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Vascular robustness: The missing parameter in cardiovascular risk prediction☆

Lutz E. Kraushaar[a,*], Alexander Dressel[b], Alexander Maßmann[c]

[a] Adiphea (Alliance for Disease Prevention & Healthy Aging) GmbH, Werbach, Germany
[b] CaRe High Cascade Screening and Registry for High Cholesterol, D-A-CH-Gesellschaft Prävention von Herz-Kreislauf-Erkrankungen e.V., Industriestr. 41, 68169 Mannheim, Germany
[c] Clinic of Diagnostic and Interventional Radiology, Saarland University Medical Center, 66421 Homburg, Saar, Germany

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ABSTRACT

Undetected high risk for premature death of cardiovascular disease (CVD) among individuals with low-to-moderate risk factor scores is an acknowledged obstacle to CVD prevention. The vasculature's functional robustness against risk factor derailment may serve as a novel discriminator of mortality risk under similar risk factor loads. To test this assumption, we hypothesized that the expected inverse robustness-mortality association is verifiable as a significant trend along the age spectrum of risk factor-challenged cohorts.

This is a retrospective cohort study of 372 adults (mean age 56.1 years, range 21–92; 45% female) with a variety of CV risk factors.

An arterial model (VascAssist 2, iSYMED GmbH, Germany) was used to derive global parameters of arterial function from non-invasively acquired pulse pressure waves. Participants were stratified by health status: apparently healthy (AH; n = 221); with hypertension and/or hypercholesterolemia (CC; n = 61); with history of CV event(s) (CVE; n = 90). Multivariate linear regression was used to derive a robustness score which was calibrated against the CVD mortality hazard rate of a sub-cohort of the LURIC study (n = 1369; mean age 59.1 years, range 20–75; 37% female).

Robustness correlated linearly with calendar age in CC ($F(1, 59) = 10.42$; $p < 0.01$) and CVE ($F(1, 88) = 40.34$; $p < 0.0001$) but not in the AH strata, supporting the hypothesis of preferential elimination of less robust individuals along the aging trajectory under risk factor challenges.

Vascular robustness may serve as a biomarker of vulnerability to CVD risk factor challenges, prognosticating otherwise undetectable elevated risk for premature CVD mortality.

1. Introduction

As the pandemic of chronic cardiovascular disease (CVD) accelerates, the UN has recently prioritized the goal of reducing premature CV mortality by 30% by 2030 ("WHO|NCD and the Sustainable Development Goals", 2016). A prerequisite to achieving this target is the ability to detect the progressive impairment of CV function that causally precedes symptomatic disease manifestation (Taddei et al., 2003). However, the screening performance of all conventional risk factor models depends almost entirely on calendar age (CA) alone, such that the addition of all other biomarkers combined only marginally improves detection rates (Simmonds and Wald, 2012; Wald et al., 2011). This uncertainty of prediction is the inevitable result of estimating an individual's disease risk using algorithms that have been derived from epidemiological cohort studies of biomarker-disease associations (Wald et al., 1999). Given the overlap of each biomarker's frequency distribution between sub-populations with and sub-populations without the disease, to be a useful discriminator of risk, each marker's association with CVD needs to be at least two orders of magnitude larger than what is typically observed (Pepe et al., 2004).

While this explains why the past 20 years of biomarker research have produced only marginal improvements to the risk factor models' predictive power (Folsom, 2013), it does not explain why, under a given risk factor 'stress', some people die prematurely whereas others

Abbreviations: AH, apparently healthy group; aoPWV, aortic pulse wave velocity; ATH, athletic group; BA, vascular biological age; CA, calendar age; CC, chronic condition group; CVD, cardiovascular disease; CVE, cardiovascular endpoint group; FMD, flow mediated vasodilation; PWV, pulse wave velocity; RCR, retrospective chart review; UN, United Nations; VA2, VascAssist 2

☆ Subject Terms: Robustness, Biomarkers, Primary Prevention, Cardiovascular Disease

* Corresponding author at: Zieglersgrübe 47, 97956 Werbach, Germany.
E-mail address: lutz.kraushaar@adiphea.com (L.E. Kraushaar).

