 cardiovascular monitor; Pulsecor, Auckland, New Zealand) to generate aortic pressure waveforms. The BP+ device has been shown to: 1) yield central SBP that correlates strongly with that measured by aortic catheterization [11] and, 2) measure central SBP with good intra-test and inter-test reliability.[12] To improve the quality of the waveforms used in analyses, we decided *a priori* to exclude readings with a signal-to-noise ratio of <3dB.

Left-ventricular contractility was estimated as the maximum positive gradient of the aortic pressure waveform.[13] In addition to this and aortic SBP, several other parameters, which predict cardiovascular events independently of brachial BP, were calculated from the aortic pressure waveform (Figure S1).[1-6] AIx (%),[1] a presumed index of arterial stiffness and wave reflection,[14] was calculated with algorithms that identify the augmentation point based on the zero-crossing of the 4th derivative of the pressure.[15] Aortic PWV [5] was calculated from validated algorithms.[16, 17] Aortic pressure was separated into reservoir and excess components using custom-written Matlab software (Mathworks, Natick, MA), with reservoir pressure being calculated from pressure measurements only, as described elsewhere.[2] Excess pressure was calculated as measured pressure minus reservoir pressure.[2] The integral of (area under) the excess pressure waveform over the cardiac cycle was used to calculate excess pressure integral (measures pressure associated with excess ventricular work [2]) and the amplitude of the reservoir pressure waveform was quantified.[6] Aortic pressure was separated into forward-

and backward-travelling pressure waves using wave separation analysis.[3] Their amplitudes – forward pressure amplitude and backward pressure amplitude [3] – were then calculated by a technique that yields values similar to those obtained using true aortic flow waves measured by Doppler ultrasound.[18] Wave intensity analysis was used to calculate wave reflection index (WRI).[4]

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Excess pressure integral and WRI were positively skewed and, thus, were log-transformed. PCA was applied to arterial waveform parameters to reduce these to fewer variables called "PCA factors (components)": uncorrelated, linear combinations of the original variables.[19] Each component has an associated eigenvalue, which represents the variance in the original variables explained by that component (each original variable is standardized to have a variance of 1). We retained principal components based on both those with eigenvalues of >1 and a scree-plot analysis of eigenvalues (the result from each method was identical), and used these in subsequent analyses. Varimax rotation (an orthogonal method) was then applied to the selected factors, thus resulting in them remaining uncorrelated with each other. PCA factor loadings (which indicate the relative contribution of each original variable to a given factor; that is, correlation coefficients for these relationships) of ≥0.3 were considered significant.[20] These analyses were carried out in the total sample, major demographic groups and in other BP-related groups.

We also applied promax rotation (an oblique method) to the selected factors, which allows the rotated factors to be correlated with each other.[20] This was followed up by applying cluster analysis to the original arterial waveform parameters using the VARCLUS procedure. This method organizes variables into hierarchical clusters, which are allowed to be correlated

with each other and can be used to examine redundancy between variables. Results were presented in a dendrogram, illustrating variables in each grouping and the distance (degree of similarity) between groups.[20] For these analyses, both linear combinations based on principal and centroid components were calculated. To quantify how well-defined clusters were, we used the ratio value $1-(R^2_{own}/R^2_{nearest})$, where the R^2 values represent the degree to which a variable belonging to one cluster is explained by the remaining variables in that cluster (R^2_{own}) and the nearest cluster ($R^2_{nearest}$). In a well-defined cluster, variables within it correlate strongly with that cluster (high R^2_{own}) and weakly with other clusters (low $R^2_{nearest}$), thus giving low values of $1-(R^2_{own}/R^2_{nearest})$.[20]

PCA factor scores (which have a mean of 0 and standard deviation (SD) of 1) were calculated for each individual by multiplying each standardized arterial waveform parameter value (number of SDs away from the mean) by the corresponding standardized scoring coefficient (reported, along with mean and SD values, in Table S2).[21] Multiple linear regression was used to examine predictors of these factor scores. Guided by associations in previous studies, these relationships were adjusted for age, sex, ethnicity, antihypertensive treatment, smoking, diabetes, NZDep13, total:HDL cholesterol ratio, BMI and height. Associations with age, BMI and BP-related parameters as predictors were quantified with standardized regression coefficients. These are unitless and thus allow the strength of relationships with different variables to be directly compared; in our results, they represent the effect per SD increment in the predictor as a proportion of the SD of the factor score. To allow for non-linear relationships of factor scores with cardiovascular events, we performed multivariable-adjusted restricted cubic-spline Cox regression analysis, using 3 “knots” placed at the 5^{th}, 50^{th} and 95^{th}, percentiles, and with median factor scores as reference values.[22] The results are presented as smoothed plots of hazard ratios and 95% confidence intervals, and were adjusted for potential confounders: age, sex, ethnicity, smoking, diabetes, atrial

fibrillation, NZDep13, antihypertensive treatment, lipid-lowering treatment, antithrombotic treatment and total:HDL cholesterol ratio.[9] To avoid multicollinearity, we did not include brachial SBP (traditional risk factor) *per se* as a covariate; but it was nevertheless adequately controlled for as the factor scores (with eigenvalues of >1) collectively explained 97% of its variance. Vitamin D treatment had no impact on cardiovascular events [23] and thus was not adjusted for. For simplicity, we also applied linear Cox regression (adjusted for the same variables). As the factor scores have a SD of 1, the hazard ratios generated are standardized: based on per unit SD. We checked the proportional hazards assumption of Cox models using weighted Schoenfeld residuals. We also applied these statistical methods for analyzing relationships between individual arterial waveform parameters (standardized with a SD of 1 to permit direct comparisons of association size) and cardiovascular events. The statistical significance for all analyses was set at $P<0.05$.

