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Resting Heart Rate and Relation to Disease and Longevity

– *Past, Present, and Future*

Magnus T. Jensen MD PhD MSc

Doctoral Dissertation

University of Copenhagen

Faculty of Health and Medical Sciences

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International Journal of Cardiology. 2011 Sep 1;151(2):148-54.

II. Resting heart rate is associated with cardiovascular and all-cause mortality after adjusting for inflammatory markers: The Copenhagen City Heart Study
Jensen MT, Marott JL, Allin KH, Nordestgaard BG, Jensen GB
European Journal of Preventive Cardiology. 2012 Feb;19(1):102-8.

III. Resting heart rate is a predictor of mortality in COPD
Jensen MT, Marott JL, Lange P, Vestbo J, Schnohr P, Nielsen OW, Jensen JS, Jensen GB
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Heart. 2013 Jun;99(12):882-7.

V. Heart rate at discharge and long-term prognosis following percutaneous coronary intervention in stable and acute coronary syndromes--results from the BASKET PROVE trial
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European Heart Journal Acute Cardiovascular Care. 2018 Mar; 7(2): 149-157.

VII. Heritability of Resting Heart Rate and Association with Mortality in Middle-Aged and Elderly Twins
Jensen MT, Wod M, Galatius S, Hjelmborg JvB, Jensen GB, Christensen K
Heart. 2018; 104(1): 30-36

Preface

Heart rate has, in more than on sense, been my companion for the last decade. My interest in heart rate as a risk factor has followed me, alongside my other scientific and clinical interests, since my first introduction to this fascinating area 10 years ago. The initial stimulus to study heart rate came from my father, Professor Gorm B. Jensen, who allowed me to look into resting heart rate in the Copenhagen City Heart Study. Now, a decade later, I have been very fortunate to be able to study heart rate in multiple cohorts, collaborate with some of the finest researchers in Denmark and abroad, and participate in international scientific and health policy papers on heart rate. In recent years, with the emergence of wearable technology, there is, more than ever, an increased interest and relevance of the study of heart rate and health.

The present doctoral thesis represents research I have performed in the area of heart rate over the past years, and provides a contemporary review of the literature on heart rate as a risk marker and possible risk factor.

The individual papers listed in the *List of Papers* originates from five different cohorts. Each cohort has unique features of interest for the study of heart rate and risk from an epidemiological perspective.

The first three papers are from The Copenhagen City Heart Study (CCHS). I would like to thank Dr. Peter Schnohr, Merete Appleyard, and the other members of the CCHS steering committee for the opportunity to work with the CCHS, and particularly statistician Jacob Marott, who has been an inspirational sparring partner in the wonderful world of epidemiological biostatistics.

Paper I describes the association between resting heart rate and mortality, and the interaction between resting heart rate, smoking, and risk.

Paper II is an investigation into the association between resting heart rate and inflammatory markers. Here, the underlying question was two-fold – whether resting heart rate is related to subclinical inflammation, and, whether resting heart rate still relates to mortality when possible subclinical chronic inflammation is accounted for. I would particularly like to thank Professor Børge Nordestgaard for great sparring and permission to use data on inflammatory markers.

Paper III explores the role of resting heart rate in different strata of airflow obstruction. The idea to study resting heart rate and pulmonary function came from the clinical setting where individuals with chronic obstructive pulmonary disease often are found to have high heart rates. Despite being a common clinical observation, the association between pulmonary function and resting heart rate had not previously been systematically investigated and this was, therefore, an exciting topic. As expected from the clinical setting, resting heart rate and pulmonary function were strongly associated. Interestingly, when resting heart rate was added to conventional risk factors, the ability to predict prognosis in participants from the Copenhagen City

Heart Study was improved. I would particularly like to thank Professor Peter Lange for sharing his insights into respiratory epidemiology.

A key question, when investigating resting heart rate and prognosis, is the relationship between physical fitness level, resting heart rate, and mortality. I have often heard the argument that any relationship between resting heart rate and longevity most likely would be explained by underlying unmeasured differences in physical fitness level. The Copenhagen Male Study (CMS) is a unique cohort, which was established in 1970-71. One of the most impressive features of the CMS is that information about estimated VO_2max is available in all participants. The CMS therefore represents an extraordinary opportunity to account for levels of cardiorespiratory fitness when studying the relationship between resting heart rate and longevity, which is the focus of paper IV. Interestingly, the results from this study demonstrated that resting heart rate remained associated with risk even after accounting for levels of cardiorespiratory fitness. I would like to thank the founder of CMS, Professor Finn Gyntelberg, who gave me permission to study resting heart rate in the CMS, and who has always been incredibly supportive throughout our work together.

Where CCHS and CMS represent cohorts with individuals from the background population, the BASKET-PROVE randomized study includes patients with ischemic heart disease undergoing percutaneous coronary intervention. This population was investigated in Paper V. The relationship of discharge heart rate with outcome was an important and topical subject to investigate as this potentially could identify patients at particular risk of adverse events. The BASKET-PROVE Study included patients from 11 centers from Switzerland, Austria, Italy, and Denmark. With the support of Dr. Søren Galatius, my application to investigate heart rate at discharge in the study population was approved. As it turned out, however, heart rate was not collected as part of the BASKET-PROVE study protocol. Nevertheless, in a great effort from 10 of 11 centres, ECGs from discharge were collected by each centre. For the 11th centre, I was kindly invited by Professor Burkhard Hornig to St. Claraspital in Basel and, with the help of Dr. Erik Sandsten, we made an enjoyable trip to Basel and collected ECGs from the patient medical files. I would like to extend my grateful thanks to Dr. Galatius, Dr. Hornig, Dr. Sandsten and the rest of the BASKET-PROVE study group, who all worked together to make this study possible.

Following the study of discharge heart rate in the BASKET-PROVE study, it was relevant to also investigate admission heart rate in ischemic heart disease and risk of mortality, which was the focus of Paper VI. The EURHOBOP Study is a multicenter European study of the management of acute coronary syndromes across different jurisdictions in Europe. With the support from Dr. Marta Pereira, Professor Ana Azevedo, and the steering committee of the EURHOBOP collaboration, the study on admission heart rate and in-hospital mortality in acute coronary syndrome patients was made possible. I would like to extend particular thanks to Dr. Marta Pereira for a great collaboration and Professor Ana Azevedo for her collaboration and support.

Another key question is whether resting heart rate is influenced mainly by acquired factors or if resting heart rate also has a heritable component, which was the focus of Paper VII. As it were, Professor Kaare Christensen, and his group at University of Southern Denmark, are world experts in the field of twin research and heritability. With the expertise from Professor Christensen and his team, we were able to study the heritability of resting heart rate using the unique Danish twin data. We found that resting heart rate has a considerable heritable component. I would like to particularly thank Dr. Mette Wod and Professor Christensen for a very enjoyable and fruitful collaboration, for which I am very grateful.

Also, I would like to thank Professor Lars Køber for his valuable comments and review of this thesis.

None of the studies included in the present thesis would have been possible without the prodigious efforts by the great leaders in cardiovascular medicine, who established the cohorts and enabled my research - I do indeed feel that I am standing on the shoulders of giants.

Thank you to the steering committees and participants of the Copenhagen City Heart Study, the Copenhagen Male Study, the BASKET PROVE Study, the EURHOBOP Study, and the Danish Twin Registry.

I look forward to continuing my work within the field of heart rate in cardiovascular prevention. I expect that we, in the coming years, will experience a move from heart rate as an epidemiological phenomenon to a clinically applicable, generally accessible, widely recognized, and integrated part of personalized medicine in public health and cardiovascular prevention.

Lastly, I would like to give my endless thanks to my family and, above all, my wife Martina.

Magnus T. Jensen

Copenhagen, Denmark, June 2019

Resumé (dansk)

Pulsen er et af de mest basale tegn på liv og kan nemt måles. Sammenhængen mellem lav puls og sundhed har man kendt igennem tusindvis af år.

Både i dyrestudier og i epidemiologiske studier af baggrundsbefolkningen finder man en sammenhæng mellem lav hvilepuls og længere levelængde. Et centralt spørgsmål er, om pulsen alene er en markør for underliggende dårligt helbred eller om pulsen også er en selvstændig risikofaktor.

Hvilepulsen er relateret til andre kendte kardiovaskulære risikofaktorer, herunder body mass index, blodtryk, lungefunktion, inflammatoriske markører og lipider. Men selv når man tager højde for disse risikofaktorer er hvilepulsen relateret til levelængden. Det er velkendt at hvilepulsen er særligt relateret til konditionen idet god kondi er forbundet med lav hvilepuls og omvendt. Hos personer fra baggrundsbefolkningen, har man derfor overvejet om sammenhængen mellem lav hvilepuls og levelængde mon kunne forklares ved bedre underliggende kondi hos personer med lav hvilepuls. Det viser sig dog, at selv når man tager højde for konditallet er der en sammenhæng mellem lav hvilepuls og levelængde.

Også hos patientpopulationer, f.eks. diabetespatienter, lungepatienter og patienter med hjertekarsygdom, er der en sammenhæng mellem puls og dårlig prognose. Hos patienter som indlægges med akut koronart syndrom er høj puls målt ved indlæggelse stærkt forbundet med død under indlæggelse. Pulsen ved udskrivelse hos hjertepatienter i den stabile fase, efter en perkutan koronar intervention, er også forbundet med prognosen. Man har gennemført flere randomiserede undersøgelser af effekten af pulssænkning med selektiv sinusknudehæmning i tillæg til standardbehandling hos patienter med hjertesygdom. Ved iskæmisk hjertesygdom har man dog ikke kunnet finde en effekt af yderligere pulssænking, mens man hos patienter med hjertesvigt og høj puls over 70 bpm har fundet en formindsket risiko for genindlæggelse for hjertesvigt.

Der er flere studier som tyder på at der kunne være en direkte kausal sammenhæng mellem pulsen og levelængde. Man har i dyrestudier fundet at pulssænkning med både digoxin og selektiv sinusknudehæmning medfører en øget levelængde. I baggrundsbefolkningen har man ved brug af mendelsk randomisering fundet at der er en fælles genetisk baggrund for både puls og levelængde. Samlet set kunne disse studier derfor støtte hypotesen om at sammenhængen mellem lav hvilepuls og levelængde er kausal og ikke alene en markør for underliggende dårligt helbred.

Der foreligger aktuelt ikke nogle retningslinjer i forhold til hvordan man i primærsektoren skal forholde sig til høj puls. Traditionelt set opfattes hvilepuls over 100 bpm som værende forhøjet. I Østerbroundersøgelsen havde 25% af befolkningen en hvilepuls over 80 bpm. Det er fundet, at en hvilepuls over 80 bpm medfører samme risiko for tidlig død som et blodtryk over 140 mmHg. I regi af primærsektoren kunne man derfor overveje om 80 bpm potentielt kunne benyttes som en tommelfingerregel til at gøre status over livsstilsfaktorer, som potentielt kunne have betydning for en høj puls. Wearables, som for eksempel smartwatches og fitness trackers, har medført at viden om pulsen er nemt tilgængelig hos stort set alle. Pulsmåling vil derfor formentlig spille en tiltagende rolle i den kliniske hverdag og især i præventiv kardiologi.

Summary (English)

Heart rate is one of the most fundamental signs of life and an easily accessible physiological parameter. The relationship between heart rate and health has been known for millennia.

In both animal studies and in epidemiological studies of general populations, an association between lower heart rate and longevity has been shown. A key question in relation to heart rate and longevity is whether heart rate is only a marker of risk or also an independent risk factor.

Resting heart rate is associated with other known cardiovascular risk factors such as body mass index, blood pressure, pulmonary function, blood lipids, and inflammatory markers. However, when taking these factors into account, the association between resting heart rate and longevity persists. A particularly interesting factor is the relationship between resting heart rate and cardiorespiratory fitness as there is a well-known relationship between high fitness level and low resting heart rate. Low resting heart rate, and in turn longevity, was therefore generally thought to be a mere marker of good cardiorespiratory fitness, which is known to be related to a longer and healthier life. Interestingly, even after accounting for cardiorespiratory fitness level and other factors, resting heart rate is associated with longevity in the general population.

In patient populations, resting heart rate is predictive of adverse outcomes in diabetes, lung disease, and heart disease. Heart rate, both at admission, in the acute phase of ischemic heart disease, and at discharge, in the stable phase, are highly related to outcome. Interestingly, randomized controlled trials investigating the addition of selective sinus-node inhibiting drugs to standard medication, including other heart rate reducing medication, did not find an effect on heart rate lowering on adverse events in patients with ischemic heart disease. There was, however, a decreased risk of readmissions in patients with heart failure and high heart rate (>70 bpm).

There is evidence to suggest a direct causal link between heart rate and longevity. In animal studies, reduction of heart rate with both digoxin and selective sinus-node inhibiting led to an increased lifespan. Furthermore, Mendelian randomization studies from the general population suggest that heart rate and longevity share common genes, which could suggest causality.

There are currently no clinical guidelines regarding the management of elevated resting heart rate in primary cardiovascular prevention. Resting heart rate is traditionally considered elevated at 100 bpm. In the Copenhagen City Heart Study, 25% of the population had a resting heart rate above 80 bpm. It has been shown that a resting heart rate above 80 bpm carries the same risk as a blood pressure above 140 mmHg. A resting heart rate of 80 bpm could therefore serve as a potential guide for both the individual and the healthcare practitioner to assess lifestyle factors potentially related to elevated resting heart rate.