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are 'robust' enough to survive. Here we suggest that vascular robustness against risk factor stress is an important but unexplored parameter that may improve the risk factor models' detection rates more substantially than additional biomarkers of risk.

Our rationale finds support in the recent suggestion that adopting insights of systems biology into risk evaluation may help us achieve the target of individualized prevention (Thomas and Lip, 2017). Incorporating principles of the sciences of complex systems, systems biology posits that biological systems display properties that can neither be predicted nor explained from the systems' molecular constituents (Aderem, 2005; Kitano, 2002; Regenmortel, 2004). Termed 'emergence' this phenomenon is a fundamental property of all complex systems. Closely related to emergence is the phenomenon of robustness, a system's ability to maintain a functional phenotype against a range of internal and external challenges and stochastic events (Kitano, 2007; Kitano et al., 2004; Stelling et al., 2004; Whitacre, 2012). Hence it is our intention to investigate robustness' utility in risk prediction.

First, using plausible mechanistic parameters, we attempt to quantitate the robustness criterion. We then use this criterion to formulate hypotheses that we test in a retrospective cohort study. We aim specifically at answering the question whether our proposed robustness criterion warrants the execution of more resource-intensive prospective studies that examine the predictive utility of robustness for efforts to reduce premature CVD mortality as demanded by the UN.

2. Methods

2.1. Parameterization of robustness

While the term robustness lacks a precise definition there is broad agreement that it encapsulates the maintenance of function against internal and external perturbations (Kitano, 2004; Rosenfeld, 2011; Whitacre, 2012). Here we conceptualize cardiovascular robustness as the CV system's ability to maintain integrity of function against genetic variations, environmental challenges and stochastic events (Stelling et al., 2004).

The CV system's function is to cushion the pulsatile left ventricular output into a constant blood flow, and to maintain that flow to all tissues and cells in accordance with their nutritional, energetic and waste disposal needs. Being essentially a hydraulic system that consists of a pulsating pump (heart) and elastic tubes (arterial segments), the parameterization of the cardiovascular system's functional properties requires reference to the laws of physics. This dependence of flow and pressure on compliance, resistance and inertia is evident in the Hagen-Poiseuille and Moens-Korteweg equations which allow for the mathematical description of arterial vascular function.

Based on the electric-hydraulic analogy this system has been represented by networks of electronic circuits (Chen et al., 2014; Olufsen and Nadim, 2004; Stergiopulos et al., 1999; Westerhof et al., 1969), in which the passive elements of resistance, capacitance and inductance represent their hydraulic equivalents of resistance, compliance and inertance.

Given the importance of vascular function as a benchmark of cardiovascular health, calls have been made to develop methods that provide a non-invasive assessment of all these parameters as the determinants of vascular function (Thijssen et al., 2015; Tomiyama and Yamashina, 2010).

Correspondingly, a recently developed system (VascAssist 2, iSYMED GmbH, Germany) applies the electronic-hydraulic analogy to a model of the arterial tree which consists of 721 electronic circuits representing central and peripheral arterial sections. By modulating the circuits' capacitance, resistance, inductance, voltage and current the system replicates a person's non-invasively acquired pulse pressure wave, thereby uncovering the arterial functional parameters that generated the wave in the biological original. The system is described in Appendix A.

2.2. Quantitation of robustness

Robustness, as conceptualized above, acts as an effect modifier to the biomarkers of risk to which an individual is exposed. Only if this effect modification is large enough to become measurable by a significant modification of CA - the risk factor models' dominant marker -, will robustness be useful for risk stratification. Consequently, it makes sense to express robustness in units of years to quantify its impact on the age-mortality association. The resulting difference between calendar age and the robustness-corrected age represents the vascular robustness score, which, from here onwards, is referred to as *delta_age*. The algorithms that we developed to derive the parameters and dimensions of robustness from the data supplied by the VA2 system are hereinafter summarily referred to as *vasometrix*.

