Measuring senescence in human populations

Koopman, J.J.E.

11

MEASURING SENESCENCE THROUGH HEART RATE AND HEART RATE VARIABILITY

Published as:
J. J. E. Koopman, D. van Bodegom, A. C. Maan, Z. Li,
J. B. Ziem, R. G. J. Westendorp, J. W. Jukema.
Heart rate variability, but not heart rate, is associated with handgrip strength and mortality in older Africans at very low cardiovascular risk: a population-based study.
International Journal of Cardiology 2015; 187: 559-561

Background • Heart rate and heart rate variability are associated with functional impairment, morbidity, and mortality in western populations. It is unclear whether these associations are mediated by lifestyle-related cardiovascular risk factors. Therefore, we studied these associations in a population where an affluent sedentary lifestyle is absent and risk factors of cardiovascular disease and diabetes are rare.

Methods • Among 822 community-dwelling inhabitants aged 50 years and older in a traditional rural African population in Northeast Ghana, we measured cardiovascular risk factors, including body mass index (BMI), waist circumference, glucose level, diastolic and systolic blood pressure, and ankle-arm index. Heart rate and heart rate variability, measured as SDNN and RMSSD, were derived from electrocardiograms (ECGs) recorded at rest. Physical function was determined by handgrip strength. Mortality was documented during a follow-up period of two years.

Results • Heart rate increased slightly with age and was dependent on BMI, glucose level, and diastolic blood pressure. Heart rate variability decreased with age and was not dependent on cardiovascular risk factors. Heart rate was associated with neither handgrip strength nor mortality. A lower heart rate variability was associated with lower handgrip strength and a higher risk of mortality, independent of age, sex, tribe, and cardiovascular risk factors.

Conclusion • Heart rate variability, but not heart rate, is associated with handgrip strength and mortality in a traditional rural African population, which indicates that this association is independent of lifestyle-related cardiovascular risk factors and probably a reflection of a universal deterioration of the body's autonomic regulation during ageing.

Heart rate and heart rate variability at rest are established risk factors of various forms of morbidity and mortality. In the general population, a high heart rate and a low heart rate variability are associated with an accelerated progression of atherosclerosis[1-3] and predict hypertension, coronary heart disease, heart failure, stroke, and cardiovascular death.[1-8] In addition to cardiovascular disease, a high heart rate and a low heart rate variability are associated with insulin resistance and diabetes mellitus[6,9-11] and predict mortality due to cancer[12] and all-cause mortality.[3,10] A low heart rate variability not only marks morbidity and mortality, but is also associated with measures of functional impairment, such as a weak handgrip strength.[13,14]

Two explanations can be given for the associations of heart rate and heart rate variability with functional impairment, morbidity, and mortality. On one hand, these associations are attributed to the deterioration of the autonomic nervous system during ageing.[13,14] The autonomic nervous

system continuously adjusts the heart rate in response to changes in physiologic conditions to maintain hæmodynamic stability. A high heart rate and a low heart rate variability are thought to reflect dysfunction of the flexible autonomic regulation of the heart rate in particular and of the body's functioning in general.[6,10] On the other hand, a high heart rate and a low heart rate variability can be brought about by the risk factors of age-related diseases such as cardiovascular disease and diabetes. Heart rate and heart rate variability depend on body mass index (BMI),[2,6,10,15-18] lipid levels,[2,6,10,15,17] glucose levels,[6,10,15] blood pressure,[2,6-8,10,15,16,18] inflammation,[10,19] nutrition,[20] and physical inactivity.[6,10,16,18] While these risk factors are closely related to lifestyle, research on heart rate and heart rate variability has almost exclusively been conducted in western societies with an affluent sedentary lifestyle and high prevalences of these risk factors. It has therefore been difficult to determine whether or not heart rate and heart rate variability are associated with functional impairment, morbidity, and mortality independently of cardiovascular risk factors.[1-4] To disentangle the effects of ageing and the lifestyle-related cardiovascular risk factors, the associations of heart rate and heart rate variability with functional impairment, morbidity, and mortality should also be studied in societies where an affluent sedentary lifestyle is absent and these risk factors are rare.

We investigated the associations of heart rate and heart rate variability with handgrip strength and mortality among older persons in a traditional rural African population. In this population, contrary to western populations, food is scarce, lifelong manual labour is necessary for subsistence, and obesity, hyperlipidæmia, diabetes, hypertension, and cardiovascular diseases are rare (Chapters 9 and 10 of this thesis).[21-23] We have recently shown that handgrip strength strongly and independently predicts mortality in this population (Chapter 8 of this thesis).[24]

Methods

Research area

This study was conducted in the Garu-Tempane District in the Upper East Region in Ghana. The area is rural, remote, and one of the least developed in the country. The vast majority of the inhabitants are involved in non-commercial agriculture performed by manual labour without proper means of transportation or mechanised farming. Hospital care is absent. Infectious diseases are highly endemic and constitute the main causes of death, although the prevalence of human immunodeficiency virus (HIV) is low (< 4%) compared with other African regions.[25]