Results

A total of 4253 participants (2347 male) were included (Table S3). Mean age was 65 years and ranged from 50-84 years.

Clustering patterns

PCA (with varimax rotation, which results in factors that are uncorrelated with each other) of 14 arterial waveform variables – brachial SBP, brachial DBP, brachial pulse pressure, mean brachial BP, aortic SBP, aortic DBP, aortic pulse pressure, AIx, excess pressure integral, reservoir pressure amplitude, forward pressure amplitude, backward pressure amplitude, WRI and PWV – identified three independent components in the total sample (Table 1 and Figure S2), in major demographic groups (Figure S2) and in other groups of BP-related variables (Figure S3). As shown in Table 1, in the total sample, the first factor explained 59% of the

total variance and was loaded positively by all variables except DBP (brachial and aortic), AIx and WRI. The second factor explained 20% of the variance and was loaded positively by DBP and SBP (brachial and aortic), with the former having stronger loadings of almost 1. The third factor explained 11% of the total variance and was loaded positively by three variables: most strongly with WRI and AIx and less strongly with backward pressure amplitude. Similar patterns were attained by carrying out PCA with promax rotation (Figure S4). Given this similarity with these additional analyses, the factor analyses for all subsequent results used varimax rotation.

In addition, we applied cluster analysis (based on principal components) to examine the hierarchical arrangement of the clustering patterns (Figure 1). As observed with PCA, this diagram shows that DBP variables clustered into one group (cluster 2) and wave reflection indices clustered into another group (cluster 3). The remaining variables clustered into a third group (cluster 1) with varying degrees of relatedness amongst them, as can be seen from the hierarchical arrangement of parameters in that cluster. The values of $1-(R^2_{own}/R^2_{nearest})$ were small for clusters 2 (0.02 for DBP variables; 0.13 for mean brachial BP) and 3 (0.07 for WRI and AIx), indicating that these clusters were well-defined. Cluster 1 was less well-defined; values of $1-(R^2_{own}/R^2_{nearest})$ ranged from 0.05 (for aortic pulse pressure) to 0.54 (for aortic SBP). Similar results (three clusters) were obtained with cluster analysis based on centroid components (Figure S5).

Multivariable-adjusted predictors of factors

Table 2 shows multivariable-adjusted predictors of these factors scores. As illustrated, the first factor was positively associated with age and contractility. Further, this factor was inversely correlated with pulse rate and unrelated to BMI. In contrast, the second factor was inversely associated with age and positively related to other parameters (BMI and BP-related

variables). Factor 3 was inversely associated with contractility (unlike factors 1 and 2) and pulse rate, and was weakly related to other parameters.

We also performed analysis among those on antihypertensive monotherapy (n=659; Table 2). Across six antihypertensive classes, there were significant variations in factor 3 (P<0.0001), being highest with β-blocker use; but not in factors 1 (P=0.69) and 2 (P=0.15). As a comparison, there were no differences in brachial SBP (P=0.54) or DBP (P=0.31) (data not tabulated).

Relationships with cardiovascular events

After baseline, we followed up the participants for a median duration of 4.6 years (range: 3.9 to 5.5 years) and, over this time-period, 300 cardiovascular events accrued. Higher levels of multiple established risk factors were associated with this composite cardiovascular endpoint (Table S3), which comprised 62% cardiac, 31% cerebrovascular and 7% other vascular events (Table S1). Figure 2 shows multivariable-adjusted hazard ratios for relationships between the three arterial waveform factors (scores) and the cardiovascular events. Factors 1 and 3 had positive, monotonic associations with cardiovascular events. Applying linear Cox regression instead, the adjusted standardized hazard ratios (95% confidence interval) for these associations were 1.33 (1.18-1.50) and 1.15 (1.02-1.30) for factors 1 and 3, respectively. In contrast, for factor 2, there was a J-shaped relationship; the nadir of the curve was at a score of -0.4, with the cardiovascular risk point estimate increasing below this point and more so above it (Figure 2). A score of -0.4 corresponds to the 35^{th} percentile, and since factor 2 is almost perfectly correlated with DBP (loading = 0.99; Table 1), this score equates to a brachial DBP of ~75 mmHg (35^{th} percentile of this parameter).

We repeated the analyses for Figure 2 with cardiac and cerebrovascular events as outcomes instead (Figure 3). The hazard ratio point estimate increased monotonically in the

cardiac and factor 1-cerebrovascular event plots, but only below the 79th percentile for factor 3 in its association between cerebrovascular events. In contrast, factor 2 had a U-shaped relationship with cerebrovascular events; the nadir of the curve was at the 43th percentile (the cerebrovascular risk point estimate increased below and above this point), which equates to a brachial DBP of ~77 mmHg (43th percentile of this parameter).