Heart rate is an easily accessible physiological parameter. Wearable technologies, such as smart watches and fitness trackers, have made heart rate available to all, and will therefore possibly play an increasingly prominent role in clinical medicine and particularly preventive cardiology.

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ORIGINAL ARTICLE

Resting heart rate and relation to disease and longevity: past, present and future

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ABSTRACT

Assessment of heart rate has been used for millennia as a marker of health. Several studies have indicated that low resting heart rate (RHR) is associated with health and longevity, and conversely, a high resting heart to be associated with disease and adverse events. Longitudinal studies have shown a clear association between increase in heart rate over time and adverse events. RHR is a fundamental clinical characteristic and several trials have assessed the effectiveness of heart rate lowering medica-tion, for instance beta-blockers and selective sinus node inhibition. Advances in technology have pro-vided new insights into genetic factors related to RHR as well as insights into whether elevated RHR is a risk factor or risk marker. Recent animal research has suggested that heart rate lowering with sinus node inhibition is associated with increased lifespan. Furthermore, genome-wide association studies in the general population using Mendelian randomization have demonstrated a causal link between heart rate at rest and longevity. Furthermore, the development in personal digital devices such as mobile phones, fitness trackers and eHealth applications has made heart rate information and know-ledge in this field as important as ever for the public as well as the clinicians. It should therefore be expected that clinicians and health care providers will be met by relevant questions and need of advice regarding heart rate information from patients and the public. The present review provides an overview of the current knowledge in the field of heart rate and health.

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Heart rate; mortality; longevity; prognosis; pulse; cardiovascular system

Introduction

A heart beat is the most fundamental sign of life. Several studies have indicated that low resting heart rate (RHR) is associated with health and longevity, and conversely, a high RHR is associated with disease and adverse events.

RHR is a fundamental clinical characteristic and several trials have assessed the effectiveness of heart rate lowering medication, for instance beta-blockers and selective sinus node inhibition.

The overwhelmingly rapid development in technology has provided new insights into genetic factors relating to RHR as well as insights into whether elevated RHR is a risk factor or risk marker.

Furthermore, the development in digital health and personal digital devices such as mobile phones, fitness trackers and eHealth applications indicates that RHR is an increasingly relevant topic not only for the scientific community but also for the general public.

The aim of this review is to provide an overview of contemporary knowledge in the field of RHR as a risk marker and possibly a risk factor—from general population studies to studies of patient populations.

Heart rate is an ancient marker of health

Assessment of heart rate has been an indicator of health and disease in millennia and across many different ancient cultures, ranging from the Greek, Chinese and Indian, to the present day. A description of how to measure the pulse rate was written in detail in Egyptian papyri drafted between 3000 and 1600 BC [1,2].

It has been described how particularly skillful readers of the pulse rate, such as the Indian physician Hoamti, were able to foresee death up to 35 years into the future based solely on pulse rate measurements [3].

The Greek physician and Sphygmologist Galen (A.D. 129–200) was famous for his predictions based on pulse rate. According to Galen, there were 27 features of the pulse, which were important in determining health. The most important feature, however, was the heart rate [3,4]. Heart rate is, also in modern medicine, a powerful predictor of disease and mortality both in general populations and in patient populations.

Regulation of the heart beat

Several factors and pathways, including the sinus node autonomous nervous system, central cortex, baroreceptors and cardiac mechanics, regulate the heart rate. Cardiac out-put is determined by stroke volume multiplied by heart rate. The heart rate therefore plays an integral role in maintain-ing sufficient cardiac output, and thereby, a necessary circu-lating blood volume, blood pressure and systemic oxygenation in the healthy as well as the diseased state.

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The sinus node is an area of specialized cells located in the right atrium and serves as the main pacemaker in the heart. The impulse generation in the sinus node is generated by four major currents, the f-current is an inward $Na^{þ}$-cur-rent occurring early in the diastolic depolarization, two $Ca^{2þ}$-currents are responsible for the late diastolic depolar-ization phase and a $K^{þ}$-current is responsible for the repola-rization phase[5,6].

The heart rate is under the influence of the autonomic nervous system, which is the main mediator of regulation on heart rate. The parasympathetic influence on heart rate is almost instantaneous whereas the effect of sympathetic nervous stimulation is more prolonged [7].

Higher centers also regulate heart rate and include mainly the anterior part of the brain including the frontal lobe and the orbital cortex; simulation of the thalamus has been shown to result in tachycardia and hypothalamic tem-perature changes alter heart rate and peripheral resistance. Baroreceptors, located in the aortic arch and in the carotid sinus, respond to changes in arterial pressure leading to change in heart rate [8]. Respiration also have an effect on heart rate [9], elicited in a complex interplay of mechanisms including stimulation of parasympathetic nerves, stretch receptors in the lungs, changes in intrathoracic pressure, stretch of the atria eliciting the Bainbridge reflex and stimu-lation of the baroreceptors during left ventricular contrac-tion and increase in arterial pressure [10,11].

Coronary flow and myocardial oxygenation is highly dependent on heart rate, as this occurs during diastole. When heart rate is low diastolic filling time is increased, and the time for coronary perfusion is prolonged.

Heart rate and longevity

Resting heart rate, basal metabolic rate and Life expectancy

There is a remarkable relationship between RHR and lon-gevity across the animal kingdom. Levine demonstrated [12] a linear relationship between RHR and longevity across dif-ferent species. For instance, the mouse has a very fast heart rate of about 4–600 bpm and lives for a few years, while the whale has a RHR of 30–40 bpm and has a lifespan of several decades [13]. Interestingly, despite a very wide range in the magnitude of RHR, when calculating the average number of heart beats per life, this number is nearly constant across species and is in the order of 10^9. Azbel [14] determined how the basal oxygen consumption per body atom and per heart beat pr. lifetime is the same across all animals with a heart, and is around 10^8 oxygen molecules per heartbeat. There appears to be a universal relationship between basal energetics and lifespan across mammals, birds, fish, inverte-brates, unicellular mechanisms and even on a subcellular level to mitochondria [14–17]. From this, it has been theor-ized, that heart rate is an epiphenomenon of the rate of basal oxygen consumption and thus longevity.

Targeting heart rate in animal studies

Experimental animal studies have suggested that longevity may be extended by decreasing heart rate, and thus, that there might be a causal link between the magnitude of RHR and longevity. Heart rate reduction by 50% using digoxin increased life span by 20% in mice [15], however, these mice also decreased their body weight, which may also be related to increased lifespan [18]. However, in a recent important study, Gent and colleagues [16] used selective sinus node inhibition with ivabradine to decrease heart rate versus placebo in mice. In the ivabradine-treated mice, median heart rate was lowered 14%, and median lifespan was extended 6% compared to the placebo group. These results therefore suggest that RHR is a modifiable determin-ant of life expectancy. Gent et al. furthermore estimated the average number of heart beats per life to be approximately $8\ 10^8$ in mice, which corresponds to previously suggested estimate across animals' species [12]. The authors estimated further, that the observed increase in longevity of 6%, from a 14% decrease in RHR, would translate into 5 years increased life span in humans. Interestingly, these numbers roughly translate into observations from the Copenhagen City Heart Study where a 19% lower heart rate (65 versus 80 bpm) was associated with 4.6 years longer life expectancy in men and 3.6 years in women [17].

Examining the relationship between RHR and develop-ment of atherosclerosis in monkeys fed on an atherogenic diet, Beere et al. [19], after 6 months, found monkeys in the high heart rate group to have twice as much coronary ath-erosclerosis as monkeys in the low heart rate category. Similar results [20] were found by Kaplan et al. using beta-blockers. Also, in type 2 diabetic mice with heart failure with preserved ejection fraction selective sinus node inhib-ition increased diastolic function and improved vascular function [21]. Changes in heart rate in animals therefore seems to exert a causal effect on development of cardiovas-cular disease.

Normal limits of RHR in man

The reference interval of RHR has traditionally been consid-ered to be between 60 and 100 bpm [22]. In a recent survey from the U.S. National Health and Nutrition Examination Survey, 1999–2008, the distribution of RHR in more than 35,000 individuals without cardiovascular disease was assessed. The mean heart rate in men above age 40 was 71 bpm with a 2.5 percentile of 49 bpm and a 97.5 percentile of 95 bpm. The corresponding number in women above 40 years of age was a mean RHR of 73 bpm with a 95% range of 53–97 bpm. Overall, there is a gender difference in the magnitude of RHR in that women tend to have higher heart rates compared to men. RHR is surprisingly stable with age in healthy individuals. In subjects above 40, RHR is similar across age groups [23], even into high age [24]. It is worth noting, however, that a given heart rate may be within the reference interval but still considered deleterious. Consider for instance the 2017 ACC/AHA guidelines for hypertension where 63% of the population between 45 and

75 years of age would be eligible for anti-hypertensive therapy [25].

RHR and association with other cardiovascular risk factors

Individuals with higher RHRs tend to have, for instance, higher blood pressure, higher body mass index, inferior pulmonary function and lower level physical activity. Also, there is a correlation between RHR and markers of subclin-ical inflammation, such as high-sensitivity CRP and fibrino-gen, in individuals without apparent cardiovascular disease [17,26,27]. Whether increased heart rate directly or indir-ectly causes increased inflammation or whether the caus-ation is reverse is not known. Physical exercise is known to decrease systemic inflammation [28] and is related to lower heart rate, which may be amongst the possible mechanisms. It is a common observation that physical fitness level and level of RHR are closely related. This has for example been demonstrated in subjects from the Copenhagen Male Study (CMS) where estimated VO_{2max} and RHR was closely associated [29] as well as in the Whitehall Study of British civil servants where physical activity level was associated with RHR [30]. In the CMS, we showed that the association between RHR and mortality was robust for adjustments also including estimated VO_{2max}, indicating that the association between heart rate and mortality is not explained alone by poor fitness. These findings were confirmed in a study of more than 56,000 patients from the Henry Ford Exercise testing project [31].

Heritability of RHR

Several genome-wide association scans of genetic loci associated with RHR have been performed, and so far, 64 loci have been found [32,33]. However, only a few percent of the variation in RHR has been explained by genetic factors. Another method for assessing genetic heritability is through twin studies [34,35]. Using the classic twin study methodology, a higher correlation in RHR between MZ twin pairs as compared with DZ twin pairs reflects genetic influences. Using information from the Danish Twin Study [24] almost 4300 twins were included to investigate the heritability of RHR. Here, there was a significant heritability of RHR, which was estimated to explain 23% (95% CI 15–30%) of the variation in RHR. A significant proportion of the vari-ance in RHR is therefore attributable to heritable factors.

RHR and prognosis in general populations

Elevated RHR has been shown to be prognostically associated with adverse events across several population studies [36–40]. There have been consistent findings in populations spanning several decades and many different geographical regions. Overall, mounting epidemiological evidence indicates that increased RHR is associated with increased risk of adverse events in general populations even after adjusting for common confounding factors. Dyer et al. [36] found RHR to be associated with coronary heart disease and all-cause mortality in individuals from three epidemiological studies from Chicago, and Kannel et al. found similar results in the Framingham Study [41]. In healthy subjects from the Paris Prospective Study, a high RHR was associ-ated with mortality [42], and in a German general popula-tion a high heart rate was associated with risk of both all-cause mortality and coronary events [43]. Also, in an Israeli population [44] and a Japanese [45] population elevated RHR was related to mortality.

Estimated risk of an elevated RHR

The risk estimate for high heart rate varies somewhat between studies. In the Copenhagen City Heart Study, every 10 bpm increase in resting heart was associated with a 14% increase in risk of cardiovascular mortality after multivari-able adjustments including inflammatory markers, and 10% increase in risk for all-cause mortality [17]. The association between RHR and mortality has generally been shown to be stronger for cardiovascular disease compared to all-cause mortality [46,47]. In a large meta-analysis of results from 1.2 million individuals across 46 studies, the overall estimate per 10 bpm increase in RHR was 1.11 (HR 95% CI 1.06–1.16) for all-cause mortality, and 1.13 (1.07–1.19) for cardiovascular mortality [39]. As demonstrated in the Copenhagen City Heart Study, there is a log-linear relation-ship between increased RHR and risk of mortality [48].

Temporal changes in RHR and risk

In initially healthy subjects from the Paris Prospective Study both high baseline RHR and increase in RHR over time was independently associated with increased risk of mortality [42]. In the Norwegian Nord-Trøndelag County Health Study, increase in RHR was also associated with both death from ischemic heart disease and all-cause mortality [49], and in subjects from the British National Survey of Health and Development increase in RHR in midlife was associated with increased risk of mortality [50]. Change in RHR could therefore be an indicator of deterioration of health. Frequent assessments of RHR and assessment of possible change could therefore be a very easy and inexpensive marker of health status and would be easily implementable for primary prevention.

Heart rate and prognosis in patient populations

RHR in cardiovascular disease

High blood pressure is directly related to elevated heart rate [51–54] both cross-sectionally and prognostically. For example, apparently healthy young individuals with elevated heart rate have been shown to be more likely to develop subsequent hypertension [55]. Several other studies have investigated the association between heart rate and progno-sis in relation to ischemic heart disease [56–60] and myo-cardial infarction. In the CASS registry of 25,000 patients

Table 1. Studies of admission heart rate and prognosis in ACS.