Since 2002, we have kept a demographic registry of the population within a research area of 375 km^2 comprising 32 villages. During yearly visits we registered the name, age, sex, tribe, and location of living of each inhabitant. In 2007 we determined the property value of each household. From this value, an index of the socioeconomic status with a standard normal distribution was calculated according to the Demographic and Health Survey method.[26]

In addition, we registered the main drinking water source of each household. Water from boreholes was classified as safe and water from open wells and rivers as unsafe, based on their pathogen contents and their effects on survival.[27] Annual migration relative to the study population's size was 2% into and 1% out of the research area. Elaborate descriptions of this study population have been given elsewhere.[21-24,26]

Ethical approval was given by the Ethical Review Committee of Ghana Health Services, the Committee Medical Ethics of Leiden University Medical Center, and the local chiefs and elders. Because of illiteracy, informed consent was obtained orally in the participant's own language after explanation of the purpose and conduction of this research project. The study conforms to the ethical guidelines of the Declaration of Helsinki.

Participants and measurements

In 2009 and 2010 we conducted measurements in the morning among 924 inhabitants aged 50 years and older, who were recruited in villages visited consecutively. To ensure maximal participation, we set up a mobile field work station in the villages and, if necessary, brought less mobile participants by car. Reasons of non-participation were death of the individual since the last registration (n = 48), refusal of participation (n = 35), absence from the research area during our visits because of migration or travelling (n = 30), and other reasons (n = 46).

Height, weight, and waist circumference were measured and BMI was calculated as weight in kilograms divided by squared height in metres. Glucose level was measured in a random capillary blood sample from a finger (Accutrend Plus, Roche, Rotkreuz, Switzerland). Blood pressure was measured on one arm in a lying and resting position. Systolic blood pressures were measured on the dorsalis pedis artery and the posterior tibial artery of both ankles with a Doppler ultrasound machine (ImexDOP CT+, Natus-Nicolet, Golden, CO, USA). As a measure of peripheral arterial disease, the ankle-arm index was calculated by dividing the average systolic pressure at the ankles by the systolic arm pressure.[23]

Twelve-lead electrocardiograms (ECGs) were obtained as two sequential recordings of ten seconds in a lying and resting position (AT-104 PC, Schiller, Baar, Switzerland). Three participants with atrial fibrillation, described in Chapter 10 of this thesis,[22] were excluded from the analyses. The recordings of the other participants displayed sinus rhythm with positive P waves in leads I and II and uniform QRS complexes. The timing of the QRS complexes was identified automatically. All recordings were manually reviewed in detail to verify the automatic identification of QRS complexes and to ensure that only normal RR intervals were included in the analyses. Recordings with ectopic complexes were excluded from the analyses, except for twelve participants with an ectopic complex in the last two seconds of the recording, in which cases all complexes from the ectopic complex onward

were excluded. Heart rate in beats per minute (bpm) and two measures of heart rate variability in milliseconds (ms) were determined based on standard methods.[28] Heart rate variability was calculated as the standard deviation of normal RR intervals (SDNN) and as the root mean square of the differences between successive normal RR intervals (RMSSD).

Handgrip strength was measured using a calibrated Jamar hand dynamometer (Sammons Preston, Bolingbrook, IL, USA) while the participant was standing in an upright position with the arms unsupported parallel to the body. Participants were instructed to exert maximal force with each hand once. The handgrip strength of the hand with the highest measurement was registered.[29]

Data on mortality after the measurements in 2009 and 2010 were available from the demographic registry. Follow-up started at the time of the measurements and lasted until death, migration out of the research area, loss to follow-up, or our last visit to the research area in 2011.

Analyses

Because of their skewed distributions, SDNN and RMSSD were transformed logarithmically. Changes in heart rate and heart rate variability with age were assessed using linear regression with age and sex as independent variables. Changes in the variances of heart rate and heart rate variability with age were assessed using Levene's test comparing 5-year age groups. Associations of heart rate and heart rate

Number of individuals	822
Men, *n* (%)	421 (51.2)
Age, years	65 (56–72)
Tribe, *n* (%)	
Bimoba	572 (69.6)
Kusasi	195 (23.7)
other	55 (6.7)
Household property value, US$	1085 (516–1944)
Safe drinking water, *n* (%)	721 (87.7)
Waist circumference, cm	77 (72–81)
Body mass index, kg/m^2	18.1 (16.6–19.6)
Blood pressure, mmHg	
diastolic	70 (65–80)
systolic	120 (110–135)
Ankle-arm index	1.15 (1.08–1.23)
Heart rate, bpm	70 (62–78)
Heart rate variability, ms	
SDNN	19.6 (13.6–29.3)
RMSSD	18.0 (11.4–28.4)

Table 11.1 • General characteristics of the Ghanaian study population. Data are presented as medians with interquartile ranges unless specified otherwise. Heart rate variability was calculated as the standard deviation of normal RR intervals (SDNN) and as the root mean square of the differences between successive normal RR intervals (RMSSD). Bpm: beats per minute.