The hazard ratios at 1-SD points on these plots are reported in Tables 3 and S4-S5. For a comparison, we repeated these analyses with individual waveform parameters (standardized) as predictors instead and show the corresponding results in these tables too. For cardiovascular events (Table 3), the sizes of the standardized hazard ratios for factor 1 were generally intermediate of those for their main constituent (individual) waveform parameters (unshaded rows). There was more similarity between factor 2 and its constituent parameters (light-gray rows) and less so for factor 3 (dark-gray rows)._ Of all parameters, PWV had the strongest association, consistently having the highest and lowest hazard ratios above and below the median, respectively. Similar patterns were observed too for cardiac (Table S4) and cerebrovascular (Table S5) events.

Discussion

As new methods have expanded the scope of measurable parameters from the arterial pressure waveform, it is timely to formally identify distinct patterns in this increasingly heterogeneous but correlated data using PCA. This study developed three new, distinct variables (PCA factors) comprising combinations of 14 arterial waveform parameters. The first factor (BP pulsatility) correlated with all original waveform parameters except DBP and wave reflection indices. The second (mean BP) was very strongly associated with DBP, while the third (wave reflection) was highly correlated with wave reflection indices (the justification for these terms is explained below). These clustering patterns were consistently observed in different

subgroups and the factors had different correlations with age and physiological variables. Differences in antihypertensive monotherapies were associated with significant variations in factor 3 but not brachial SBP and DBP. Finally, factors 1 and 3 were positively associated with cardiovascular events, while the factor 2 had a J-shaped relationship.

To our knowledge, this is the first investigation of how multiple arterial waveform parameters cluster. Given that these clusters together captured a high proportion (90%) of the variance of the original waveform data and are uncorrelated, they can be used to reliably study associations of different aspects of arterial function, with the advantage that these relationships will be unique (non-redundant) and additive. The clustering of these correlated parameters into factors suggests shared aetiologies, which may be the elements involved in variations in arterial function. The clustering of these parameters into three independent components suggests that variations in arterial function (physiological or those leading to CVD) can be grouped into three distinct mechanisms.

To understand these mechanisms, we note that pulse pressure increases with age and contractility,[24] and decreases with increasing pulse rate.[25] Therefore, the finding that factor 1 was positively associated with age, contractility, pulse pressure and amplitudes of various pressure waves, plus inversely related to pulse rate (Tables 1 and 2), suggests that it reflects the pulsatile component of BP. This is expected to be influenced by ventricular ejection patterns, large artery compliance and the timing of reflected waves.[24] As for factor 2, diastolic BP is known to decline with older age [24] and factor 2 had a strong, positive association with this parameter and correlated inversely with age. Thus, this factor seems to reflect the minimum BP level and because it correlated with SBP also (less strongly), it appears to be largely driven by mean BP (with which it correlated strongly). Finally, factor 3 appears to represent wave reflection as it had strong, positive relationships with wave reflection indices.

To evaluate the usefulness of the derived factors, we investigated their relationships with antihypertensive monotherapies. The fact that, across the six drug classes, factor 3 varied significantly, but brachial BP did not, implies that using the latter as a target in antihypertensive therapy may not fully capture effects on the arterial waveform factors. This appears particularly pertinent to β-blocker treatment as this was associated with the highest factor 3 (which correlates strongly with AIx) level (Table 2); consistent with clinical trials showing β-blockers having weak effects on AIx relative to other antihypertensive drugs [26, 27]. Thus, since antihypertensive medications have associations with cardiovascular events beyond those expected from effects on brachial BP,[28, 29] factor 3 may help assess the clinical benefit of antihypertensive therapy more comprehensively than brachial BP alone.

Factor 1 predicted increased cardiovascular risk. In line with this, forward and backward pressure amplitudes, to which factor 1 was strongly related (Table 1), associate positively with cardiovascular events.[3] The positive relationship we observed with factor 3 (Figure 2) concurs with previous reports that cardiovascular risk increases with higher AIx or WRI,[1, 4] which both correlated strongly with factor 3 in our sample (Table 1). Brachial BP is unable to capture this wave reflection-related risk since factor 3 was not significantly loaded by brachial BP in the PCA (Table 1). We infer that simple maximum and minimum BP level (captured by brachial SBP and DBP) provides limited information regarding the morphology of the BP waveform, which is shaped by wave reflection.

Further, our finding that factor 2, which strongly reflects diastolic BP, had a J-shaped relationship with cardiovascular events is consistent with an elevated cardiovascular risk when diastolic BP is low or high.[30] The lowest point of this association corresponded to a brachial DBP of ~75 mmHg, which is in the range of nadirs of DBP-CVD relationships observed in past cohort studies and clinical trials.[30] This non-linear relationship was largely explained by a U-shaped association with cerebrovascular events (Figure 3). A few studies

have observed J-shaped DBP-stroke relationships (the nadirs being 65 to ~75 mmHg).[31-33] Those findings differ from ours as we observed a stronger, U-shaped association that was prominent for cerebrovascular events (but not cardiac events) and with a slightly higher brachial DBP nadir (~77 mmHg). The reasons for these differences are not clear; mechanisms accounting for J-shaped diastolic BP-CVD associations have been proposed [32] but they would not be expected to affect cerebrovascular events exclusively. Another mechanism, reduced cerebral perfusion during diastole, is a proposed explanation for a J-shaped DBP-stroke relationship in the presence of cerebral ischemic disease, where cerebral autoregulatory BP control is compromised.[33] However, this may not explain our findings as our participants were apparently healthy people without established CVD and our statistical models adjusted for CVD risk factors that may be related to underlying cerebral ischemic disease.