2.3. Hypotheses

We test the following two hypotheses: when stratified by degree of biomarker stress (non-age risk factors) into healthy and exposed strata, the exposed population strata will show a significant positive correlation between robustness and CA (hypothesis A). The robustness-CA correlation in the exposed strata will be significantly stronger than the correlation in the unexposed stratum (hypothesis B). Hypothesis A emerges from the rationale that individuals with lower robustness will be subject to preferential elimination (premature mortality) such that older cohorts are relatively "depleted" of these less robust individuals. Hypothesis B is founded on the assumption that robustness acts predominantly as an effect moderator of non-age risk factors.

2.4. Study population & data acquisition

This study is a retrospective chart review (RCR) of a cohort of 410 adults (mean age 56.1 years, range 21–92; 45% female; from here on referred to as the vasometrix cohort) with a variety of CV risk factors. Appropriately sized inflatable cuffs were used for acquisition of the pulse pressure curves using the oscillometric VA2 device. The participants rested supine for 15 min before pressure measurements were obtained. Measurements were performed in triplicate at the brachial and radial arteries. Sampling frequency was 1 kHz.

2.5. Inclusion and exclusion criteria

A replication fidelity of simulated PP curves vs. sampled curves of $\leq$97% (for definition of fidelity see Appendix A), and/or age $<$ 21 years served as the exclusion criteria. We excluded (a) 36 of the 410 participant records for reasons of inadequate replication fidelity, and (b) another 2 records of participants with resting tachycardia (HR $>$ 100 beats per minute, a $>$ 3 SD difference from the cohort mean). All records that were not explicitly excluded by these criteria were included.

2.6. Confidentiality and ethical considerations

All data had been recorded and processed such that subjects cannot be identified.

This RCR was conducted in conformance with the Declaration of Helsinki and under the approval of the local ethics committee (Ethikkommission des Saarlandes, 66111 Saarbrücken/Germany).

2.7. Statistical analyses

The study cohort was first divided into three main groups: apparently healthy (AH; n = 221), with hypertension and/or hypercholesterolemia but without having a history of CV events (CC; n = 61), with history of CV event(s) which we defined as a history of myocardial infarction, stroke or heart failure (CVE; n = 90). Given the known

effects of exercise on cardiovascular function (Pal et al., 2013), we identified the recreational athletes (self-reported frequency of moderate-to-high intensity endurance training > 3 times a week for a total of ≥4 h per week). Since all athletes were members of the AH group we separated them into a fourth group (ATH; n = 21).

2.8. Selection of robustness predictor variables

Only those biomarkers which reflect physical parameters of arterial function were considered for inclusion into our exploratory regression models (electronic circuit equivalents in brackets):

- Compliance (capacitance)
- Resistance (resistance)
- Inertia (inductance)
- Blood pressure (voltage)
- Aortic pulse wave velocity; aoPWV
- Heart rate

All predictor variables except heart rate were Box-transformed to achieve normality of distribution. Univariate linear regression was performed on all transformed and standardized predictor variables for an initial test of regression assumptions and to identify potential outliers. Derivation of the regression models is described in Appendix B.

2.9. Derivation of robustness score

The gender-specific derivation of the robustness formula consists of the following steps:

Step 1: Stepwise multiple linear regression of CA over all predictor variables was performed on subsamples to derive a score – *age_score*.

Step 2: Linear regression of *age_score* over CA on the healthy subpopulation as reference population. For any individual, the deviation of *age_score* from the value of the regression function thus obtained characterizes the deviation (*age_res*) of the individual's fatal CVD event probability from its age-appropriate fatal CVD event probability on the reference population.

Step 3: With the aid of the following two-stage approach, we derive a transformation of *age_res* into its risk equivalent in calendar years. This risk equivalent serves as an estimation of *delta_age* in hypotheses A and B.

Using the method described in Appendix C, we simulate the missing time-to-event data for our population for a period of 10 years using the beta coefficients of CA derived from Cox regression over a reference population drawn from the Ludwigshafen Risk and Cardiovascular Health (LURIC) follow-up study - the Diadexus cohort of the LURIC study (n = 1369; mean age 59.1 years, range 20–75; 37% female) (Winkelmann et al., 2001).