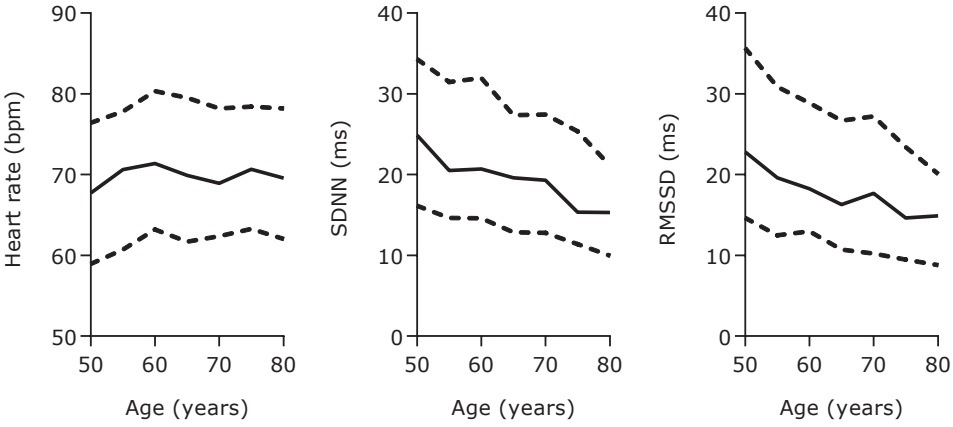

Figure 11.1 • Distributions of heart rate and heart rate variability over age in the Ghanaian study population. The data represent age-specific medians (continuous lines) and interquartile ranges (dashed lines) of heart rate and heart rate variability. Heart rate variability was calculated as the standard deviation of normal RR intervals (SDNN) and as the root mean square of the differences between successive normal RR intervals (RMSSD). Bpm: beats per minute.

variability with handgrip strength were tested with three linear regression models: one without adjustments; one minimally adjusted for age, sex, tribe, and height; and one fully adjusted for height and all demographic and cardiovascular characteristics shown in Table 11.1. Hazard ratios were determined by three Cox regression models: one without adjustments; one minimally adjusted for age, sex, and tribe; and one fully adjusted for all demographic and cardiovascular characteristics shown in Table 11.1. In the fully adjusted models, the associations of heart rate with handgrip strength and mortality were adjusted for SDNN, but the results were similar when adjusting for RMSSD instead. The analyses were performed with SPSS Statistics 20 (IBM, Armonk, NY, USA).

Results

Table 11.1 provides the demographic and cardiovascular characteristics of the Ghanaian study population. Of the 924 individuals who participated in the measurements, 822 could be included with data on heart rate, heart rate variability, and handgrip strength. Both measures of heart rate variability, SDNN and RMSSD, correlated with Spearman's $\rho = 0.83$ ($p < 0.001$). After logarithmic transformation, median (with interquartile range) SDNN was 2.98 ln ms (2.61–3.38), median RMSSD was 2.89 ln ms (2.43–3.35), and their correlation remained similar with Pearson's $r = 0.84$ ($p < 0.001$).

Figure 11.1 shows the distributions of heart rate and heart rate variability over age. As age increased one year, heart rate increased with 0.15 bpm, SDNN decreased

Table 11.2 • Determinants of heart rate and heart rate variability in the Ghanaian study population

	Difference in heart rate in bpm (95% CI)	Difference in SDNN in ln ms (95% CI)	Difference in RMSSD in ln ms (95% CI)
Age, years	+0.16 (+0.08 to +0.25) **	-0.010 (-0.014 to -0.005) **	-0.011 (-0.016 to -0.006) **
Men	-9.45 (-11.13 to -7.78) **	-0.023 (-0.109 to +0.063)	-0.060 (-0.161 to +0.034)
Tribe			
Bimoba	Ref.	Ref.	Ref.
Kusasi	+1.13 (-0.74 to +3.00)	+0.014 (-0.075 to +0.104)	+0.024 (-0.078 to +0.125)
other	-1.78 (-5.15 to +1.59)	-0.156 (-0.317 to +0.006)	-0.157 (-0.339 to +0.026)
Wealth index	-0.26 (-0.86 to +0.33)	+0.038 (+0.010 to +0.067) *	+0.050 (+0.018 to +0.083) *
Safe drinking water	-0.26 (-2.64 to +2.11)	-0.103 (-0.217 to +0.010)	-0.049 (-0.178 to +0.079)
Body mass index, kg/m^2	-0.50 (-0.99 to -0.01) *	+0.010 (-0.013 to +0.033)	0.000 (-0.027 to +0.026)
Waist circumference, cm	0.00 (-0.18 to +0.18)	-0.008 (-0.017 to 0.000)	-0.004 (-0.014 to +0.005)
Capillary glucose, mmol/l	+2.11 (+1.31 to +2.91) **	-0.004 (-0.042 to +0.035)	-0.010 (-0.054 to +0.034)
Diastolic blood pressure, mmHg	+0.24 (+0.14 to +0.35) **	-0.001 (-0.006 to +0.004)	0.000 (-0.005 to +0.006)
Systolic blood pressure, mmHg	+0.01 (-0.04 to +0.06)	+0.001 (-0.001 to +0.003)	+0.002 (-0.001 to +0.004)
Ankle-arm index	+1.96 (-1.70 to +5.61)	-0.153 (-0.328 to +0.022)	-0.081 (-0.280 to +0.117)
Heart rate, bpm	—	-0.019 (-0.022 to -0.016) **	-0.030 (-0.034 to -0.026) **