PWV had a significant loading with factor 1 only but not a very strong one. This would have limited the prognostic importance of our factors, given that the parameter most strongly related to CVD was PWV. Further, the factors did not outperform all of their constituent waveform parameters in CVD prediction (Tables 3 and S4-S5). Nevertheless, they are useful for quantifying *combined* CVD risk as, being uncorrelated, their associations with CVD are truly additive. For example, compared to having median scores for all 3 factors, the hazard ratio associated with having scores 2 SDs higher for factors 1 (hazard ratio=1.82), 2 (hazard ratio=1.88) and 3 (hazard ratio=1.46) is ~5 (Figure 2). Thus, if these scores were used as cardiovascular-related outcomes (in clinical practice, observational studies or BP trials), the *net* CVD-risk effect/association could be quantified; but otherwise difficult to do because of correlations amongst individual waveform parameters (Figure 1).

In clinical practice, calculating factor scores for each patient would require connecting the BP+ device to a computer and having the scores automatically computed from the collected arterial waveform data using published standardized scoring coefficients (e.g., those

in Table S2).[21] Through the adoption of more advanced computerized decision support systems for CVD risk assessment,[34] the opportunities to do this may be realized.

A study strength is that we adjusted for numerous confounders, which enhanced the validity and novelty of our findings. Second, our study sample was population-based, since most New Zealand residents (94%) are registered with a family practice.[35] Another strength is that we continuously tracked participants (using their unique National Health Index numbers), which permitted us to comprehensively capture drug dispensing, cardiovascular hospitalisations and deaths during follow-up.

As for limitations, further work needs to evaluate whether interventions targeting improvement in arterial waveform factors result in improved cardiovascular outcomes. Our findings have uncertain applicability to adults aged <50 years as these people were not included in this study.

Perspectives

In this population-based cohort study, 14 arterial waveform parameters clustered into three, novel uncorrelated variables that independently predicted cardiovascular events. These clusters represent unique physiological variations of arterial function and can be used to summarize arterial waveform data into a small number of prognostically meaningful, non-redundant measures. We encourage further studies to evaluate the utility of BP-parameter clusters in different populations and using different BP devices.

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Disclosure

None.

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Novelty and significance

What is new?

To our knowledge, this is the first assessment of how multiple arterial waveform parameters cluster

What is relevant?

- Arterial waveform parameters clustered into 3 uncorrelated factors: blood pressure (BP) pulsatility, mean BP and wave reflection.
- These clusters predicted cardiovascular events independently of both one another and traditional risk factors

Summary

BP pulsatility, mean BP and wave reflection are prognostically meaningful, distinct aspects of arterial function that can summarize physiological variations in multiple arterial waveform parameters and identify *truly* cumulative (non-redundant) associations when used as cardiovascular-risk outcomes. We encourage additional cohort studies to further explore their usefulness.

Titles and legends to figures

Figure 1. Dendrogram showing the clustering of arterial waveform parameters based on principal components. From left to right, clusters are progressively merged until a single, all-inclusive cluster is formed at the root (right-most fusion) of the diagram. Vertical branches (lines) represent the combination of two clusters or variables. The length of horizontal branches represents the degree of dissimilarity between variables; the longer they are, the greater the difference between combined clusters or variables. The three identified clusters form when the proportion of variance explained is ~0.85, indicating that they explain ~85% of the total variation in the original data. aDBP=aortic DBP; AIx=augmentation index; aPP=aortic pulse pressure; aSBP=aortic SBP; bDBP=brachial DBP; bMAP=mean brachial BP; bPP=brachial pulse pressure; bSBP=brachial SBP; EPI=$\log_e$(excess pressure integral); Pb=backward pressure amplitude; Pf=forward pressure amplitude; Pres=reservoir pressure amplitude; PWV=pulse wave velocity; WRI=$\log_e$(wave reflection index).