Author	Treatment Era Population	Years	No. Included	Patients	Outcome	Comments
Hjalmarson et al. [67]	Pre-thrombolysis Patients from West Coast, North America	1979–1984	1807	STEMI and NSTE-ACS	In-hospital mortality and CV events	Double increase in risk from 90 bpm and gradual increase
Disegni et al. [64]	Pre-thrombolysis SPRINT (Israel)	1985–1986	1,358	STEMI and NSTE-ACS	In-hospital mortality	Three times increased risk with HR >90 bpm
Granger et al. [62]	Revascularization GRACE Registry (US)	1999–2001	11,389	STEMI and NSTE-ACS	In-hospital mortality	30% increase in risk per 30 bpm increase in HR
Bangalore et al. [63]	Revascularization CRUSADE (US)	2001–2005	139,194	NSTE-ACS	In-hospital mortality and CV events	J-shape, 61% increase for HR < 50 and 49% increase for >90 bpm
Jensen et al. [65]	Revascularization EURHOBOP (Europe)	2008–2010	10,374	STEMI and NSTE-ACS	In-hospital mortality	Three to five time the risk with HR >80 bpm

bpm: beat per minute; HR: heart rate; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction.

with suspected or proven coronary artery disease followed for 15 years, heart rate at rest above 82 bpm was associated with a 32% increased risk of mortality compared to patients with heart rates below 62 bpm [61].

Admission heart rate and in-hospital mortality

In the acute setting in patients with acute myocardial infarction, elevated heart rate has also been shown to be associated with poor outcome [62–68] both in the pre-thrombolytic and contemporary eras. In the US Global Registry of Acute Coronary Events (GRACE) registry, heart rate at admission was determined as one of the eight most important predictors of in-hospital mortality, and in the contemporary EURHOBOP Collaboration of ACS patients admitted across 58 European hospitals admission heart rate was highly predictive of in-hospital mortality. In these patients, an admission heart rate above 80 bpm was associated with 3–5 times the risk of mortality compared to lower heart rates. Table 1 displays findings from studies of admission heart rate and in-hospital events in different eras. As shown in Table 1, even though treatment has improved dramatically during the last several decades, there is still a close association between elevated admission heart rate and increased in-hospital mortality. In a study of open-chest anesthetized dogs, Bolli et al. [69] studied the determinant of ischemia-induced ventricular arrhythmias. The authors found that the three major predictors of ventricular arrhythmias during the course of a myocardial infarction was the magnitude of the coronary collateral flow, the size of the occluded bed and lastly, the heart rate.

Discharge heart rate and prognosis

In a study of 2029 patients undergoing PCI for STEMI and NSTE-ACS from the Basel Stent Kosten-Effektivität Trial-Prospective Validation Examination (BASKET PROVE) randomized trial, discharge heart rate was incrementally associated with risk of cardiovascular and all-cause mortality [70]. A discharge heart rate from 60 to 90 bpm was associated with a 4-fold increased risk, and heart rate above 90 beats per minute was associated with a 17 times increased risk of mortality within 2 years. Conversely, none of the STEMI patients discharged with a heart rate below 60 bpm died during follow-up. In a Dutch population of STEMI patients similar results was found; here, a heart rate above 70 bpm versus heart rate below 70 bpm was associated with a hazard ratio of 3.2 (1.4–7.0) for all-cause mortality, and 2.4 (1.0–5.8) for cardiovascular mortality.

Observations of heart rate reduction using beta-blockers

The observational studies of patients with ischemic heart disease are in line with results from randomized controlled trials of beta-blocker use post-myocardial infarction. In a meta-regression of 25 randomized clinical trials of beta-blockers and calcium antagonists post-myocardial infarction, there was a strong relationship between heart rate reduction and decrease in risk. In fact, it was demonstrated that the survival benefit was closely related to the reduction in RHR and not in the particular drug or dosage of beta-blocker [71]. These findings are essentially similar to those of Kjekshus et al. [72] who 20 years previously found both difference in infarct size as well as reduction in mortality to be related to reduction in heart rate across a number of beta-blocker trials. Heart rate in relation to heart failure has also received particular attention [73]. It has been thoroughly demonstrated that heart rate reduction is particularly beneficial in patients with left ventricular heart failure. In a meta-analyses of 23 beta-blocker trials, it was found that the reduction in mortality was associated not to the dose of beta-blocker but to the magnitude of heart rate reduction [74]. Furthermore, another meta-analysis of 35 trials showed that improvements in left ventricular ejection fraction was highly significantly correlated with change in heart rate [75].

RHR and disease

Elevated RHR has been shown to be prognostic in other patient categories. It is a common clinical observation that RHR is elevated in patients with chronic obstructive pulmonary disease (COPD). This clinical observation was found to be a general phenomenon in subjects stratified by degree of COPD [76]. Here, increased level of pulmonary disease was related to increase in RHR. The difference

between subjects without COPD to subjects in GOLD IV (most severe) was almost 10 bpm after adjusting for confounding factors. In addition, RHR was found to improve the prediction of prognosis when added to information about pulmonary function.

RHR is in general elevated in patients with diabetes [77]. Elevated RHR has been shown to predict development of diabetes and subsequent mortality [78,79] in individuals without diabetes at baseline. Factors such as increased sympathetic activity, cardiac autonomous neuropathy [80,81] and possibly cardiac remodeling, could contribute to the observed increase in heart rate [82–84]. In data from the ADVANCE trial of patients with type 2 diabetes, increased RHR was shown to predict both mortality and adverse events relating to cardiovascular complications [85]. Conversely, in the Diabetes Control and Complications Trial (DCCT), intensive diabetes management was associ-ated with lower heart rate in type 1 diabetes. If may there-fore be, that some of the effect on mortality and complications seen in the DCCT was related to changes in RHR [86].

RHR has been shown to be elevated in rheumatoid arthritis patients compared to healthy individuals, and was found to be significantly higher in patients who later devel-oped arthritis. Also, RHR is higher in patients with irritable bowel syndrome [87].There therefore appears to be a con-sistent link between increased heart rate and inflammatory states [17,88].

The relationship between elevated heart rate and cancer risk has also been investigated but is not completely consistent. In a study of men from the Paris Prospective Study those with the highest quartile of resting heart-rate had 2.4 fold increased risk for cancer deaths compared to the lowest RHR quartile [89]. In a British cohort, a heart rate above 90 bpm was associated with increased risk of cancer [90]. Furthermore, in cohorts from Chicago, elevated heart rate was associated with cancer in both men and women [37]. However, in a study of 6007 patients with vascular disease RHR was associated with all-cause mortality, but not cancer mortality [91]. Another study in breast cancer patients found resting heart to be associated with all-cause mortality but not with cancer recurrence [92].

Elevated heart rate: RISK factor or risk marker

Several clinical trials performed during recent decades have investigated the effect of interventions with heart rate lowering properties in patients with heart disease. Interventions with beta blockers [71] and cardiac glycoside [93] demonstrated decreased risk of adverse events in risk populations. However, beta-blockers and cardiac glycosides have pleiotropic effects [94,95] and do not exclusively target heart rate. The most intriguing question in relation to elevated RHR is, whether high heart rate is a mere marker of risk, or if elevated heart rate is an independent risk factor. If high RHR is in fact a true risk factor it may be a possible target for intervention. The f-current is only present in the sinus node, and thus inhibition induces selective heart rate reduction. Within the last few years, three large randomized controlled trials of the f-current inhibitor ivabradine have tested the effect of selective heart rate reduction in different heart patient populations.

In the BEAUTIFUL trial almost 11,000 patients with coronary artery disease and left ventricular ejection fraction, <40% were included and randomized to ivabradine or placebo in addition to usual care. In the intervention arm, heart rate was reduced by 6 bpm. In this trial, a reduction in heart rate significantly decreased the risk of admission for fatal or non-fatal myocardial infarction and coronary revascularization [96]. In a subgroup analyses, it was found that a patients with heart rates above 70 bpm were of par-ticular risk of coronary events [97]. Ivabradine versus pla-cebo in heart failure was subsequently tested in the SHIFT trial of 6500 patients with left ventricular ejection fraction below 35%, with sinus rhythm and heart rate above 70 bpm [98]. Ivabradine resulted in a significant reduction in the primary endpoint of cardiovascular death or hospital admis-sion for worsening heart failure, which was mainly driven by reductions in hospitalizations for heart failure. However, there was no significant difference in all-cause or cardiovas-cular death between the ivabradine and placebo group. The SIGNIFY study [99] was conducted in 19,000 patients with stable coronary artery disease and preserved ejection frac-tion. In these patients, there was no difference in the pri-mary composite outcome of death from cardiovascular causes and non-fatal myocardial infarction. A subanalysis revealed an increased risk of the primary endpoint in patients with a Canadian Cardiovascular Society (CCS) score of II or higher, although patients in the ivabradine group experienced less symptoms compared to patients in the pla-cebo group. Altogether, these results of heart rate reduction with ivabradine in addition to usual care in patients with cardiovascular disease have been somewhat disappointing. It has been argued that the discrepancies between study findings suggest that heart rate reduction is more beneficial in patients with left ventricular dysfunction than in patients with coronary artery disease [100]. Others have argued that the evidence from these trials point toward a beneficial effect of ivabradine in the particular subpopulation of patients with non-ischemic heart failure where the event rate reduction in the treatment arm of the SHIFT trial was similar to the event rate reduction from digoxin in a com-parable population [93]. The current indication for ivabra-dine in heart disease is mainly patients with heart failure on optimal treatment and with a RHR above 70 bpm [101].

Heart rate, mortality and Mendelian randomization: indications of a causal relationship

So far, no large-scale studies have investigated the relationship between selective heart rate lowering agents and longevity in healthy subjects, however, genetic evidence have provided new knowledge in this area. Eppinga et al. published highly intriguing findings from a Mendelian randomization study including more than 265,000 individuals [33]. Here, the random population distribution of genetic variants

related to increased RHR can be utilized to provide a 'natural' study design similar to a randomized comparison [102]. In the Eppinga study, individuals with genetically ele-vated RHR had a shorter life expectancy, independent of other factors, compared to individuals with genetically lower RHRs. Thus, the findings suggest that RHR could be caus-ally linked to longevity.

Contemporary and future use of heart rate measurement

Very few biomarkers have gained such attention and use by the general public as heart rate. In addition to the wide-spread use in clinical medicine, monitoring of heart rate is increasingly used in everyday life. Electronic heart rate mon-itoring devices are available at a low cost and in most elec-tronic stores. Heart rate equipment is used for fitness, and specific heart rate apps are available for the most common smart phones. Measurement of heart rate, in activity and at rest, has gained great interest as a measure of exercise inten-sity. Furthermore, as our knowledge of heart rate and asso-ciation with morbidity and mortality increases the application of heart rate monitoring is also likely to increase. The wearable health care technology sector is growing rapidly [103] and ranges from blood sugar meas-urement, sleep trackers, mindfulness meditation assistants and many others. Heart rate, however, is the most promin-ent and most commonly used physiological perform-ance indicator.

From a public health perspective, the increased availabil-ity and use of physiological measurements provides an opportunity to identify early markers of disease for use in primary and secondary prevention. As described above, ele-vated heart rate and increase in heart rate over time is asso-ciated with disease, however, there are, at this point in time, no general recommendations to guide the general public in this area. As these individual data about heart rate and other physiological information become increasingly avail-able, healthcare providers will be met by an increasing num-ber of patients demanding for counsel and clinical advice relating to these personal data. With this in mind, the for-mulation of general recommendations from relevant author-ities would be highly valuable to guide the clinician and the public alike.

When should RHR be considered elevated?

The traditional threshold of 100 bpm is an arbitrary cut-off, which does not reflect the linear relationship between increased risk of mortality with increase in RHR. As with the ongoing discussion of a suitable cut-off for determining hypertension, the threshold of what should be considered an elevated heart rate is a discussion between benefits and harm of treatment. Recommendations in this area will appropriately be based on decision limits rather than on ref-erence intervals as in the area of blood lipids. No such authoritative decision limits are available for treating ele-vated RHR for primary prevention in healthy individuals.

A RHR above 80 bpm is present in 25% of the general population [17], and in NHANES, a RHR above 90 bpm was present in 5.2% of men and 8.4% of women [23]. In the Cooper Clinic Study, a RHR of >80 bpm was associated with a similar risk as a blood pressure 140/90 mmHg. This could therefore perhaps be taken as a current reasonable guide [104,105]. A threshold of >80 bpm should not be taken as indication of disease but a practical rule of thumb for encouraging individuals to improve lifestyle factors related to increased RHR. These factors could include known cardiovascular risk factors, such as reducing smok-ing, increasing physical activity level, assessment of blood pressure, lipids and diabetes, and considering alcohol con-sumption and diet [17]. In order to facilitate behavior change, the framework suggested by the European Association for Cardiovascular Prevention and Rehabilitation of the European Society of Cardiology [106] could be utilized including ten strategic steps from involving individuals in identifying and selection risk factors to change, to designing a life-style modification plan and mon-itoring progress through follow-up contact. Due to the easy of monitoring RHR, individuals would be able to measure RHR at home thereby encouraging patient involvement and potentially telemonitoring [107].