With the aid of the simulated time-to-event data from a) and the method in Appendix C, we derive the formula for *delta_age* in terms of *age_score* (Davison and Hinkley, 1997).

Step 4: The desired vascular biological age (BA) was then obtained by adding *delta_age* of Step 3 to CA.

Regression diagnostics were applied to test the final gender-specific multivariate regression models for normality of residuals, homoscedasticity, multicollinearity and linearity. All statistical calculations were performed using Stata 11, with the exception of power analyses for which G*Power software was used (Faul et al., 2007).

3. Results

CA significantly predicted BA, b = 1, t(370) = 48.11, $p < 0.001$, explaining 92.8% of the variance in BA (R2 = 0.86, F(1, 370) = 2314.45, $p < 0.0001$ (Fig. 1).

To analyze the differences in *delta_age* between the health status groups, we divided the study sample into 4 groups (ATH: recreational athletes; AH: apparently healthy; CC: diagnosed with a chronic condition, i.e. hypertension or/and hypercholesterolemia; CVE: history of cardiovascular disease endpoint(s), i.e. myocardial infarction or/and stroke).

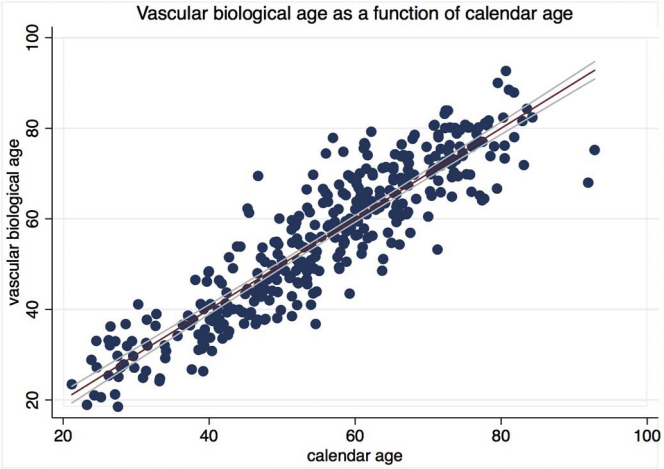

Fig. 1. Scatter plot: biological age as a function of calendar age.

Parameters for all groups are shown in Table 1.

Fig. 2A shows the boxplot of *delta_age* for the four health status groups for all ages ≥21 years. One-way-analysis of variance (ANOVA) using Bonferroni adjustment showed that the difference in delta-age between groups was significant, F(2,369) = 22.61, $p < 0.0001$. Post hoc analyses using the Scheffé post hoc criterion for significance indicated that *delta-age* was significantly different in ATH and CVE groups vs. all remaining three groups respectively (Table 1). The difference between AH and CC groups was not significant ($p = 0.48$).

Since our hypothesis implies a preferential elimination of the less robust individuals the difference in delta-age between the challenged and unchallenged strata should be more pronounced when comparing the younger age cohorts of the strata. We therefore repeated the ANOVA and post hoc analyses over the 4 groups while limiting the age range to 21–65 years. In this analysis, the differences between each of the groups became significant at $p < 0.01$, with mean *delta_age* for the ATH, AH, CC and CVE groups of −4.8, −0.9, 2.0 & 7.4 years respectively (Fig. 2B).

Significant inverse linear correlations between *delta_age* and CA were observed for the CC & CVE but not for the AH strata (Fig. 3). While the negative trend in the regression line of the healthy individuals, approached significance at $p = 0.061$ (R2 = 0.016), the trend was

Table 1
Summary statistics vasometrix population by health status group.