Figure 2. Smoothed plot of hazard ratios for cardiovascular events according to scores of factors 1-3. The hazard ratios (solid line) and 95% confidence intervals (dotted lines) were estimated by restricted cubic-spline Cox regression (adjusted for covariates described in text), with median factor scores as reference values

Figure 3. Smoothed plot of hazard ratios for cardiac and cerebrovascular events according to scores of factors 1-3. The hazard ratios (solid line) and 95% confidence intervals (dotted lines) were estimated by restricted cubic-spline Cox regression (adjusted for covariates described in text), with median factor scores as reference values

Table 1. Eigenvalues of the correlation matrix and loadings in the principal component analysis for arterial waveform variables

Parameter		Factor 1	Factor 2	Factor 3
Eigenvalues of the matrix	Eigenvalue	8.314	2.798	1.540
	Proportion of total variance	0.594	0.200	0.110
	Arterial waveform parameter			
Loading (correlation coefficient)*	Brachial SBP	**0.727**	**0.656**	0.119
	Brachial DBP	-0.028	**0.991**	0.093
	Brachial pulse pressure	**0.950**	0.153	0.088
	Brachial MAP	**0.371**	**0.919**	0.117
	Aortic SBP	**0.691**	**0.674**	0.231
	Aortic DBP	-0.016	**0.993**	0.081
	Aortic pulse pressure	**0.941**	0.148	0.247
	Augmentation index	0.252	0.128	**0.922**
	$\log_e$(excess pressure integral)	**0.756**	-0.040	0.196
	Reservoir pressure amplitude	**0.856**	0.176	0.198
	Forward pressure amplitude	**0.969**	0.138	0.048
	Backward pressure amplitude	**0.851**	0.115	**0.443**
	Pulse wave velocity	**0.781**	0.090	0.052
	$\log_e$(wave reflection index)	0.176	0.141	**0.948**

*Factors>0.3 are in bold, which indicates that the variable can be considered a significant constituent of that factor.

Table 2. Predictors of factor scores*

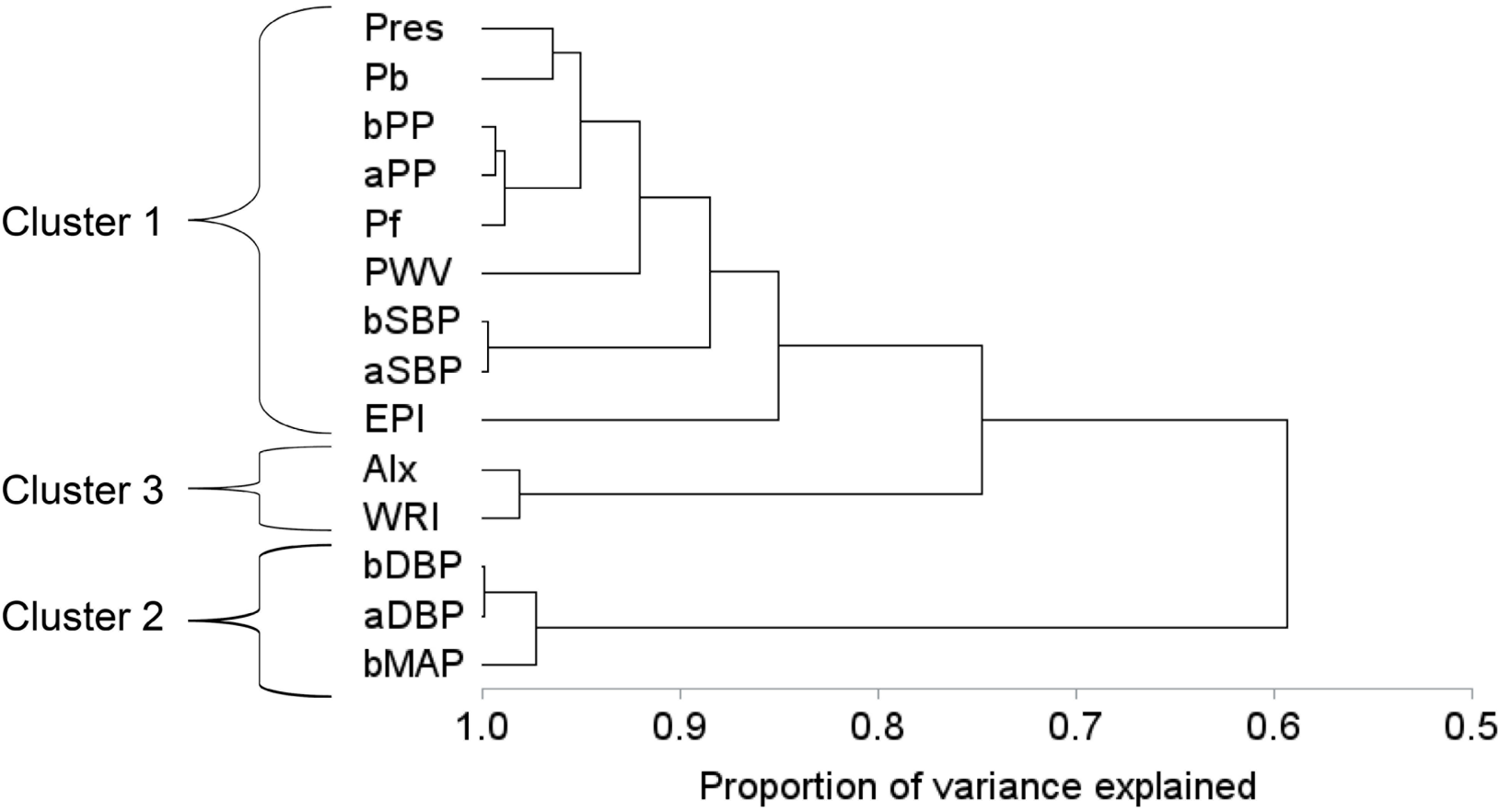
Total sample (n=4253)	Predictor	Standardized regression coefficient		
		Factor 1	Factor 2	Factor 3
	Age	**0.513**‡	**-0.157**‡	**0.038**†
	BMI	**0.052**‡	**0.199**‡	**-0.144**‡
	Contractility	**0.720**‡	**0.082**‡	**-0.385**‡
	Pulse rate	**-0.177**‡	**0.191**‡	**-0.392**‡
Participants on antihypertensive monotherapy (n=659)	Predictor	Mean (standard error)		
		Factor 1	Factor 2	Factor 3
	ACE inhibitor (n=289)	0.11 (0.10)	-0.13 (0.10)	-0.12 (0.09)
	α-blocker (n=45)	0.18 (0.17)	-0.41 (0.17)	0.05 (0.16)
	ARB (n=62)	0.13 (0.14)	0.04 (0.15)	-0.24 (0.14)
	β-blocker (n=85)	0.22 (0.13)	-0.26 (0.13)	0.42 (0.12)
	CCB (n=105)	0.01 (0.12)	-0.25 (0.13)	-0.13 (0.12)
	Diuretic (n=73)	0.09 (0.14)	-0.18 (0.14)	0.02 (0.13)
		P=0.69	P=0.15	**P<0.0001**