The data represent the differences in heart rate or heart rate variability per unit change in each characteristic. Tribes are compared with the Bimoba tribe as reference (Ref.). Men and safe drinking water source are compared with women and unsafe drinking water source as references. Heart rate variability was calculated as the standard deviation of normal RR intervals (SDNN) and as the root mean square of the differences between successive normal RR intervals (RMSSD). Each association of each characteristic with heart rate or heart rate variability was adjusted for those of the other characteristics. Bpm: beats per minute. * $p < 0.05$; ** $p < 0.001$.

Table 11.3 • Associations of heart rate and heart rate variability with handgrip strength in the Ghanaian study population

	Difference in handgrip strength in kg (95% CI)		
	Without adjustments	**Adjusted for age, sex, tribe, and height**	**Fully adjusted**
Heart rate, bpm	-0.16 (-0.21 to -0.12) **	-0.03 (-0.06 to +0.01)	-0.01 (-0.05 to +0.03)
Heart rate variability, ln ms			
SDNN	+2.53 (+1.58 to +3.48) **	+1.01 (+0.26 to +1.77) *	+0.91 (+0.15 to +1.67) *
RMSSD	+2.23 (+1.44 to +3.01) **	+0.80 (+0.17 to +1.42) *	+0.78 (+0.11 to +1.46) *

The data represent the difference in handgrip strength per unit change of each measure of heart rate and heart rate variability. Heart rate variability was calculated as the standard deviation of normal RR intervals (SDNN) and as the root mean square of the differences between successive normal RR intervals (RMSSD). The fully adjusted effects were adjusted for age, sex, tribe, height, socioeconomic status, drinking water source, body mass index, waist circumference, glucose level, diastolic and systolic blood pressure, ankle-arm index, and heart rate or heart rate variability. Bpm: beats per minute. * $p<0.05$; ** $p<0.001$.

Table 11.4 • Associations of heart rate and heart rate variability with mortality in the Ghanaian study population

	Hazard ratio (95% CI)		
	Without adjustments	**Adjusted for age, sex, and tribe**	**Fully adjusted**
Heart rate, bpm	1.02 (0.99 to 1.04)	1.02 (0.99 to 1.04)	1.00 (0.97 to 1.03)
Heart rate variability, ln ms			
SDNN	0.49 (0.29 to 0.82) *	0.53 (0.31 to 0.91) *	0.55 (0.29 to 1.01)
RMSSD	0.65 (0.43 to 1.00) *	0.71 (0.46 to 1.10)	0.75 (0.45 to 1.25)

The data represent the difference in handgrip strength per unit change of each measure of heart rate and heart rate variability. Heart rate variability was calculated as the standard deviation of normal RR intervals (SDNN) and as the root mean square of the differences between successive normal RR intervals (RMSSD). The fully adjusted effects were adjusted for age, sex, tribe, socioeconomic status, drinking water source, body mass index, waist circumference, glucose level, diastolic and systolic blood pressure, ankle-arm index, and heart rate or heart rate variability. Bpm: beats per minute. * $p<0.05$; ** $p<0.001$.

with 0.013 ln ms, and RMSSD decreased with 0.016 ln ms (all $p < 0.001$). The variances of heart rate and heart rate variability were constant with age.

As shown in Table 11.2, we explored the determinants of heart rate and heart rate variability in a multivariate model including all demographic and cardiovascular characteristics. Heart rate was higher in older individuals, in women, in individuals with a lower BMI, in individuals with a higher glucose level, and in individuals with a higher diastolic blood pressure. Both SDNN and RMSSD were lower in older individuals, higher in individuals with a higher wealth index, and lower in individuals with a higher heart rate.

Heart rate, heart rate variability, and handgrip strength

Table 11.3 describes the associations of heart rate and heart rate variability with handgrip strength. Handgrip strength was lower in individuals with a higher heart rate and higher in individuals with a higher SDNN or RMSSD (all $p < 0.001$). After adjustment for age, sex, tribe, and height, heart rate was not associated with handgrip strength, but handgrip strength remained higher in individuals with a higher SDNN ($p = 0.009$) or RMSSD ($p = 0.013$). After additional adjustment for other demographic and cardiovascular characteristics, these associations did not change ($p < 0.025$). When stratifying the fully ad-