Conclusion

Heart rate is one of the most readily available clinical parameters, has been used for millennia, and is one of the few biomarkers who are widely known by the general popu-lation. Longitudinal studies have shown a clear association between elevated RHR, increase in heart rate over time and deterioration of health in both general and patient popula-tions. A key question is whether heart rate at rest is a risk marker or a risk factor. Recent animal research as well as genome-wide association studies in the general population using Mendelian randomization have demonstrated a robust relation between heart rate at rest and longevity. The increasing use of personal heart rate monitors and fitness trackers has made knowledge in the field of heart rate as important as ever for the public and for the healthcare pro-fessional alike. It should be expected that clinicians will be met by relevant questions and need of advice regarding heart rate from patients.

Recommendations for decision limits of RHR for use in health policy and clinical practice are needed from relevant professional organizations. In the meantime, a RHR 80 bpm is a reasonable rule of thumb for encouraging individ-uals to improve lifestyle factors related to RHR.

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Disclosure of interest

No potential conflict of interest was reported by the authors.

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Elevated resting heart rate is associated with greater risk of cardiovascular and all-cause mortality in current and former smokers

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ABSTRACT

Background: Elevated resting heart rate is associated with mortality in general populations. Smokers may be at particular risk. The association between resting heart rate (RHR), smoking status and cardiovascular and total mortality was investigated in a general population.
Methods: Prospective study of 16,516 healthy subjects from the Copenhagen City Heart Study. 8709 deaths, hereof 3821 cardiovascular deaths, occurred during 33 years of follow-up.
Results: In multivariate Cox models with time-dependent covariates RHR was significantly associated with both cardiovascular and total mortality. Current and former smokers had, irrespective of tobacco consumption, greater relative risk of elevated RHR compared to never smokers. The relative risk of all-cause mortality per 10 bpm increase in RHR was (95% CI): 1.06 (1.01–1.10) in never smokers, 1.11 (1.07–1.15) in former smokers, 1.13 (1.09–1.16) in moderate smokers, and 1.13 (1.10–1.16) in heavy smokers. There was no gender difference. The risk estimates for cardiovascular and all-cause mortality were essentially similar.
In univariate analyses, the difference in survival between a RHR in the highest (>80 bpm) vs lowest quartile (<65 bpm) was 4.7 years in men and 3.6 years in women. In multivariate analyses, the difference was about one year in never smokers and about two years in current and former smokers.
Conclusions: In a healthy population resting heart rate is associated with total and cardiovascular mortality. Elevated resting heart rate is associated with greater risk in subjects with a history of smoking than in never smokers.

1. Introduction

Elevated resting heart rate (RHR) as a risk factor for morbidity and mortality has received much attention in recent years [1,2]. In a recent study of 129,000 women from the Women's Health Initiative, RHR independently predicted myocardial infarction and coronary deaths [3]. Also, in a large study of almost 380,000 Norwegians followed for 12 years high RHR was associated with mortality [4]. In the latter study, the highest mortality was observed in smoking subjects and especially in the high heart rate groups. Even though the factors that the authors could control for were limited, the relative risk of a 10 bpm increase in RHR was statistically significant only in smoking men but not in non-smokers or in women.

Smoking is known to increase heart rate [5] and is a well-known risk factor in atherogenesis. There may therefore be a possible interaction between smoking and the deleterious effects of a high resting heart rate.

In the Copenhagen City Heart Study, detailed information on smoking habits as well as pulmonary function and other possible confounding factors are available through a 33 year follow-up period.

In the present study, we aim to investigate the association between RHR, smoking status, and cardiovascular and total mortality.

2. Methods

2.1. Population

The Copenhagen City Heart Study (CCHS) is a prospective cardiovascular study of 18,974 men and women aged 20 and older recruited in a random population sample from the Copenhagen Population Register. The study was initiated in 1976 and has to date included four examinations — CCHS 1: 1976–78, CCHS 2: 1981–83, CCHS 3: 1991–94, and CCHS 4: 2001–03. The first cross-sectional survey included 14,223 individuals. Subjects aged 20–49 years have subsequently been added throughout the following surveys to the current total number. The sampling background and methods have previously been described in several publications [6,7].

2.2. Examinations

Examinations included a self-administered questionnaire providing medical history, smoking and drinking habits, leisure time physical activity, medication, history

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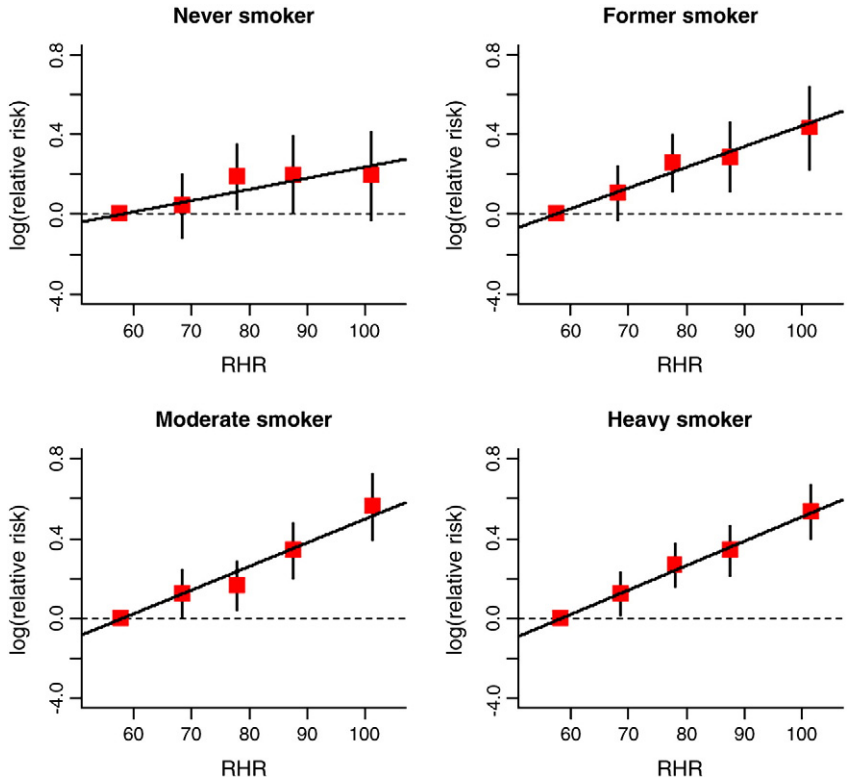

Fig. 1. The Cox model assumes log-linearity of the covariates. As demonstrated, this assumption seems reasonable for RHR. Red squares show log(relative risk) estimates for 10 bpm intervals of RHR. Solid lines are RHR estimates from *model B* (RHR as continuous covariate).

Table 1
Baseline demographics.

	Men ($n=7528$)					Women ($n=8988$)				
Resting heart rate (bpm)	<65	65–71	72–80	>80	*p*	<65	65–71	72–80	≥80	*p*
Age, median ± SD (years)	46.8 ± 14.1	48.4 ± 13.1	50.1 ± 13.2	52.3 ± 12.8	<0.001	48.4 ± 13.7	50.0 ± 12.9	50.5 ± 13.1	52.2 ± 12.9	<0.001
SBP, median ± SD (mm Hg)	128.0 ± 17.0	132.0 ± 18.1	135.0 ± 19.2	141.0 ± 20.1	<0.001	120.0 ± 19.0	124.0 ± 19.3	128.0 ± 20.7	135.0 ± 22.8	<0.001
BMI, median ± SD (kg/m^2)	24.6 ± 3.3	25.0 ± 3.6	25.2±3.6	25.5 ± 4.0	<0.001	23.1 ± 3.8	23.2 ± 4.1	23.5 ± 4.3	23.7 ± 4.6	<0.001
FEV_1, % of expected, median ± SD (%)	90.1 ± 17.3	87.4 ± 17.6	87.2 ± 18.7	83.4 ± 20.2	<0.001	88.0 ± 16.5	87.0 ± 16.8	86.1 ± 18.1	85.2 ± 18.4	<0.001
Sedentary physical activity, %	14.5	16.2	18.1	20.3	<0.001	13.7	15.4	17.5	20.9	<0.001
Smoking, %										
Never	20.5	14.8	13.3	10.6	<0.001	30.3	27.2	28.0	28.3	0.15
Former	20.6	19.2	17.5	15.5	<0.001	15.5	15.8	13.7	13.2	0.03
Moderate (<15 g/day)	22.9	22.7	20.3	23.7	0.08	31.3	30.6	29.2	27.1	0.01
Heavy (≥15 g/day)	36.0	43.4	48.9	50.2	<0.001	22.9	26.4	29.1	31.4	<0.001
Alcohol, %										
Never	9.2	9.6	9.7	10.5	0.58	21.5	26.4	25.5	29.5	<0.001
Monthly	23.8	23.7	19.4	15.3	<0.001	40.6	38.5	37.3	34.2	<0.001
Weekly	36.3	32.1	30.5	27.4	<0.001	28.1	25.0	26.2	24.1	0.02
Daily	30.7	34.7	40.4	46.8	<0.001	9.8	10.2	11.0	12.2	0.05
Triglycerides, median ± SD (mmol/L)	1.4 ± 1.1	1.6 ± 1.3	1.7 ± 1.3	1.8 ± 1.8	<0.001	1.1 ± 0.6	1.2 ± 0.8	1.2 ± 0.8	1.3 ± 1.1	<0.001
Cholesterol, median ± SD (mmol/L)	5.5 ± 1.1	5.7 ± 1.2	5.7 ± 1.1	5.9 ± 1.2	<0.001	5.7 ± 1.3	5.8 ± 1.3	6.0 ± 1.3	6.1 ± 1.4	<0.001

Bpm, beats per minute; sedentary physical activity, leisure time sedentary physical activity; SD, standard deviation; SBP, systolic blood pressure; BMI, body mass index; FEV_1, forced expiratory volume in 1 s

	Men ($n=1774$)					Women ($n=2403$)				
Resting heart rate (bpm)	<65	65–71	72–80	>80	*p*	<65	65–71	72–80	>80	*p*
Age, median ± SD (years)	51.4 ± 15.3	56.0 ± 15.4	55.4 ± 15.7	58.4 ± 15.5	<0.001	53.1 ± 16.6	57.3 ± 17.0	59.4 ± 17.2	61.4 ± 17.0	<0.001
Hemoglobin, median ± SD (mmol/L)	9.1 ± 0.6	9.2 ± 0.6	9.3 ± 0.7	9.4 ± 0.7	<0.001	8.3 ± 0.6	8.3 ± 0.6	8.5 ± 0.6	8.5 ± 0.7	<0.001
TSH, median ± SD (mIU/L)	1.4 ± 3.6	1.5 ± 1.7	1.4 ± 8.4	1.4 ± 1.2	0.20	1.6 ± 1.7	1.5 ± 2.5	1.5 ± 3.0	1.6 ± 1.6	0.12
Creatinine, median ± SD (mmol/L)	85 ± 11.8	85 ± 12.9	85 ± 14.4	85 ± 11.5	0.33	73 ± 10.9	74 ± 11.4	72 ± 12.4	73 ± 11.8	0.33
LVEF<50%, # subjects (%)	2 (0.4)	1 (0.4)	2 (1.1)	0 (0.0)	0.61	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.6)	0.10

Bpm, beats per minute; SD, standard deviation

of contacts with the health-care system and a full physical examination. Blood pressure was measured in a standardized way using the London School of Hygiene Sphygmomanometer. Cholesterol, triglycerides and blood glucose values were measured on non-fasting venous blood samples. CCHS 2 did not include triglycerides and observations from CCHS 1 were carried forward for this variable. Also, pulmonary function was measured. A 12-lead ECG was recorded at rest in a supine position and coded according to the Minnesota code. RHR was obtained from the ECG. Echocardiography was performed only in CCHS 4. Also, data on creatinine, hemoglobin and TSH (Thyroid Stimulating Hormone) were only available in CCHS 4. Crude data from CCHS 1–3 have previously been published [6,7].

2.3. Variables

Systolic blood pressure was measured in a sitting position after 5 min at rest and divided into 4 groups: <120 mm Hg, 120–139 mm Hg, 140–159 mm Hg, and ≥160 mm Hg.

Body mass index (BMI) was categorized into four groups as follows: underweight — BMI<18.5, normal weight — 18.5≤BMI<25, overweight — 25≤BMI<30, and obese — BMI≥30.

Smoking was categorized into 4 groups: never smoker, former smoker, moderate smoker — defined as use of 1–15 g tobacco per day — and heavy smoker — defined as use of >15 g tobacco per day. A cigarette was equated to 1 g of tobacco, a cheroot to 3 g, and a cigar to 5 g.

Alcohol consumption was categorized into 4 groups: never drinker, monthly drinker, weekly drinker, and everyday drinker.

Physical activity during leisure time was classified into 3 groups: sedentary activity, referring to "light activity less than 2 h per week", moderate activity, referring to "light activity 2–4 h per week", and high activity, referring to "light activity >4 h per week" or "high activity >2 h per week".

Cholesterol and *triglycerides* were measured non-fasting [8] in mmol/L.

Pulmonary function was assessed as FEV_1 in% of expected.

Left ventricular ejection fraction (LVEF) was measured by echocardiography and described in percent. We considered an LVEF above 50% to rule out major systolic ventricular dysfunction.

Creatinine was measured in μmol/L, *hemoglobin* in mmol/L and *TSH* in mIU/L.

2.4. Follow-up

Follow-up was carried out by data linkage to national registers. Deaths were obtained from The Civil Registration System and causes of death from The National Register of Causes of Death. Cardiovascular death was defined as ICD-8: 390–458 and ICD-10: I00–I99. Information about morbidity leading to hospitalization was obtained from The National Patient Register.