	Full sample	ATH*	AH†	CC‡	CVE§
Age	56.11	41.79#	49.74#	62.12#	69.54#
	(14.71)	(10.12)	(12.94)	(9.824)	(9.627)
BP systolic	130.55	126.02	126.60	133.07	138.66**
	(14.87)	(12.44)	(12.31)	(16.35)	(16.05)
BP diastolic	73.12	76.10#	72.78	76.77	70.70#
	(10.29)	(11.45)	(9.536)	(10.44)	(10.86)
HR brachial	67.19	56.57#	68.75	67.81	65.81
	(10.46)	(7.646)	(9.985)	(10.93)	(10.27)
Delta-age	0.00	−4.79#	−1.06	0.35	3.25#
	(5.881)	(4.017)	(4.909)	(6.378)	(6.367)
Gender:					
Male	0.55	0.76	0.46	0.57	0.70
N	372	21	200	61	90

Mean (proportions for gender); sd in parentheses. * = athletic; † = apparently healthy; ‡ = chronic CV condition w/o CV endpoints; § = history CV endpoints.
Significantly different from all other sub-groups at $p < 0.05$.
** Significantly different from sub-groups ATH & AH at $p < 0.05$.

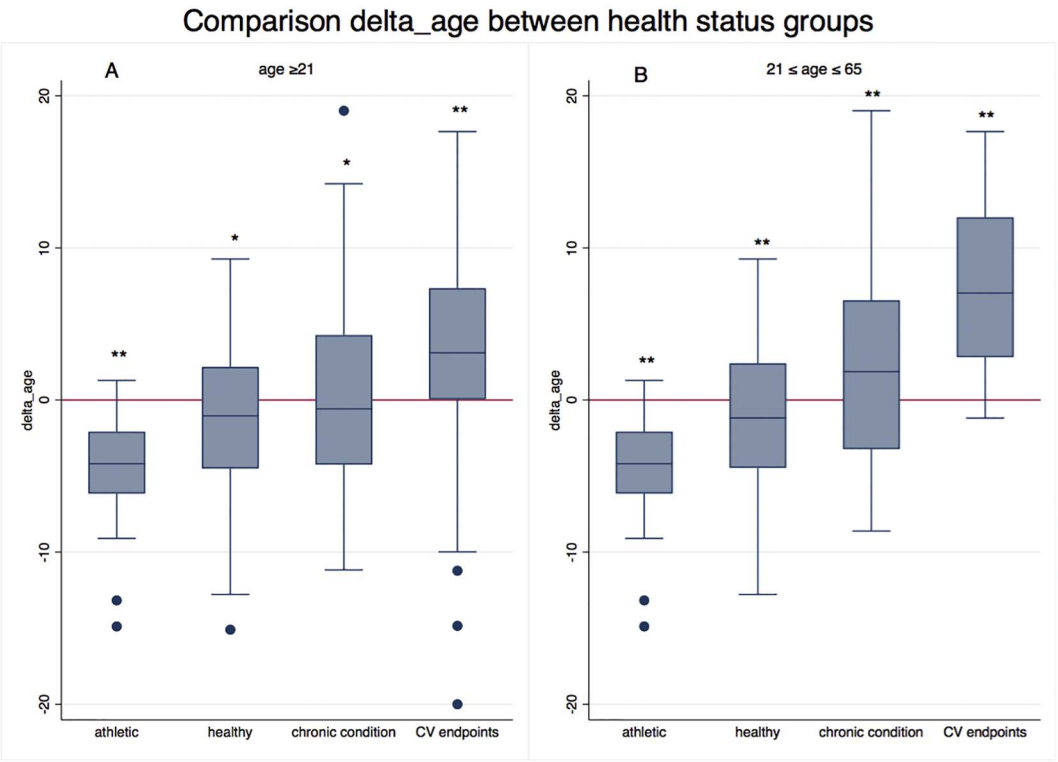

Fig. 2. Box plot comparing delta-age (biological age - calendar age) between health status groups.
(A): comparison across all ages ≥21
(B): comparison across the age range 21–65.
*Significantly different from the group with CV endpoints
**Significantly different from all other groups.