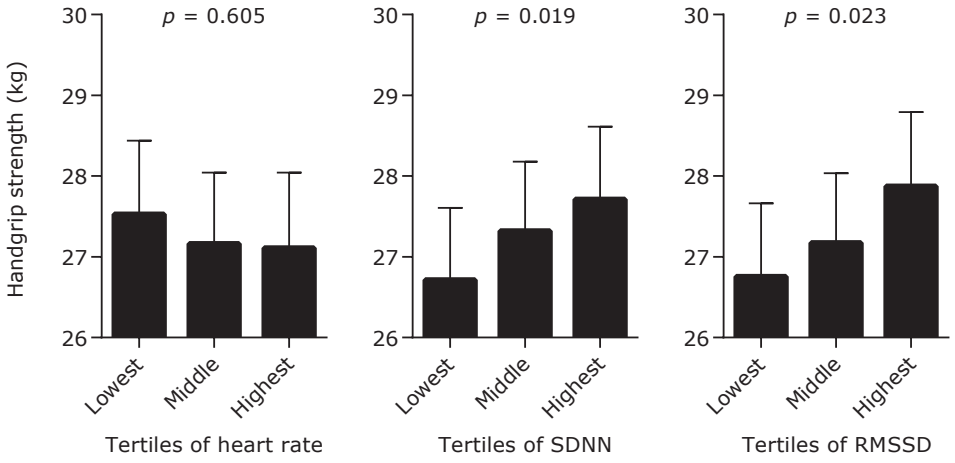

Figure 11.2 • Estimates of handgrip strength per tertiles of heart rate and heart rate variability in the Ghanaian study population. The data represent estimated means of handgrip strength per tertiles of heart rate and heart rate variability. Heart rate variability was calculated as the standard deviation of normal RR intervals (SDNN) and as the root mean square of the differences between successive normal RR intervals (RMSSD). The estimated means were fully adjusted for age, sex, tribe, height, drinking water source, body mass index, waist circumference, glucose level, diastolic and systolic blood pressure, ankle-arm index, and heart rate or heart rate variability (p values for trends). Bpm: beats per minute.

justed model, the association of heart rate variability with handgrip strength was not different between men and women, individuals younger and older than 65 years, or individuals with and without underweight, defined as a BMI below 18.5 kg/m^2.

Figure 11.2 provides estimates of handgrip strength per tertiles of heart rate and heart rate variability, adjusted for all demographic and cardiovascular characteristics. From the lowest to the highest tertile of heart rate, handgrip strength declined non-significantly with 0.57 kg. From the lowest to the highest tertile of SDNN, handgrip strength increased with 1.00 kg. From the lowest to the highest tertile of RMSSD, handgrip strength increased with 1.12 kg.

Heart rate, heart rate variability, and mortality

Table 11.4 describes the associations of heart rate and heart rate variability with mortality. Data on follow-up were available for 814 (99.0%) participants and comprised 1396 person-years and 42 deaths. Heart rate was not associated with mortality. Heart rate variability was inversely associated with mortality: risk of mortality was lower in individuals with a higher SDNN (p = 0.006) or RMSSD (p = 0.048). After adjustment for age, sex, and tribe, these associations remained similar and remained significant for SDNN (p = 0.021), but lost significance for RMSSD (p = 0.121). After additional adjustment for other demographic and cardiovascular characteristics, the associations remained similar.

Sensitivity analyses

To examine the consistency of the results, we repeated the analyses in restricted groups of participants. Firstly, we excluded twelve participants who had shown ectopic complexes in the last two seconds of the ECG. The associations of heart rate with handgrip strength and mortality remained absent in the minimally and fully adjusted models. The associations of heart rate variability with handgrip strength and mortality remained similar. Secondly, we excluded 28 participants with sinus arrhythmia, defined as the presence of consecutive normal RR intervals differing by more than 120 ms. The associations of heart rate with handgrip strength and mortality remained absent in the minimally and fully adjusted models. The associations of heart rate variability with handgrip strength were strengthened; their associations with mortality remained similar (data not shown).

Discussion

This study aims to assess whether heart rate and heart rate variability at rest are associated with handgrip strength and mortality among older persons in a traditional rural African population where obesity, hyperlipidæmia, diabetes, hypertension, and cardiovascular diseases are rare (Chapters 9 and 10 of this thesis).[21-23] Heart rate increased slightly with age and was dependent on BMI, glucose level, and diastolic blood pressure. Heart rate variability decreased with age and was not dependent on cardiovascular risk factors. Heart rate was associated with neither handgrip strength nor mortality. A lower

heart rate variability was associated with lower handgrip strength and, corresponding with our previous report that low handgrip strength predicts mortality,[24] a higher risk of mortality. These associations were independent of age, sex, tribe, and cardiovascular risk factors.