2.5. Exclusion criteria

Subjects reporting previous myocardial infarction, stroke, diabetes or a fasting glucose higher than 11.1 mmol/L, and subjects with atrial fibrillation or electrocardiographic evidence of ischemic heart disease by Minnesota Codes 1-1 and 1-2 were initially excluded from the analyses. Furthermore, subjects reporting use of heart medication or antihypertensives were excluded from the analyses. This was done to remove the possible influence of heart rate modifying drugs (beta-blockers, calcium-antagonists, and digitalis).

2.6. Statistical analysis

For demographics, Fisher's exact test was used for categorical covariates and Kruskal–Wallis rank sum test for continuous covariates. In the Kaplan–Meier survival curves RHR is described in quartiles based on the distribution in the population (RHR <65 bpm, 65–71 bpm, 72–80 bpm, and >80 bpm). All Kaplan–Meier survival curves are based on total mortality with time-dependent covariates by the method of Snapinn et al. [9]. Predicted survival (mean residual lifetime) was calculated as the area under the curve of the respective survival curves. The association between RHR and mortality was studied using Cox proportional hazards models. To rule out preexisting illnesses and test the robustness of the findings, the analyses were also carried out after removal of subjects dying within 5 years of the initial examination.

The population was divided into different datasets according to smoking status.

Pulmonary function (FEV_1% of expected) was log-transformed to account for a progressive worsening in prognosis with deterioration in pulmonary function.

Three Cox models were fitted for each dataset; *Model A*: A baseline analysis of total mortality for CCHS 1–3 individually in sex-stratified Cox models with age as underlying time scale and inclusion of significant covariates as possible confounders. *Model B:* In order to adjust for possible changes in the covariates between CCHS 1–4 a second sex-stratified model with time-dependent covariates was fitted for both cardiovascular and total mortality. If a subject reported use of antihypertensives, use of heart medication, or developed atrial fibrillation during the follow-up period observations from the cross-sectional survey would be excluded but event/censoring maintained in the model. Any other initial exclusion criteria reported during the follow-up period did not lead to exclusion of observations. We used robust estimators of the standard error. A test for interaction between gender and RHR was performed. In *model C*, the data was analyzed as in *model B* but split by gender with the purpose of assessing gender differences in the estimates. In *model A–C*, RHR was a continuous covariate. *p*-values below 0.05 were considered statistically significant. Statistical analyses were performed with R version 2.8.1.

2.7. Goodness of fit

The assumption of proportionality in the Cox regression models for the different groups of smoking status was tested with the Lin, Wei, and Ying score process test [10]. The former smoker group was further tested in an extended Cox model due to greater heterogeneity in this group. The assumption of linearity for RHR in *model B* was examined as shown in Fig. 1. Misspecifications of the functional form of the covariates were tested by plotting the continuous covariates against the cumulative residuals and compare them to random realizations under the model.

3. Results

16,516 subjects participated. 2458 were excluded for reasons mentioned above. Follow-up was 98.6%. Up to 2009, 8709 deaths, hereof 3821 cardiovascular deaths, had occurred. Maximal follow-up time was 33 years (mean 21.2 years). Distribution of relevant risk factors according to gender and RHR quartiles is shown in Table 1. Subjects with a high RHR were more likely to be older, have higher systolic blood pressure, higher BMI, worse pulmonary function, a greater tobacco consumption, be less physically active, and have higher blood levels of triglycerides and cholesterol. Interestingly, subjects in the highest RHR quartiles were more likely to be either daily drinkers or never drinkers. There was no association between RHR and levels of creatinine or TSH. Hemoglobin was positively associated with RHR. Echocardiography was performed in 2513 of the 4177 included subjects in CCHS 4. Only 7 subjects (0.3% of the population) had LVEF<50%.

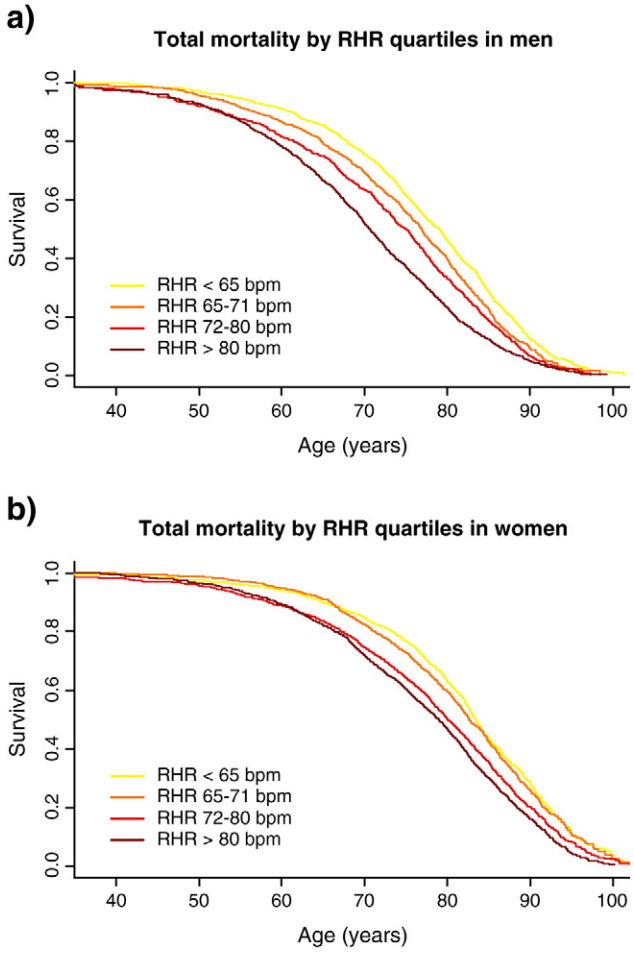

Fig. 2. Total mortality and resting heart rate. Kaplan–Meier survival curves with time-dependent covariates by quartiles of RHR in men (a) and women (b).

3.1. Total mortality by RHR

Fig. 2a and b shows Kaplan–Meier survival curves for total mortality with time-dependent covariates for the male and female population stratified by quartiles of RHR. In both men and women, high RHR was associated with shorter survival. The survival benefit in the lowest RHR quartile compared to the highest was 4.7 years in men and 3.6 years in women. These results were essentially unchanged after removal of subjects dying within the first 5 years after inclusion (men 4.1 years and women 3.1 years).

3.2. Total mortality by RHR and smoking status

3.2.1. Univariate analyses

There was a noticeable difference in the association between RHR and survival between never smoking subjects and subjects with a

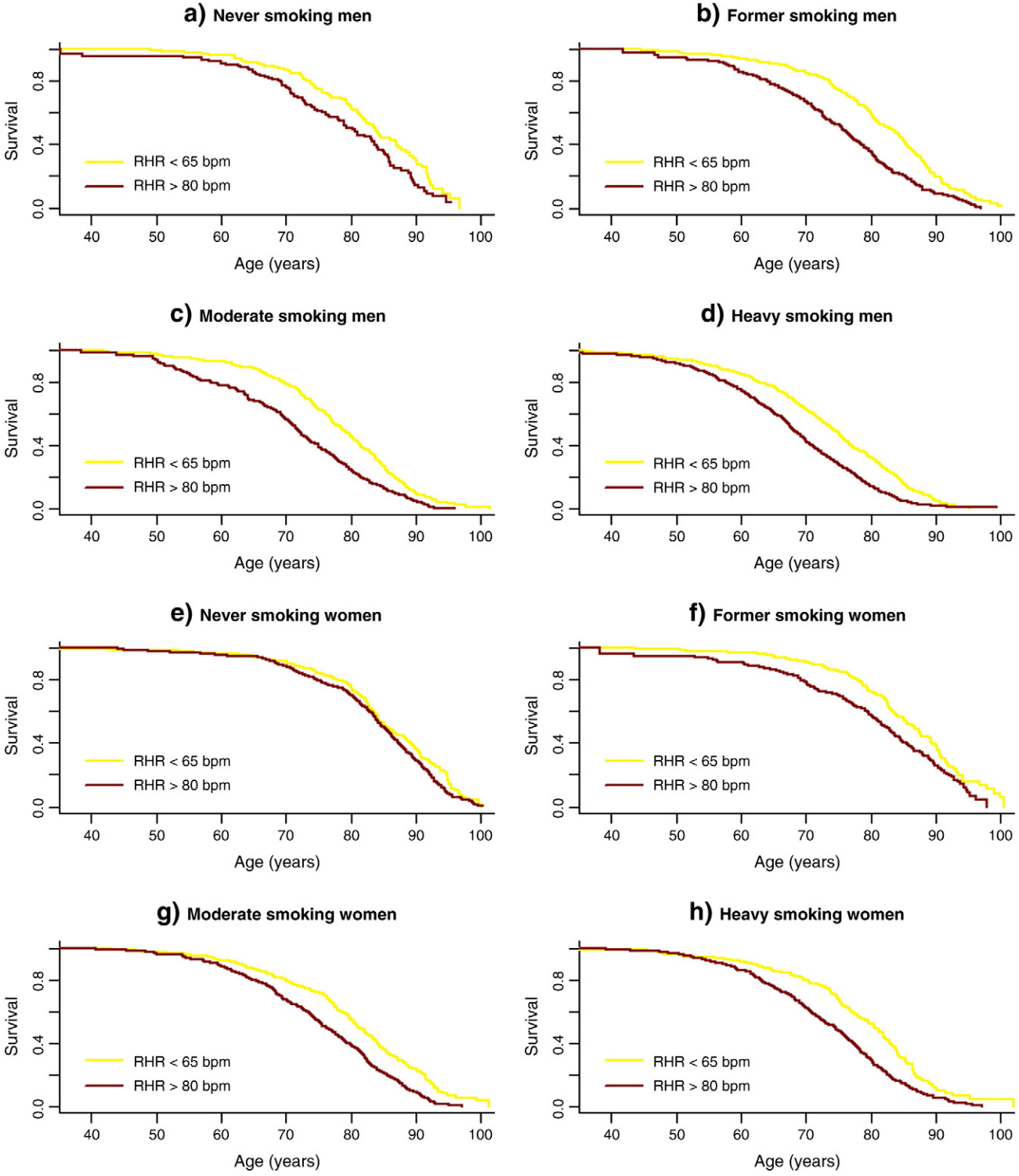

Fig. 3. Total mortality and resting heart rate. Kaplan–Meier survival curves with time-dependent covariates in never, former, moderate, and heavy smoking men (a–d) and women (e–h). Highest (>80 bpm) and lowest (<65 bpm) RHR quartiles shown.

Table 2
Difference in survival (all-cause mortality) between subjects in the lowest vs highest RHR quartile.

	Univariate RHR <65 bpm vs >80 bpm		Multivariate[a] RHR 64 bpm vs 81 bpm	
	Men (years)	Women (years)	Men (years)	Women (years)
Never smokers	3.2	1.4	0.8	0.8
Former smokers	3.6	2.8	1.6	1.6
Moderate smokers	3.6	3.8	1.9	1.9
Heavy smokers	4.6	4.5	2.3	2.0

[a] Adjusted for SBP, BMI, pulmonary function, physical activity, alcohol, triglycerides. Age as underlying time scale.

history of smoking. In Fig. 3a–d and e–h, time-dependent univariate survival curves of total mortality show, that a high RHR was associated with a greater risk in current and former smokers than in never smokers. The difference in survival between subjects in the lowest RHR quartile (<65 bpm) compared to subjects in the highest (>80 bpm) is shown in Table 2. The univariate estimates are compared with multivariate adjusted estimates (see below).

3.3. Total and cardiovascular mortality by RHR and smoking status

3.3.1. Multivariate analyses

In the multivariate analyses (*models A–C*) leisure time physical activity, BMI, SBP, pulmonary function, alcohol consumption and triglycerides were included as covariates. Total cholesterol was insignificant and not included.

3.3.1.1. Baseline analyses (model A). In Table 3, relative risk estimates of a 10 bpm increase in RHR is shown. In the baseline analyses (*model A*) for CCHS 1–3, RHR was associated with total mortality in all smoker groups, except the former smoker group in CCHS 3. Baseline estimates were not significant in any of the never smoker groups.

3.3.1.2. Time-dependent covariates (model B). In the time-dependent multivariate analyses (*model B*), elevated RHR was associated with increased relative risk of all-cause mortality across all groups, see Table 3. All estimates were highly significant ($p=0.01$ for never smokers, $p<0.001$ for all other groups). There was no interaction between gender and RHR ($p>0.26$, irrespective of smoking status). Risk estimates in former, moderate and heavy smokers were significantly greater than the risk estimate in never smokers (all $p<0.05$), while there was no difference between former, moderate, and heavy smokers (all $p>0.22$). The relative risk estimates for cardiovascular mortality were essentially similar to the estimates for total mortality.

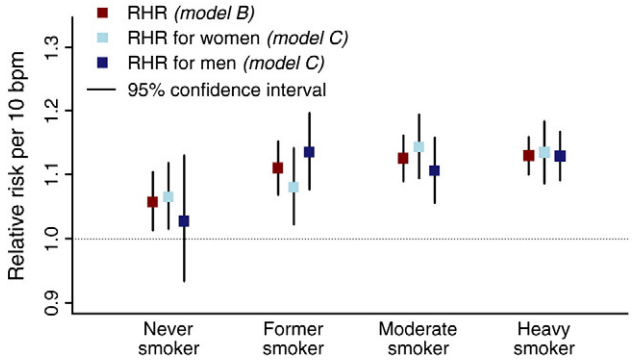

Fig. 4. Relative risk of all-cause mortality per 10 bpm increase in RHR for the whole population (*model B*) and in men and women separately (*model C*).