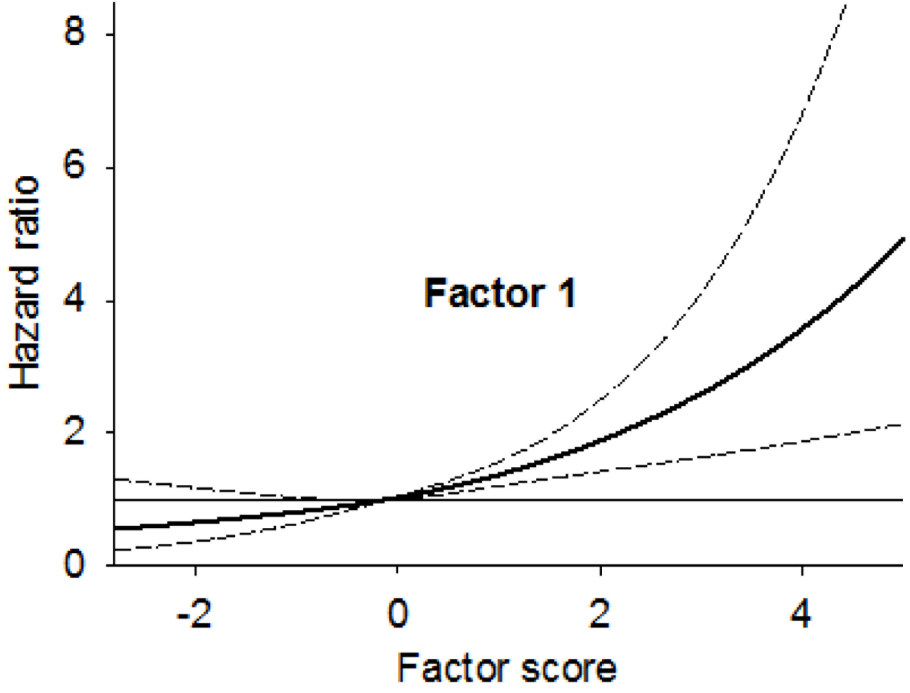
*Adjusted for age, sex, ethnicity, smoking, diabetes, NZDep13, total:HDL cholesterol ratio, BMI and height. Total-sample models are also adjusted for antihypertensive treatment. P-values test for differences across monotherapies: †P<0.05, ‡P<0.001. ARB=angiotensin receptor blocker; CCB=calcium channel blocker.

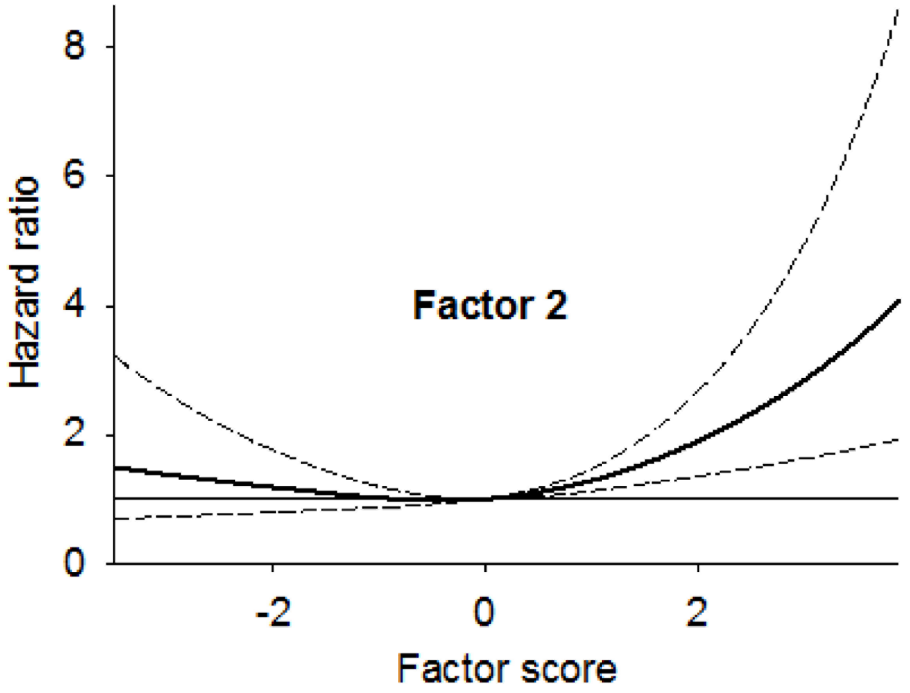
Table 3. Multivariable-adjusted standardized hazard ratios (95% confidence intervals)* for associations of arterial waveform parameters with cardiovascular events