This study is the first to investigate heart rate and heart rate variability in relation to physical function and mortality in traditional Africa. Few studies have assessed heart rate at rest and its associations with cardiovascular risk factors in rural African populations and have reported results that are in accordance with our results. Heart rate was, compared with the Ghanaian study population, similar in rural Tanzanian populations[8,30] and among hypertensive patients attending hospitals in different Sub-Saharan countries,[31] but higher in a population close to our research area with younger participants and higher prevalences of cardiovascular risk factors.[32] In these populations, heart rate was constant with age, higher in women, and positively related with blood pressure and lipid levels, although less strongly than in western populations.[8,16,30,32] Heart rate was found to be higher in Congolese children and adolescents with a lower socioeconomic status and with malnutrition or obesity.[33] Heart rate variability has been measured only in hospitals in several Sub-Saharan countries and without assessing its associations with physical function, morbidity, or mortality. In these studies, heart rate variability declined with age and was higher in women.[30,31]

Heart rate and heart rate variability at rest vary across populations and ethnicities due to both genetic and environmental factors,[16,30,34] which complicates comparisons between populations. Still, the study of heart rate and heart rate variability in populations without an affluent sedentary lifestyle aids the solution of questions that remain despite the research conducted in western populations. Heart rate in western populations is higher in women and dependent on various cardiovascular risk factors, as in the Ghanaian study population, but it has been inconsistently described to decrease, be constant, or increase with age.[7,8,15-18] Conflicting results have also been reported on differences in heart rate between European and African Americans.[11,35-37] A study comparing Americans of European origin, Americans of African origin, and American immigrants from Ghana without hypertension, cardiovascular disease, and diabetes found no differences in heart rate.[38] Other studies showed that differences in heart rate between European and African Americans can be attributed to cardiovascular risk factors.[37,39] The findings from traditional African populations reinforce the possibility that heart rate is dependent on cardiovascular risk factors rather than age and that it is only associated with functional impairment, morbidity, and mortality when these risk factors are present. As a biological explanation, cardiovascular risk factors such as obesity, hyperlipidæmia, hypertension, and diabetes can increase heart rate by inducing hæmodynamic alterations, cardiac conduction abnormalities, and sympathetic hyperactivation.[6,10,15,40]

Heart rate variability decreases with age in western populations as in the Ghanaian study population and other African populations.[2,16,17,41-43] Heart rate variability in the Ghanaian study population was similar to that in different western populations investigated with comparable methodologies, despite differences in cardiovascular risk factors.[44-47] Although conflicting results have been reported on differences in heart rate variability between European and African Americans, these differences seem independent of cardiovascular risk factors.[34,41,48] Not only in the Ghanaian study population, but also in western populations heart rate variability has been reported to be unaffected by cardiovascular risk factors.[18,34,42,49] These findings, combined with those from traditional African populations, suggest that heart rate variability is associated with functional impairment, morbidity, and mortality through mechanisms independent of cardiovascular risk factors. Most likely, heart rate variability declines during ageing as a result of a deteriorating autonomic regulation of the heart rate that occurs across populations with different lifestyles.[13,14,20,50] More research in populations without an affluent sedentary lifestyle is required to substantiate our interpretations.

Since a high heart rate is a long-established predictor of morbidity and mortality, it is regarded as a potential therapeutic target of cardiovascular disease.[1,3,7] While pharmacological lowering of the heart rate has been found to benefit patients with heart failure, it fails to do so in patients without heart failure.[51] In line with our study, it is posited that the heart rate is accelerated not as a cause, but as an effect of cardiovascular disease.[1,51] It could be that in the detection and prevention of cardiovascular disease the role of heart rate is overrated, while that of heart rate variability has remained underrated.

This study has the following limitations. Firstly, ECGs were recorded during 20 seconds, while longer recordings are often preferred.[28] Heart rate variability in short recordings cannot be measured by frequency-domain methods, cannot be compared with longer recordings used in most studies, and is determined with less precision. However, SDNN and RMSSD as measures of heart rate variability can be used to investigate short recordings[28] and several studies of similarly short recordings have demonstrated that these measures are associated with morbidity and mortality.[44-47] Moreover, the less precise determination of heart rate variability in short recordings is thought to result in underestimation rather than overestimation of the true associations.[45,47] Secondly, mortality was registered during only a short follow-up period, which attenuates the statistical power of the mortality analyses. Thirdly, associations of heart rate and heart rate variability with incidence of morbidity could not be assessed, since diseases were not registered. Lastly, the effects of some lifestyle-related risk factors on heart rate and heart rate variability could not be studied. Although nutritional status was reflected by BMI, dietary composition, physical activity, and smoking were not formally documented.

In conclusion, this study shows that a high heart rate is not, but a low heart rate variability is associated with handgrip strength and mortality among older persons in a traditional rural African population as it is in western populations. This suggests that the association of heart rate with physical function and mortality as described in western populations is predominantly mediated by lifestyle-related risk factors of cardiovascular disease and diabetes. By contrast, the association of heart rate variability with physical function and mortality probably reflects a universal deterioration of the body's autonomic regulation during ageing. Across various environments, heart rate variability can be measured to predict functional impairment and mortality.

Acknowledgements

We are grateful for the dedicated assistance of the local staff of the research team in the Garu-Tempane District in Ghana, for the help of dr. U.K. Eriksson, T. Menger, and H. Sanchez-Faddiev in the field work, and for the sagacious comments of dr. A.J.M. de Craen. This research was supported by the Netherlands Foundation for the Advancements of Tropical Research (WOTRO 93-467), the Netherlands Organization for Scientific Research (NWO 051-14-050), the European Union-funded Network of Excellence LifeSpan (FP6 036894), a grant of the Board of Leiden University Medical Center, and Stichting Dioraphte. None of these organisations had any role in the design, analysis, interpretation, or report of the study.