In Table 2, multivariate adjusted differences in survival between a RHR of 81 bpm and a RHR of 64 bpm are shown. In the Cox models, RHR is a continuous variable with no cut-off; 81 bpm vs 64 bpm thus represent a conservative estimate of the survival difference between a high and low RHR quartile. As shown, the difference in expected survival is between 0.8 years and 2.3 depending on smoking status and gender. Furthermore, the gender difference suggested in the univariate analysis appears to be due to confounding factors.

3.3.1.3. Gender difference (model C). In Fig. 4, the relative risk estimates of a 10 bpm increase in RHR are shown in men and women separately (*model C*). There was no gender difference in any of the groups ($p>0.10$). The estimate in never smoking men was equal to that of women but did not reach statistical significance. The relative risk estimates from *model B* are shown for comparison.

4. Discussion

In the Copenhagen City Heart Study, RHR is a predictor of both cardiovascular and total mortality in a population followed through 33 years with 8709 deaths occurring.

The main finding of this study is, that the risk of an elevated RHR is greater in subjects with a history of smoking, irrespective of prior or current tobacco consumption, compared to never smokers. Furthermore, our findings suggest yet another detrimental effect of tobacco smoking, and consequently another argument for prevention of smoking.

The deleterious effects of a high RHR have been demonstrated in numerous studies. High RHR has been associated with the

Table 3
Relative risk (95% CI) with an increase of 10 bpm in RHR. (n = no. subjects, obs. = no. observations).

	Baseline All-cause mortality (*Model A*)			Time-dependent All-cause mortality (*Model B*)	Time-dependent CV mortality (*Model B*)
	CCHS 1 $n=14{,}223$	CCHS 2 $n=12{,}698$	CCHS 3 $n=10{,}135$	CCHS 1–4 43,293 obs.	CCHS 1–4 43,293 obs.
Never smoker	1.03 (0.98,1.08) $n=2283$	1.03 (0.97,1.08) $n=2068$	1.06 (0.96,1.16) $n=1817$	1.06 (1.01,1.10) 7778 obs.	1.06 (0.99–1.13) 7778 obs.
Former smoker	1.07 (1.02,1.12) $n=1811$	1.12 (1.07,1.17) $n=1924$	1.06 (0.99,1.14) $n=1681$	1.11 (1.07,1.15) 6949 obs.	1.11 (1.05–1.17) 6949 obs.
Moderate smoker	1.09 (1.05,1.13) $n=3201$	1.16 (1.11,1.21) $n=2631$	1.14 (1.05,1.24) $n=1380$	1.13 (1.09,1.16) 7995 obs.	1.15 (1.09–1.21) 7995 obs.
Heavy smoker	1.09 (1.06,1.12) $n=4197$	1.16 (1.12,1.20) $n=3365$	1.15 (1.09,1.22) $n=2133$	1.13 (1.10,1.16) 10,696 obs.	1.13 (1.08–1.18) 10,696 obs.
Excluded	$n=1971$	$n=2503$	$n=2563$	8497 obs.	8497 obs.
Missing	$n=760$	$n=207$	$n=561$	1369 obs.	1369 obs.

development of hypertension [11–13], all-cause mortality, mortality from cardiovascular disease and non-cardiovascular disease in general populations [2,14–17], and in populations with preexisting ischaemic heart disease [18,19]. Shaper et al. [19] investigated the effect of RHR in current smokers and non-smokers in regards to mortality and sudden death but did not report a difference. Across the literature, the association between mortality and RHR appears to be especially strong for sudden death [1,19] and in men [2,20,21]. Recently, RHR has been found to be a strong predictor of CAD also in women [3]. In the present study, the association between resting heart rate and total and cardiovascular mortality was similar in men and women.

The subjects in the present study were from a general population and considered healthy without overt disease. High RHR was associated with known cardiovascular risk factors, such as blood pressure, pulmonary function and BMI. As a clinical measure, RHR is reasonably also a marker of general fitness. However, elevated RHR remained associated with increased risk even after multiple adjustments including pulmonary function. There is no reason to suspect that undiagnosed heart failure could explain the association between elevated RHR and mortality since abnormal left ventricular function was very rare, nor was underlying anemia reason for elevated RHR.

There was no difference in the risk associated with elevated RHR between former, moderate or heavy smokers but all groups were at significantly greater risk than never smokers. The difference in survival between subjects in the highest vs lowest RHR quartile was in the univariate analysis several years and after adjusting for multiple confounding factors still in the range of years.

4.1. Pathophysiological considerations

The possible pathophysiological relationship between elevated RHR and cardiovascular mortality has been thoroughly reviewed [20,22]. High heart rate may promote the development of atherosclerosis and plaque rupture through increase in cardiac work, decreased artery compliance and increase in arterial wall stress [23]. Levine [24] showed that the number of heart beats per lifetime is the same across different mammal species thereby indicating, that also more basal metabolic effects may explain the effect of RHR on all-cause mortality.

Smoking is known to induce endothelial dysfunction and atherosclerosis and to negatively influence the coagulation cascade in case of a thrombus formation. All three components of Virchov's triad are affected: altered vessel wall, impaired blood flow and altered haemostatic [25,26]. It is therefore plausible that a high RHR exacerbates these effects and increases the likelihood of, for instance, a plaque rupture. As noted by McGill [27], smoking is associated with much more severe coronary atherosclerosis than in never smokers but not enough to account for the increase in coronary heart disease. This excess in risk may therefore partly be carried by RHR as shown in this study. A basal increase in metabolism caused by tobacco smoking may also contribute to the current findings. It is noteworthy, that in the present study former smokers had same relative risk of elevated RHR as current smokers. This may be due to lesions or damage to vessel walls already present. Yet, the mechanism behind the observed findings remains unknown.

4.2. Strengths and limitations

The current study followed a large population for 33 years with almost total follow-up in highly validated registers, many endpoints, and detailed information on study variables.

The assessment of RHR was performed at each visit and read from the ECG. It has been suggested that a Holter monitoring may be a better measurement of RHR, though studies have shown conflicting results [20]. In order to take into account possible changes in RHR throughout the observation period we fitted a model with time-dependent covariates.

Since heart medication, such as beta-blockers, is known to slow down heart rate all subjects reporting use of heart medication at the time of their first examination were excluded from the analysis. It should be noted, that information about use of asthma or COPD medication was not obtained. Some of these drugs both increase pulmonary function and increase RHR.

Residual confounding can never be excluded in observational studies. It is possible that other factors not measured in this study affect the association between RHR and survival.

4.3. Conclusion and perspective

This study suggests that elevated resting heart rate is more harmful in subjects who are current or former smokers, thereby proposing an addition to the growing numbers of adverse effects of tobacco smoking. WHO estimates that the number of smokers worldwide is currently about 1.3 billion [28], and the number is increasing — mainly in non-developed countries. Resting heart rate should be included as a risk factor in general risk assessments in primary prevention and especially in subjects with a history of smoking.

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Conflict of interest

None declared.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [29].

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Resting heart rate is associated with cardiovascular and all-cause mortality after adjusting for inflammatory markers: The Copenhagen City Heart Study

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Abstract

Aims: To investigate the association between resting heart rate (RHR) and markers of chronic low-grade inflammation. Also, to examine whether elevated resting heart rate is independently associated with cardiovascular and all-cause mortality in the general population, or whether elevated RHR is merely a marker of chronic low-grade inflammation.

Methods and results: A group of 6518 healthy subjects from the the Danish general population were followed for 18 years during which 1924 deaths occurred. Subjects underwent assessment of baseline RHR, conventional cardiovascular risk factors, high-sensitivity C-reactive protein (hsCRP), and fibrinogen. RHR was associated with hsCRP and fibrinogen in uni- and multivariate models ($p < 0.0001$). A 10 beats per minute increase in RHR was associated with increased cardiovascular and all-cause mortality in univariate models – HR (95%CI) (1.21 (1.14–1.29) and 1.15 (1.11–1.19); multivariate models adjusted for conventional risk factors – 1.16 (1.09–1.24) and 1.10 (1.06–1.14); multivariate models including hsCRP – 1.14 (1.07–1.22) and 1.09 (1.05–1.14); fibrinogen – 1.15 (1.07–1.22) and 1.09 (1.05–1.14); and both hsCRP and fibrinogen – 1.14 (1.07–1.22) and 1.09 (1.05–1.14).

Conclusion: RHR was associated with markers of chronic low-grade inflammation. However, RHR remained associated with both cardiovascular and all-cause mortality after adjusting for markers of chronic low-grade inflammation. This suggests that RHR is an independent risk factor for cardiovascular and all-cause mortality, and not merely a marker of chronic low-grade inflammation.

Keywords

Resting heart rate, inflammation, biomarkers, mortality, prevention

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Introduction

Elevated resting heart rate (RHR) associates with cardiovascular and all-cause mortality in patients with coronary heart disease and in apparently healthy subjects from the general population.[1–5] It is not clear whether elevated RHR is merely a marker of chronic low-grade inflammation associated with subclinical conditions or an independent risk factor.

In recent years, evidence suggests that biomarkers of systemic inflammation, especially plasma levels of high-sensitivity C-reactive protein (hsCRP) and fibrinogen, can identify apparently healthy subjects who are at increased risk of developing disease. In subjects without overt disease, hsCRP is characterized by its long half-life and ability to remain stable over several years.[6] In healthy subjects, elevated levels of hsCRP are

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associated with incident cardiovascular disease and mortality,[7–11] incident cancer,[12] other non-acute disease states[13] and all-cause mortality.[10,14] Fibrinogen is also involved in inflammatory processes and in epidemiological studies has been shown to be associated with both vascular and non-vascular mortality.[15] Thus, in apparently healthy subjects both levels of hsCRP and fibrinogen are elevated in response to chronic low-grade inflammation associated with subclinical disease.

The immune system communicates with the autonomous nervous system. Efferent vagus nerve stimulation is known to decrease heart rate and also to elicit inhibition of the inflammatory response through acetylcholine release in the reticulo-endothelial system, inhibiting the release of TNF and other cytokines from makrofages.[16–18] Hence, elevated RHR may also be a marker of autonomic dysfunction leading to elevated levels of circulating inflammatory markers.

Since markers of chronic low-grade inflammation are associated with subclinical conditions and have been shown to predict mortality in healthy populations we hypothesized that if RHR was a marker of risk only and not a primary risk factor, the association between RHR and mortality should be attenuated when adjusting for hsCRP and fibrinogen.

Therefore, first we studied whether increasing RHR was associated with increasing levels of hsCRP and fibrinogen. Secondly, we studied the association between RHR and cardiovascular and all-cause mortality, and thirdly, we studied the association between RHR and cardiovascular and all-cause mortality after adjusting for levels of hsCRP and fibrinogen.

Methods

The Copenhagen City Heart Study is a prospective study comprising a random sample from the Danish general population. It was initiated in 1976, with follow-up examinations in 1981–83, 1991–94 and 2001–03. The 10,135 subjects who participated in the third examination in 1991–94 were included in the present analysis.

All subjects underwent a full physical examination as well as a self-administered questionnaire providing medical history, smoking and drinking habits, leisure time physical activity,[19] medication and history of contacts with the health-care system. Blood pressure was measured in a standardized way using the London School of Hygiene Sphygmomanometer. Cholesterol, triglycerides and blood glucose values were measured on non-fasting venous blood samples.[20] Forced expiratory volume in 1 second (FEV_1) was measured and reported as per cent of expected. A 12-lead ECG was recorded at rest in a supine position and coded according to the Minnesota code. A research assistant read RHR from the ECG. Plasma levels of hsCRP were assessed by using high sensitivity turbidimetry assays (Dako, Glostrup, Denmark)[12] and plasma levels of fibrinogen were assessed using a colorimetric method (Boehringer Mannheim, Germany).

Follow-up was carried out through national registers. All deaths occurring until May 2009 were obtained from the national Danish Civil Registration System and causes of death occurring before 2007 were obtained from the national Danish Causes of Death Registry. Cardiovascular death was defined as ICD-10 codes I00-I99. Subjects were excluded from the analyses if they reported previous myocardial infarction, stroke, diabetes or had a fasting glucose higher than 11.1 mmol/l ($n = 446$). Also, subjects with atrial fibrillation or electrocardiographic evidence of ischaemic heart disease (Minnesota Codes 1–1 and 1–2) were excluded from the analyses ($n = 447$). In order to minimize the confounding effects of heart rate modifying or lipid lowering drugs, subjects reporting use of any heart medication such as beta-blockers, calcium-antagonists, digitalis, other antihypertensives, acetylsalicylic acid and statins/ fibrates were also excluded from the analyses ($n = 1884$). Finally, 1047 subjects were excluded due to missing data on RHR or plasma hsCRP, thus leaving 6518 subjects in the study. During the 18 years of follow-up (mean 14 years), 634 cardiovascular deaths and 1924 all-cause deaths occurred. Follow-up was 100%.

The ethical committee of Copenhagen and Frederiksberg, Denmark, approved the study (KF100.2039/91). All participants gave written informed consent.