Parameter	Standard deviations away from median			
	-2	-1	+1	+2
Factor 1	0.64 (0.35-1.19)	0.79 (0.61-1.04)	1.33 (1.18-1.50)	1.82 (1.40-2.37)
Factor 2	1.18 (0.78-1.77)	1.02 (0.86-1.21)	1.28 (1.13-1.45)	1.88 (1.36-2.61)
Factor 3	0.85 (0.53-1.38)	0.91 (0.74-1.12)	1.18 (1.04-1.34)	1.46 (1.05-2.04)
Brachial SBP	0.65 (0.37-1.15)	0.79 (0.62-1.01)	1.38 (1.24-1.54)	2.01 (1.53-2.64)
Brachial DBP	1.27 (0.82-1.90)	1.06 (0.90-1.25)	1.26 (1.11-1.43)	1.88 (1.35-2.60)
Brachial pulse pressure	0.65 (0.35-1.22)	0.80 (0.60-1.05)	1.37 (1.23-1.54)	1.99 (1.58-2.52)
Mean brachial BP	0.83 (0.50-1.35)	0.88 (0.72-1.08)	1.31 (1.17-1.48)	1.87 (1.38-2.55)
Aortic SBP	0.63 (0.35-1.13)	0.78 (0.61-1.00)	1.40 (1.26-1.56)	2.06 (1.59-.66)
Aortic DBP	1.25 (0.84-1.86)	1.04 (0.89-1.23)	1.29 (1.13-1.46)	1.94 (1.39-2.69)
Aortic pulse pressure	0.62 (0.35-1.12)	0.78 (0.60-1.00)	1.38 (1.24-1.54)	1.99 (1.56-2.53)
Augmentation index	0.92 (0.67-1.26)	0.90 (0.80-1.02)	1.33 (1.13-1.57)	1.93 (1.31-2.84)
$\log_e$(excess pressure integral)	0.46 (0.26-0.84)	0.70 (0.54-0.90)	1.28 (1.14-1.43)	1.51 (1.17-1.94)
Reservoir pressure amplitude	0.88 (0.52-1.48)	0.92 (0.73-1.16)	1.19 (1.07-1.32)	1.50 (1.16-1.93)
Forward pressure amplitude	0.54 (0.29-1.01)	0.74 (0.56-0.98)	1.32 (1.18-1.48)	1.71 (1.36-2.16)
Backward pressure amplitude	0.73 (0.42-1.27)	0.84 (0.66-1.08)	1.27 (1.14-1.42)	1.68 (1.30-2.17)
Pulse wave velocity	0.23 (0.10-0.56)	0.49 (0.34-0.73)	1.83 (1.43-2.33)	3.14 (1.93-5.11)
$\log_e$(wave reflection index)	1.02 (0.63-1.65)	0.98 (0.79-1.20)	1.20 (1.06-1.36)	1.58 (1.14-2.18)

*Estimated by restricted cubic-spline Cox regression (adjusted for covariates described in text), with median parameter values as reference values. Arterial waveform parameters that are most closely associated with factors 1, 2 and 3 are shaded white, light gray and dark gray, respectively.


Cluster 1
Cluster 3
Cluster 2
Pres
Pb
bPP
aPP
Pf
PWV
bSBP
aSBP
EPI
AIx
WRI
bDBP
aDBP
bMAP
1.0
0.9
0.8
0.7
0.6
0.5
Proportion of variance explained