References

1. Böhm M., Reil J.C., et al. Resting heart rate: risk indicator and emerging risk factor in cardiovascular disease. *Am. J. Med.* 2015; 128: 219-228.
2. Xhyheri B., Manfrini O., et al. Heart rate variability today. *Prog. Cardiovasc. Dis.* 2012; 55: 321-331.
3. Fox K., Borer J.S., et al. Resting heart rate in cardiovascular disease. *J. Am. Coll. Cardiol.* 2007; 50: 823-830.
4. Hillebrand S., Gast K.B., et al. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression. *Europace* 2013; 15: 742-749.
5. Woodward M., Webster R., et al. The association between resting heart rate, cardiovascular disease and mortality: evidence from 112,680 men and women in 12 cohorts. *Eur. J. Prev. Cardiol.* 2012; 21: 719-726.
6. Thayer J.F., Yamamoto S.S., Brosschot J.F. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int. J. Cardiol.* 2010; 141: 122-131.
7. Perret-Guillaume C., Joly L., Benetos A. Heart rate as a risk factor for cardiovascular disease. *Prog. Cardiovasc. Dis.* 2009; 52: 6-10.
8. Palatini P., Julius S. Heart rate and the cardiovascular risk. *J. Hypertens.* 1997; 15: 3-17.
9. Nagaya T., Yoshida H., Takahashi H., Kawai M. Resting heart rate and blood pressure, independent of each other, proportionally raise the risk for type-2 diabetes mellitus. *Int. J. Epidemiol.* 2010; 39: 215-222.
10. Thayer J.F., Lane R.D. The role of vagal function in the risk for cardiovascular disease and mortality. *Biol. Psychol.* 2007; 74: 224-242.
11. Festa A., D'Agostino R., et al. Heart rate in relation to insulin sensitivity and insulin secretion in nondiabetic subjects. *Diabetes Care* 2000; 23: 624-628.
12. Jouven X., Escolano S., et al. Heart rate and risk of cancer death in healthy men. *PLoS One* 2011; 6: E21310.
13. Varadhan R., Chaves P.H.M., et al. Frailty and impaired cardiac autonomic control: new insights from principal components aggregation of traditional heart rate variability indices. *J. Gerontol. A Biol. Sci. Med. Sci.* 2009; 64: 682-687.
14. Chaves P.H.M., Varadhan R., et al. Physiological complexity underlying heart rate dynamics and frailty status in community-dwelling older women. *J. Am. Geriatr. Soc.* 2008; 56: 1698-1703.
15. Grassi G., Arenare F., et al. Heart rate, sympathetic cardiovascular influences, and the metabolic syndrome. *Prog. Cardiovasc. Dis.* 2009; 52: 31-37.
16. Valentini M., Parati G. Variables influencing heart rate. *Prog. Cardiovasc. Dis.* 2009; 52: 11-19.
17. Silva de Paula R., Antelmi I., et al. Influence of age, gender, and serum triglycerides on heart rate in a cohort of asymptomatic individuals without heart disease. *Int. J. Cardiol.* 2005; 105: 152-158.
18. Stolarz K., Staessen J.A., et al. Host and environmental determinants of heart rate and heart rate variability in four European populations. *J. Hypertens.* 2003; 21: 525-535.
19. Stein P.K., Barzilay J.I., et al. Higher levels of inflammation factors and greater insulin resistance are independently associated with higher heart rate and lower heart rate variability in normoglycemic older individuals: the Cardiovascular Health Study. *J. Am. Geriatr. Soc.* 2008; 56: 315-321.
20. Stein P.K., Soare A., et al. Caloric restriction may reverse age-related autonomic decline in humans. *Aging Cell* 2012; 11: 644-650.
21. Engelaer F.M., Koopman J.J.E., et al. Determinants of epidemiologic transition in rural Africa: the role of socioeconomic status and drinking water source. *Trans. R. Soc. Trop. Med. Hyg.* 2014; 108: 372-379.
22. Koopman J.J.E., Van Bodegom D., Westendorp R.G.J., Jukema J.W. Scarcity of atrial fibrillation in a traditional African population: a community-based study. *BMC Cardiovasc. Disord.* 2014; 14: 87. (Chapter 10 of this thesis.)