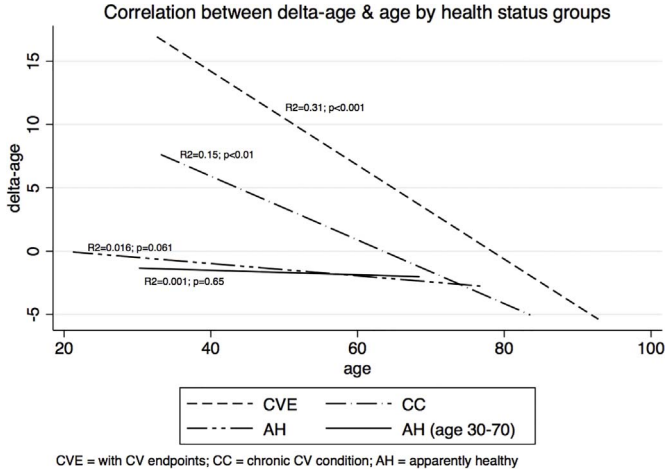

Fig. 3. Delta-age (biological age - calendar age) as a function of calendar age for different health status groups.

clearly non-significant across the 4 decades from age 30 to 70 (n = 183; R2 = 0.001, $p = 0.65$).

The trends in the regression lines of the CC (b = −0.25; t(61) = −3.23, $p < 0.01$) and CVE groups (b = −0.37; t(90) = −6.35, $p < 0.001$) differed significantly from the AH group (b = −0.048; t(221) = −1.88, $p = 0.061$) at $p < 0.01$ and $p < 0.001$ respectively.

Fig. 4a–c compares *delta_age* in the CVE group dichotomized into two sub-samples along the threshold ages of 60, 65 and 70.

ANOVA, and post hoc analyses using the Scheffé post hoc criterion for significance, showed that *delta_age* was significantly lower in the older age CVE subgroup vs. the younger age subgroup, with:

(M = 2.31, SD = 6.07) vs. (M = 8.32, SD = 5.64) F(1,88) = 11.8, $p < 0.001$ for threshold age 60; (M = 1.54, SD = 5.97) vs. (M = 7.44, SD = 5.35) F(1,88) = 19.1, $p < 0.001$ for threshold age 65; and (M = 0.57, SD = 6.34) vs. (M = 6.45, SD = 4.76) F(1,88) = 23.9, $p < 0.001$ for threshold age 70 respectively.

Fig. 4d demonstrates the same effect of lower *delta_age* in the CC group using the threshold age of 65 for dichotomization (M = −2.66, SD = 4.77 vs. M = 2.05, SD = 6.59, F(1,59) = 8.64, $p < 0.01$).

4. Discussion

Based on our results we cannot dismiss the two hypotheses which we had set out to test. We observed (a) a significant positive linear trend of the robustness-CA correlation in the risk-factor challenged cohorts, and (b) a significant difference between these correlations and the null-association in the AH cohort. These observations demonstrate two aspects that are essential to robustness' utility as a discriminator of risk: first, as illustrated in Fig. 3, the difference in robustness score is most pronounced at the front-end of the aging trajectory, that is, in the pre-symptomatic reversible stage of CVD.

Second, the flat-lining robustness-CA association in the AH cohort suggests that robustness is an indicator of an individual's ability to antagonize risk factor challenges, but possibly not an indicator of mortality risk in unchallenged individuals. Hence, the robustness score will be more useful in conjunction with conventional risk factor models than as a stand-alone predictor of mortality. This caveat needs to be examined in prospective studies that investigate time-to-death in different CV health and robustness strata.

In line with its definition, we have parameterized robustness exclusively from functional parameters. Our choice of expressing robustness in units of years is a logical consequence of the inextricable relationship between aging and functional decline. Since aging and the decline of vascular function are inextricably linked (Thijssen et al.,