Hazard ratio
8
6
4
2
0
Factor 1
-2
0
2
4
Factor score


Hazard ratio
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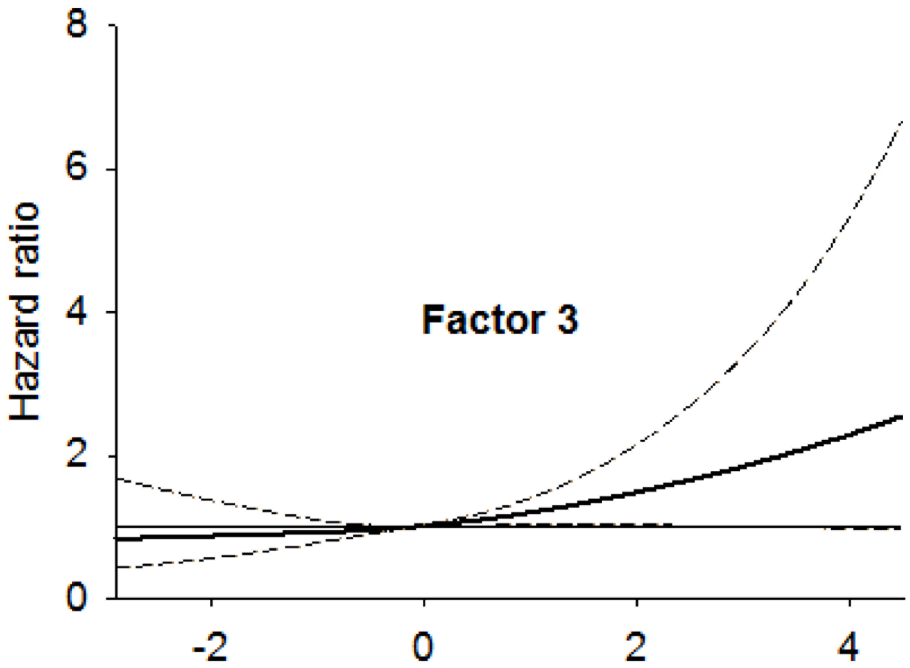
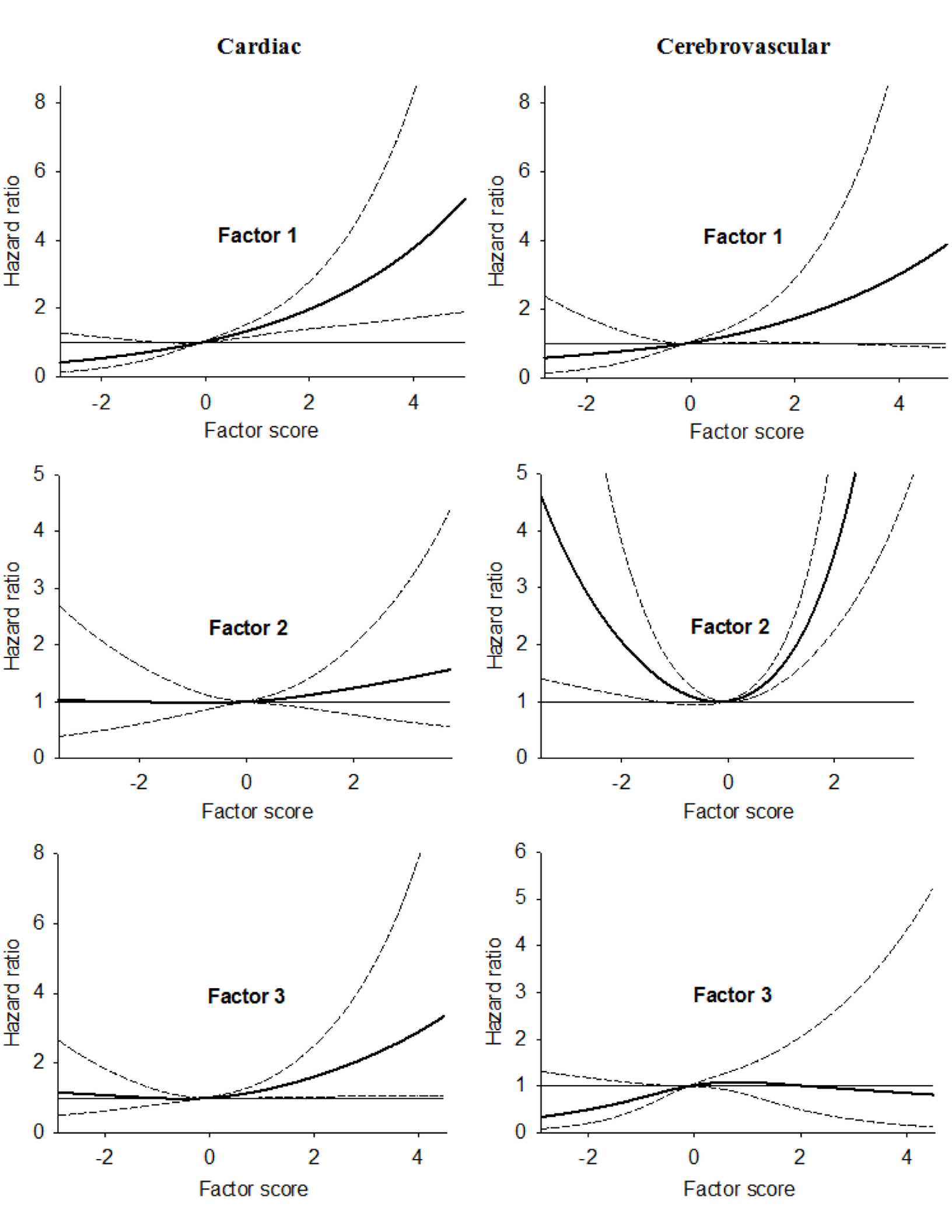
6
4
2
0
Factor 2
-2
0
2
Factor score


Hazard ratio
8
6
4
2
0
Factor 3
-2
0
2
4


Cardiac
Cerebrovascular
Factor 1
Factor 1
Factor 2
Factor 2
Factor 3
Factor 3
Hazard ratio
Factor score