Statistical analysis

All statistical analyses were carried out using the statistical software R, version 2.8.0. For demographics, descriptive statistics were used. The association between RHR and inflammatory markers, means, geometric means and medians of hsCRP and fibrinogen were calculated for each level of RHR+/−3 beats per minute (bpm). Correlations were performed with uni- and multivariate linear regression analyses. The association between RHR and cardiovascular and all-cause mortality was studied using sex-stratified Cox proportional hazards models with age as underlying timescale. The assumption of proportionality in the Cox regression models was tested with the score process test. Five Cox models were performed: a univariate model; adjusted for conventional risk factors (blood pressure, body mass index, smoking (never, former, moderate and heavy smoker), drinking habits (never, monthly, weekly and everyday drinker), log(FEV_1), log(triglycerides), physical activity (sedentary activity, referring to

'light activity less than 2 hours per week', moderate activity, referring to 'light activity 2–4 hours per week' and high activity, referring to 'light activity >4 hours per week' or 'high activity >2 hours per week'); adjusted for conventional risk factors plus log(hsCRP); adjusted for conventional risk factors plus levels of fibrinogen; and adjusted for conventional risk factors plus both hsCRP and fibrinogen. In both linear and Cox regression models, hsCRP was log-transformed to account for its non-normal positively skewed distribution. Statistical significance was assumed at a value of $p < 0.05$. To test the robustness of the findings, the analyses were also carried out after excluding subjects dying within 2 years of study inclusion.

Results

Baseline demographics of subjects from The Copenhagen City Heart Study are shown in Table 1.

Table 1. Baseline demographics of subjects from The Copenhagen City Heart Study 1991–94 examination according to RHR at study entry

	RHR Quartiles					
Covariates	Whole population	**<65** $n = 1709$	**65–71** $n = 1575$	**72–80** $n = 1699$	**>80** $n = 1535$	***p***
Males % (*N*)	43 (3155)	48.5 (947)	42.4 (743)	39.3 (751)	41.5 (714)	<0.001
Age (years) (Median, 5–95% percentile)	56.2 (28–78)	54 (27–77)	55 (28–77)	56 (29–79)	60 (31–78)	<0.001
Systolic blood pressure (mmHg) (Median, 5–95% percentile)	132 (105–175)	128 (103–169)	130 (105–169)	133 (106–175)	140 (110–184)	<0.001
Body mass index (kg/m^2) (Median, 5–95% percentile)	24.6 (19.5–32.8)	24.3 (19.5–31.2)	24.4 (19.5–32.5)	24.6 (19.4–33.3)	25.2 (19.3–33.9)	<0.001
FEV_1 (l) (Median, 5–95% percentile)	2.8 (1.4–4.7)	3.1 (1.6–5.0)	2.8 (1.5–4.7)	2.7 (1.3–4.6)	2.5 (1.1–4.4)	<0.001
Sedentary physical activity (%) (Median)	11 (796)	8.3 (161)	10.1 (174)	12.2 (229)	13.7 (232)	<0.001
Moderate physical activity (%) (Median)	51.8 (3751)	46.3 (896)	52.5 (909)	53.4 (1002)	55.8 (944)	<0.001
High physical activity (%) (Median)	37.2 (2689)	45.4 (879)	37.4 (648)	34.4 (645)	30.5 (517)	<0.001
Smoking status						
Never (%) (*N*)	25.9 (1878)	28.8 (558)	26.4 (457)	25.2 (474)	22.8 (389)	0.003
Former (%) (*N*)	23.8 (1727)	27.9 (540)	25.0 (433)	22.2 (418)	19.7 (336)	<0.001
Current, 0–15 g tobacco (%) (*N*)	19.9 (1443)	20.1 (390)	18.9 (328)	20.9 (393)	19.5 (332)	0.504
Current, 15+ g tobacco (%) (*N*)	30.4 (2209)	23.1 (448)	29.6 (513)	31.8 (599)	38.0 (649)	<0.001
Alcohol habits						
Never drinker (%) (*N*)	16.1 (1174)	13.5 (263)	16.5 (287)	17.4 (329)	17.3 (295)	<0.001
Monthly drinker (%) (*N*)	27.3 (1989)	30.6 (594)	26.8 (466)	26.9 (507)	24.7 (422)	0.001
Weekly drinker (%) (*N*)	35.1 (2555)	37.4 (727)	36.6 (638)	35.0 (660)	31.0 (530)	<0.001
Daily drinker (%) (*N*)	21.5 (1564)	18.5 (359)	20.1 (351)	20.8 (392)	27.0 (462)	<0.001
Triglycerides (mmol/l) (Median, 5–95% percentile)	1.4 (0.7–3.8)	1.3 (0.6–3.1)	1.4 (0.7–3.5)	1.5 (0.7–3.9)	1.7 (0.8–4.4)	<0.001
Cholesterol (mmol/l) (Median, 5–95% percentile)	6.0 (4.1–8.3)	5.8 (4.0–8.0)	5.9 (4.2–8.1)	6.0 (4.1–8.4)	6.1 (4.3–8.5)	<0.001
Fibrinogen (g/l) (Median, 5–95% percentile)	2.9 (1.9–4.6)	2.7 (1.8–4.1)	2.9 (1.9–4.4)	2.9 (1.9–4.6)	3.1 (2.0–4.9)	<0.001
HsCRP (mg/l) (Median, 5–95% percentile)	1.6 (0.9–8.4)	1.4 (0.9–5.9)	1.6 (0.9–7.5)	1.6 (0.9–7.9)	1.9 (0.9–12.5)	<0.001

FEV1, forced expiratory volume in 1 second; hsCRP high-sensitivity C-reactive protein; RHR, resting heart rate. *p*-values were calculated using Fisher's exact test for categorical covariates and Kruskal-Wallis rank sum test for continuous covariates. As shown, high baseline RHR was associated with cardiovascular risk factors.

Resting heart rate and inflammatory markers

There was a positive association between RHR and mean, geometric mean, and median hsCRP (Figure 1). The association between RHR and log(hsCRP) was highly significant ($p < 0.0001$, $r^2 = 3.1\%$). The difference between the mean and median levels of hsCRP suggests that subjects with high RHR had a greater variation in levels of hsCRP than subjects with lower RHR. RHR was also significantly associated with levels of fibrinogen (Figure 2; $p < 0.0001$, $r^2 = 4.0\%$).

In multivariate linear regression models including conventional risk factors as confounders, the association between RHR and log(hsCRP) remained highly significant ($p < 0.0001$, $r^2 = 15.3\%$). This was also the case for the association between RHR and fibrinogen ($p < 0.0001$, $r^2 = 22.8\%$)

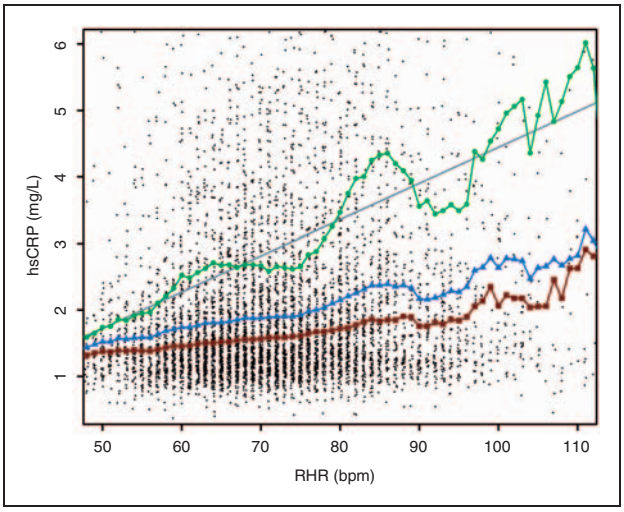

Figure 1. Resting heart rate and plasma levels of high-sensitivity C-reactive protein. Black dots, observations; red squares, medians; blue triangles, geometric means; green circles, means; grey line, best fit from univariate linear regression; bpm, beats per minute; hsCRP, high-sensitivity C-reactive protein; RHR, resting heart rate.

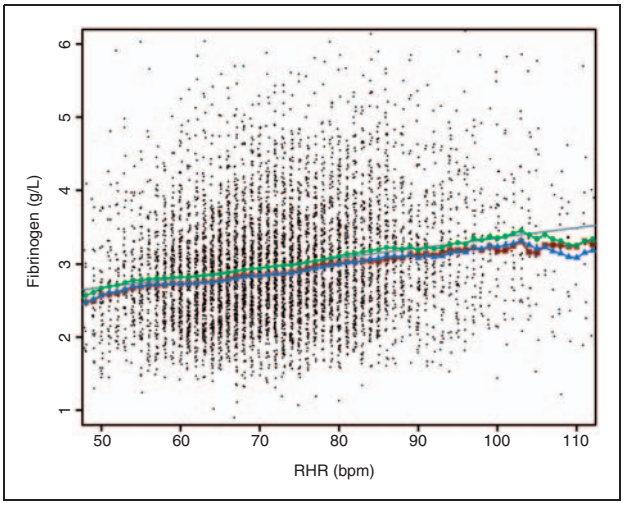

Figure 2. Resting heart rate and plasma levels of fibrinogen. Black dots, observations; red squares, medians; blue triangles, geometric means; green circles, means; grey line, best fit from univariate linear regression; bpm, beats per minute; hsCRP, high-sensitivity C-reactive protein; RHR, resting heart rate.

Resting heart rate, inflammatory markers and mortality

Cardiovascular mortality. In the univariate Cox model, the hazard ratio (HR (95%CI)) for cardiovascular mortality was 1.21 (1.14–1.29) for a 10 beats per minute increase in RHR (Figure 3). Inclusion of conventional risk factors in a multivariate model attenuated the hazard ratio slightly to 1.16 (1.09–1.24) whereas additional inclusion of either hsCRP, fibrinogen or both in the multivariate model resulted in similar hazard ratios of 1.14 (1.07–1.22), 1.15 (1.07–1.22) and 1.14 (1.07–1.22), respectively (Figure 3).

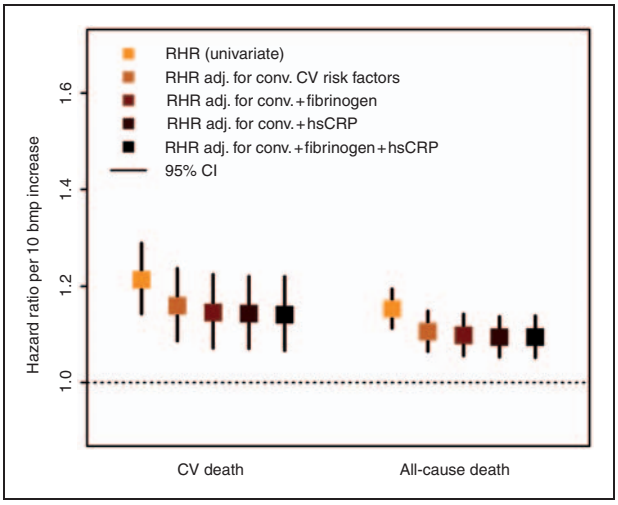

Figure 3. Resting heart rate, inflammatory markers, and mortality. Hazard ratio for cardiovascular and all-cause mortality for a 10 beats per minute increase in RHR. Univariate analyses, multivariate analyses including conventional risk factors (blood pressure, body mass index, smoking, drinking habits, log(FEV_1), log(triglycerides) and physical activity), multivariate analyses including conventional risk factors and log(hsCRP), multivariate analyses including conventional risk factors and fibrinogen, and multivariate analyses including conventional risk factors and both log(hsCRP) and fibrinogen. During follow-up, 634 cardiovascular deaths and 1924 all-cause deaths occurred. bpm, beats per minute; hsCRP, high-sensitivity C-reactive protein; FEV_1, forced expiratory volume in 1 second; RHR, resting heart rate.

All-cause mortality. The corresponding hazard ratios for all-cause mortality were 1.15 (1.11–1.19) in the univariate analysis, 1.11 (1.06–1.15) adjusted for conventional risk factors, 1.10 (1.06–1.14) adjusted for conventional risk factors and hsCRP, 1.09 (1.05–1.14) adjusted for conventional risk factors and fibrinogen and 1.09 (1.05–1.14) when adjusting for both hsCRP and fibrinogen (Figure 3).

There was no interaction between RHR and inflammatory markers on cardiovascular or all-cause mortality ($p > 0.2$). Also, there was no interaction between RHR, inflammatory markers and gender.

Exclusion of subjects dying within 2 years of inclusion. Excluding subjects dying within the first 2years of follow-up resulted in similar hazard ratios. For cardiovascular mortality, the risk estimates were 1.20 (1.13–1.28) for the univariate analysis and 1.13 (1.05–1.21) for the multivariate analysis including conventional risk factors and both hsCRP and fibrinogen. For all-cause mortality, the same analyses yielded estimates of 1.15 (1.10–1.19) and 1.09 (1.05–1.14).

Discussion

In this study of 6500 subjects from the Danish general population who were followed for 18 years, we found that RHR was associated with hsCRP and fibrinogen. However, elevated RHR remained associated with both cardiovascular and all-cause mortality, after adjusting for hsCRP and fibrinogen. This suggests that RHR is an independent risk factor for cardiovascular and all-cause mortality, and not merely a marker of conditions associated with systemic low-grade inflammation.