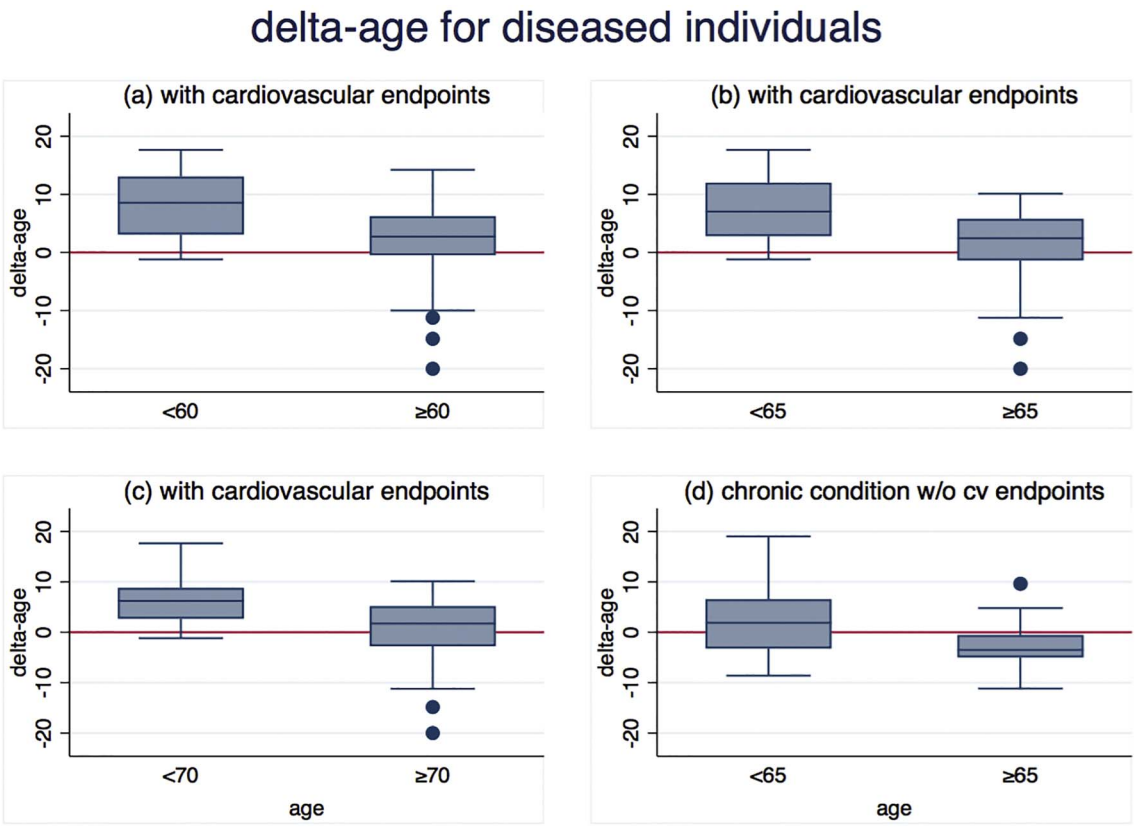

Fig. 4. Box plot comparing delta-age (biological age - calendar age) within health status groups, and across different age thresholds.

2015), vascular robustness, representing vascular functional integrity, encapsulates the markedly different rates at which the decline of vascular function affects people of similar CA (Belsky et al., 2015). With the accelerated CVD-driven decline of vascular function being the primary driver of premature mortality (Lakatta, 2007), it makes sense to express robustness in units of years as an effect modifier of the CA-mortality association.

It is important to note that the resulting BA differs fundamentally from currently available biological age scores. The latter can be distinguished by their constituents into one of three types: telomere length, DNA methylation, and baskets of biomarkers that systematically change with aging (Jylhävä et al., 2017).

While the first two correlate well with CA, they do not offer modifiable targets for preventive intervention. The third type is unlikely to improve risk prediction, as it is typically derived from compositions of the same biomarkers that constitute the risk factor models.

4.1. Limitations

There are three important limitations to our study.

First, our study population is not representative of the general population. Hence, our robustness score may deviate from a score for a specific population. However, the integration of the hazard rate that had been derived from a similar cohort of the LURIC study (Appendix C, Table C.1), somewhat moderates this limitation. Also, the selected study design is unsuitable to uncover the suggested cause-effect relationship between robustness and mortality. We chose this less resource-demanding design to probe for evidence that may either justify, or militate against, committing considerable resources to test the cause-effect hypothesis in a prospective study.

Second, our study population only allowed us a relatively global and qualitative view on risk factor exposure. For future studies, it is desirable to investigate the effects of different risk factor profiles on robustness scores. This is especially true for the CC strata which should ideally reflect the risk factor model's constituent markers.