23. Koopman J.J.E., Van Bodegom D., Jukema J.W., Westendorp R.G.J. Risk of cardiovascular disease in a traditional African population with a high infectious load: a population-based study. *PLoS One* 2012; 7: E46855. (Chapter 9 of this thesis.)
24. Koopman J.J.E., Van Bodegom D., Van Heemst D., Westendorp R.G.J. Handgrip strength, ageing, and mortality in rural Africa. *Age Ageing* 2015; 44: 465-470. (Chapter 8 of this thesis.)
25. *2012 Annual Report of the Upper East Region*. Ghana Health Service, Accra, Ghana, without date.
26. Van Bodegom D., May L., et al. Socio-economic status by rapid appraisal is highly correlated with mortality risks in rural Africa. *Trans. R. Soc. Trop. Med. Hyg.* 2009; 103: 795-800.
27. Kuningas M., May L., et al. Selection for genetic variation inducing pro-inflammatory responses under adverse environmental conditions in a Ghanaian population. *PLoS One* 2009; 4: E7795.
28. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996; 96: 1043-1065.
29. Beenakker K.G.M., Koopman J.J.E., et al. Variants of the *IL-10* gene associate with muscle strength in elderly from rural Africa: a candidate gene study. *Aging Cell* 2014; 13: 862-868. (Chapter 7 of this thesis.)
30. Torsvik M., Häggblom A., et al. Cardiovascular autonomic function tests in an African population. *BMC Endocr. Disord.* 2008; 8: 19.
31. Osakwe C.E., Jacobs L., et al. Heart rate variability on antihypertensive drugs in black patients living in sub-Saharan Africa. *Blood Press.* 2014; 23: 174-180.
32. Kunutsor S., Powles J. Cardiovascular risk in a rural adult West African population: is resting heart rate also relevant? *Eur. J. Prev. Cardiol.* 2014; 21: 584-591.
33. Longo-Mbenza B., Lukoki Luila E., M'Buyamba-Kabangu J.R. Nutritional status, socio-economic status, heart rate, and blood pressure in African school children and adolescents. *Int. J. Cardiol.* 2007; 121: 171-177.
34. Wang X., Thayer J.F., Treiber F., Snieder H. Ethnic differences and heritability of heart rate variability in African- and European American youth. *Am. J. Cardiol.* 2005; 96: 1166-1172.
35. Ostchega Y., Porter K.S., et al. Resting pulse rate reference data for children, adolescents, and adults: United States, 1999-2008. *Natl. Health Stat. Report* 2011: 1-16.
36. Gillum R.F. Epidemiology of resting pulse rate of persons ages 25-74: data from NHANES 1971-74. *Public Health Rep.* 1992; 107: 193-201.
37. Gillum R.F. The epidemiology of resting heart rate in a national sample of men and women: associations with hypertension, coronary heart disease, blood pressure, and other cardiovascular risk factors. *Am. Heart J.* 1988; 116: 163-174.
38. Osei K., Schuster D.P. Effects of race and ethnicity on insulin sensitivity, blood pressure, and heart rate in three ethnic populations: comparative studies in African-Americans, African immigrants (Ghanaians), and white Americans using ambulatory blood pressure monitoring. *Am. J. Hypertens.* 1996; 9: 1157-1164.
39. Sloan R.P., Huang M.H., et al. Cardiac autonomic control and the effects of age, race, and sex: the CARDIA Study. *Auton. Neurosci.* 2008; 139: 78-85.
40. Tentolouris N., Argyrakopoulou G., Katsilambros N. Perturbed autonomic nervous system function in metabolic syndrome. *Neuromolecular Med.* 2008; 10: 169-178.
41. Fuller-Rowell T.E., Williams D.R., et al. Race differences in age-trends of autonomic nervous system functioning. *J. Aging Health* 2013; 25: 839-862.
42. Antelmi I., De Paula R.S., et al. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *Am. J. Cardiol.* 2004; 93: 381-385.
43. Umetani K., Singer D.H., McCraty R., Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to

age and gender over nine decades. *J. Am. Coll. Cardiol.* 1998; 31: 593-601.
44. Shah S.A., Kambur T., et al. Relation of short-term heart rate variability to incident heart failure (from the Multi-Ethnic Study of Atherosclerosis). *Am. J. Cardiol.* 2013; 112: 533-540.
45. Karp E., Shiyovich A., et al. Ultra-short-term heart rate variability for early risk stratification following acute ST-elevation myocardial infarction. *Cardiol.* 2009; 114: 275-283.
46. De Bruyne M.C., Kors J.A., et al. Both decreased and increased heart rate variability on the standard 10-second electrocardiogram predict cardiac mortality in the elderly: the Rotterdam Study. *Am. J. Epidemiol.* 1999; 150: 1282-1288.
47. Dekker J.M., Schouten E.G., et al. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men: the Zutphen Study. *Am. J. Epidemiol.* 1997; 145: 899-908.
48. Lampert R., Ickovics J., Horwitz R., Lee F. Depressed autonomic nervous system function in African Americans and individuals of lower social class: a potential mechanism of race- and class-related disparities in health outcomes. *Am. Heart J.* 2005; 150: 153-160.
49. Kluttig A., Kuss O., Greiser K.H. Ignoring lack of association of heart rate variability with cardiovascular disease and risk factors. *Int. J. Cardiol.* 2010; 145: 375-376.
50. Kaye D.M., Esler M.D. Autonomic control of the aging heart. *Neuromolecular Med.* 2008; 10: 179-186.
51. Fox K., Ford I., et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N. Engl. J. Med.* 2014; 371: 1091-1099.