Third, the VA's arterial model has not been validated against any other current method that probes arterial functional parameters. The reason is that none of these other methods facilitates the derivation of the physical parameters that globally describe arterial function. The current gold standard of pulse wave velocity (PWV), an acknowledged surrogate marker for arterial function (Mancia et al., 2007), and an independent predictor of cardiovascular mortality and morbidity (Townsend et al., 2015), has been found to be affected by heart rate and blood pressure (Tan et al., 2012), but also by mechanical properties of the arterial wall, which vary across locations within the arterial tree (Townsend et al., 2015).

Another marker of arterial function is flow-mediated vasodilation (FMD). FMD is thought to reflect endothelial function (Flammer et al., 2012), thereby providing insights into the integrity of the tissue at which the atherosclerotic nidus develops. However, its utility as a clinical and research tool has acknowledged limitations in terms of validity and comparability (Thijssen et al., 2011). Moreover, FMD is inconvenient to assess, requiring considerable operator skills, which leads to substantial inter-operator differences of measurement results (Sejda et al., 2005). The results of both measurements, PWV and FMD, are limited to the arterial segment to which they are applied and cannot be extrapolated to the whole arterial tree as each arterial segment has its own viscoelastic properties (Laurent et al., 2006).

Conversely, the VA derives for each functional parameter a global correction factor that is applied uniformly to all arterial segments. The resulting markers for global compliance, resistance and inertia represent their biological equivalents. It is therefore reasonable to assume that these markers will emerge, in yet to be conducted clinical investigations, as independent predictors of disease status and risk.

Such investigations are further motivated by the lack of blood based biomarkers that would provide for the quantitative assessment of

vascular function. The biomarkers that come closest to being indicators of a functional property are N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) and B-type natriuretic peptide (BNP). As they are secreted from cardiomyocytes in correlation with ventricular wall stretch, they offer no information about the functional properties of the vascular wall (Levin et al., 1998). Correspondingly, while these markers have shown considerable power for the prediction of death in heart failure patients, their predictive value in the general population is (a) modest, providing only marginal improvements to the c-statistics of conventional risk factor scores (Blankenberg et al., 2010; Wang et al., 2006), and (b) limited to older cohorts aged 60 and above (Cushman et al., 2014; Duschek et al., 2011; Rutten et al., 2010).

4.2. Perspectives

Research of the robustness score and of its constituent parameters should advance our knowledge in three areas:

Studies of clinical validity to investigate causal associations with manifestations of the cardiovascular disease spectrum (such as essential hypertension, peripheral arterial disease, aortic aneurysms, renal insufficiency);

Studies of predictive ability to investigate the score's power to identify the false negatives and positives of current risk factor models;

Studies of preventive utility to investigate the modifiability of the score's constituent parameters and their association with disease endpoints.

The immediate utility of robustness scoring will be determined by its ability to uncover modifiable differences in mortality risk among clinical populations with similar risk factor exposure. To this end we suggest a prospective registry study that recruits its participants from among a clinic's CVD patient population. The study shall be designed to investigate in diseased populations (a) the hypothesis that *delta_age* and changes in *delta_age* correlate with disease mortality, (b) the correlation between pharmacological/surgical interventions and changes in *delta_age*, and in apparently healthy populations the effects of lifestyle and lifestyle changes on *delta_age*.

5. Conclusion

CV mortality trends suggest that we are getting incrementally better at letting the diseased live longer, thereby extending morbidity rather than compressing it (Sidney et al., 2017). But to meet the UN's goal of preventing premature mortality from chronic non-communicable diseases, the risk for CVD needs to be uncovered while CVD can be prevented. The result of our work suggests that, with its apparent ability to identify risk in the pre-symptomatic young adult, robustness may be a promising tool to minimize the blind spot of the current risk factor model, making it a worthy object of prospective follow-up investigations. Being expressible in terms of biological age makes robustness intuitively understandable to everybody, thereby potentially increasing the prematurely aging individual's motivation to correct detrimental lifestyle choices. Hence, our results suggest that vascular robustness may become as important to risk prediction and disease prevention as the risk factors whose effects it moderates.

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Disclosures

None of the authors has any conflicts of interest in relation to this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2018.01.008.

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