In other studies, elevated RHR is also associated with increased cardiovascular mortality.[1–5,10,21,22] However, whether RHR is mainly a marker of subclinical disease or a primary risk factor independent of other cardiovascular risk factors remains an issue.[23]

In healthy subjects from the general population, elevated levels of hsCRP and fibrinogen have been associated with a wide selection of disease states such as cardiovascular events,[7,10,11,15,24,25] cancer[12] and pulmonary disease.[26–28] Indeed, elevated levels of hsCRP in The Copenhagen City Heart Study robustly associate with increased all-cause mortality.[14]

RHR and levels of inflammatory markers have previously been found to be associated across different methods of assessing RHR. RHR from a single resting ECG was associated with levels of hsCRP in 179 healthy young men;[29] mean 24-hour ambulatory heart rate was associated with levels of hsCRP and white blood cell count in 643 healthy middle-aged and elderly men and women,[30] and RHR assessed by palpating radial pulse was associated with levels of hsCRP, fibrinogen and polymorphonuclear leucocytes in 4553 men.[31] Whether the association between RHR and inflammatory markers is causal, through reverse causality, or through a shared mechanism cannot be established from the current study. However, a common mechanism may be the cholinergic anti-inflammatory pathway by which both RHR and inflammatory markers are subject to change through vagal activity.[16] Experimental studies have shown that vagus nerve stimulation attenuates the endotoxin induced serum-TNF release and thereby development of systemic shock, and clinical studies have shown a possible synergy between CRP and high heart rate in relation to prediction of cardiovascular events.[32] Also, 24-h Holter recordings have shown an association between low heart rate variability, high RHR and ventricular arrhythmogenic substrates,[33] perhaps explaining the association between elevated RHR and sudden death.[34] Physical activity has been shown to improve levels of inflammation and increased vagal activity may be the mechanism.[35,36] Autonomic dysfunction, therefore, seems to play an important role in systemic inflammation.

Most importantly, chronic low-grade inflammation is observed in a number of conditions that are associated with increased mortality, and in the current study the prognostic significance of elevated RHR was unchanged after adjusting for inflammatory markers.

Study limitations

RHR was assessed as a single measurement from the ECG. It is possible that other RHR measurements, such as 24-h ambulatory ECG, are more useful. However, RHR from the ECG easily translates to a clinical setting; secondly, misclassification of RHR due to only a single measurement would bias the results toward the null hypothesis and therefore cannot explain our results.

Inclusion of markers of low-grade chronic inflammation in the analyses minimizes but does not exclude the possibility of residual confounding.

In a general population, several conditions can be associated with an altered inflammatory response. Subjects with self-reported osteoarthritis or rheumatoid arthritis ($N = 1709$), self-reported daily or almost daily use of NSAIDs ($N = 401$), self- reported asthma ($N = 341$) and self-reported medication for asthma or COPD ($N = 305$) had slightly higher levels of CRP compared to the whole population but the association between RHR, CRP and mortality were identical to the study population as a whole (data not shown).

Conclusive inferences about RHR as an independent risk factor for cardiovascular and all-cause mortality cannot be established from the present study. So far,

neither randomized placebo controlled studies of selective heart rate lowering in healthy subjects have been conducted nor have the use of instrumental variables on the causal relationship between RHR and mortality been performed.[37]

Conclusion

In conclusion, RHR was associated with the inflammatory markers hsCRP and fibrinogen. However, RHR remained an independent risk factor for both cardiovascular and all-cause mortality after adjusting for these markers, suggesting that RHR is an independent risk factor for cardiovascular and all-cause mortality, and not merely a marker of chronic low-grade inflammation.

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Conflict of interest

There are no conflicts of interest.

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Resting heart rate is a predictor of mortality in COPD

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ABSTRACT The clinical significance of high heart rate in chronic obstructive pulmonary disease (COPD) is unexplored. We investigated the association between resting heart rate, pulmonary function, and prognosis in subjects with COPD.

16 696 subjects aged ⩾40 years from the Copenhagen City Heart Study, a prospective study of the general population, were followed for 35.3 years, 10 986 deaths occurred. Analyses were performed using time-dependent Cox-models and net reclassification index (NRI).

Resting heart rate increased with severity of COPD ($p<0.001$). Resting heart rate was associated with both cardiovascular and all-cause mortality across all stages of COPD ($p<0.001$). Within each stage of COPD, resting heart rate improved prediction of median life expectancy; the difference between <65 bpm and >85 bpm was 5.5 years without COPD, 9.8 years in mild (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I), 6.7 years in moderate (GOLD stage II) and 5.9 years in severe/very severe COPD (GOLD stage III/IV), ($p<0.001$). Resting heart rate significantly improved risk prediction when added to GOLD stage (categorical NRI 4.9%, $p=0.01$; category less NRI 23.0%, $p<0.0001$) or forced expiratory volume in 1 s % predicted (categorical NRI 7.8%, $p=0.002$; category less NRI 24.1%, $p<0.0001$).

Resting heart rate increases with severity of COPD. Resting heart rate is a readily available clinical variable that improves risk prediction in patients with COPD above and beyond that of pulmonary function alone. Resting heart rate may be a potential target for intervention in COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world [1] annually accounting for over 3 million deaths [2]. COPD is associated with increased resistance in the pulmonary vasculature, pulmonary hypertension, increased right ventricular workload and in advanced cases right heart failure (cor pulmonale). Pulmonary and cardiovascular dysfunction is, thus, intimately connected.

It is a common clinical experience that patients with COPD often have high resting heart rates. High resting heart rate is present and associated with poor outcome in other clinical syndromes, *e.g.* heart failure, a disease entity that shares many clinical features with COPD, such as decreased stroke volume, dyspnoea and fatigue.

Recent studies have suggested that beta-blockers may have a beneficial effect on all-cause mortality in patients with COPD [3]. One of the main properties of beta-blockers is heart rate reduction. Heart rate may, therefore, potentially be a prognostic marker and therapeutic target in COPD as in other patient groups such as coronary heart disease and heart failure [4, 5].

Although elevated resting heart rate has been shown to be associated with increased cardiovascular and all-cause mortality in normal subjects and in subjects with heart disease [6-8] the contribution of resting heart rate to mortality in patients with COPD has never been examined in the setting of a large-scale population study.

In the present study, the relationships between COPD, resting heart rate and prognosis were studied. First, we examined whether COPD severity was associated with an increase in resting heart rate; secondly, we examined whether resting heart rate was associated with cardiovascular and all-cause mortality in COPD; thirdly, we examined whether resting heart rate could improve prediction of median life expectancy beyond that of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage [1]; and finally, using net reclassification index (NRI), we examined whether adding resting heart rate to models with GOLD stage alone or forced expiratory volume in 1 s (FEV_1) % predicted alone could reclassify subjects into clinically meaningful higher or lower risk categories of mortality.

Methods

Population

The Copenhagen City Heart Study is a prospective study of a random population sample of 18 974 males and females aged $\geqslant$20 years living in Copenhagen, Denmark. The study was initiated in 1976 and has so far included four examinations: the first survey lasted from 1976 to 1978; the second survey from 1981 to 1983; the third from 1991 to 1994; and the fourth from 2001 to 2003. The first cross-sectional survey included 14 223 individuals. Subjects aged between 20–49 years have subsequently been added throughout the following surveys to the current total number. The sampling background and methods have been described in detail in several publications [9–11].

Subjects

All subjects were of Caucasian descent. In the present study, only subjects aged $\geqslant$40 years were included. Subjects with atrial fibrillation or flutter were excluded from the analyses; also cases with missing data on resting heart rate or pulmonary function were excluded (n=375). Information on vital status and causes of death was obtained from national registers. Cardiovascular death was defined as International Classification of Diseases (ICD)-8 codes 390–458 and ICD-10 codes I00-I99. A total of 106 subjects were lost to follow-up due to emigration; follow-up was, therefore, 99.4% complete.

The regional ethical committee approved the study (H-KF-01-144/01). All participants gave written informed consent.

Measurements

All subjects underwent physical examinations as well as a self-administered questionnaire providing medical history, smoking (never, former, current) and alcohol consumption habits (never, monthly, weekly, or everyday drinker), leisure time physical activity (sedentary, referring to light activity $<$2 h per week; moderate, referring to light activity 2–4 h per week; and high, referring to light activity $>$4 h per week or high activity $>$2 h per week), medication, and history of contacts with the healthcare system. Blood pressure was measured with the London School of Hygiene sphygmomanometer. Plasma cholesterol, high-sensitivity C-reactive protein (CRP), fibrinogen and blood glucose values were measured on non-fasting venous blood samples [12]. A 12-lead ECG was recorded at rest in a supine position and coded according to the Minnesota code. Resting heart rate was read from the ECG.

In surveys one and two, FEV_1 and forced vital capacity (FVC) were measured with an electronic spirometer (Monaghan N 403; Monaghan, Littleton, CO, USA), which was calibrated daily. In surveys three and four, a dry wedge spirometer (Vitalograph, Maidenhead, UK), which was calibrated weekly, was used. The best

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FEV_1 and FVC of three were used in the analyses. Lung function data are reported as a percentage of predicted value according to age, sex and height (FEV_1 % pred) [13].

Severity of COPD was classified according to the GOLD classification [1]: mild COPD (GOLD stage I), FEV_1/FVC <70% and FEV_1 % pred ⩾80; moderate COPD (GOLD stage II) FEV_1/FVC <70% and 50⩽ FEV_1 % pred <80; severe COPD (GOLD stage III) FEV_1/FVC <70% and 30⩽ FEV_1 % pred <50; very severe COPD (GOLD stage IV) FEV_1/FVC <70% and FEV_1 % pred <30%.

Statistics

All statistical analyses were carried out using the statistical software R, version 2.13.1. (R Foundation for Statistical Computing, Vienna, Austria). For demographics, the Kruskal–Wallis test was used for continuous variables and Fischer's exact test for categorical variables.

First, we studied the association between resting heart rate and severity of COPD (GOLD stage). For each subject, only observations from the first study visit were used. The robustness of the association was examined by performing two analyses: 1) univariate; and 2) adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index (BMI), physical activity, alcohol consumption habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischaemic heart disease, electrocardiographic evidence of ischaemic heart disease (Minnesota codes 1-1 and 1-2), previous stroke, previous diagnosis of any cancer (information from the Danish Cancer Registry), and self-reported diabetes or fasting glucose >11.1 $mmol \cdot L^{-1}$. Additional subanalyses were performed in the fully adjusted model that also included covariates only available in surveys three and four. These covariates were high-sensitivity CRP, fibrinogen, use of statins, use of medication for asthma or bronchitis, and dyspnoea (Medical Research Council (MRC) scale).

Secondly, the association between resting heart rate and cardiovascular and all-cause mortality was studied using both uni- and multivariate models (as stated previously) in a Cox proportional hazards model with time-dependent covariates. The assumption of proportionality in the Cox regression models was tested with the score process test.

Thirdly, to assess if resting heart rate in addition to GOLD stage predicts mortality better than GOLD stage alone, Kaplan–Meier survival curves for all-cause mortality were fitted and median life expectancy calculated for GOLD stage alone, and for GOLD stage stratified by resting heart rate.

Finally, we studied whether the addition of resting heart rate to pulmonary function (GOLD stage or FEV_1 % pred) would improve the predictive accuracy for mortality. Firstly, we calculated Harrell's C-statistic with and without resting heart rate. C-statistics assess the prognostic ability of a variable using a binary outcome. Since C-statistics are not developed for risk prediction models [14], we also assessed the NRI [15, 16]. The dataset was split in half, one half for developing the models and the other half for validating the models [16]. For the NRI, risk categories for mortality during a 10-year follow-up period based on GOLD stages in the development dataset were determined as <25%; 25%–35%; 35%–50%; and ⩾50%. Only subjects with GOLD stage 2 or higher were included. The categorical NRI provides information about how adding resting heart rate to GOLD stage or FEV_1 % pred correctly reclassifies subjects who do not have an event into a lower risk category and subjects who get an event into a higher risk category. The category less NRI provides information on improved reclassification into higher or lower risk without predefined risk categories; *i.e.* a subject for whom risk estimation is improved from 26% to 33% would, in the categorical analysis, not be considered reclassified due to the limits of the categories, whereas in the category less analysis this person would be registered as correctly reclassified. Statistical significance was assumed at a value of $p<0.05$.

Results

A total of 16 696 subjects were included. During the 35.3 years of follow-up (mean 20.1 years), 5394 cardiovascular deaths and 10 986 all-cause deaths occurred. Clinical characteristics are shown in table 1.

COPD severity and levels of resting heart rate

Resting heart rate increased with severity of COPD (fig. 1a and 1b).

Compared to subjects with no COPD mean (95% CI) resting heart rate was 0.5 (-1.2–0.2) $beats \cdot min^{-1}$ higher in subjects with stage I COPD, 1.4 (1.0–1.9) $beats \cdot min^{-1}$ higher in subjects with stage II COPD, 4.5 (3.7–5.2) $beats \cdot min^{-1}$ higher in subjects with stage III COPD, and 10.4 (8.9–11.9) $beats \cdot min^{-1}$ higher in subjects with stage IV COPD (fig. 1a). In the multivariate model including age, sex, smoking, blood pressure, cholesterol, BMI, physical activity, alcohol, medication, diabetes, previous cardiovascular disease and cancer (see statistics) the difference in resting heart rates was -0.3 (-1.0–0.3) $beats \cdot min^{-1}$, 0.9 (0.4–1.3) $beats \cdot min^{-1}$, 3.9 (3.1–4.6) $beats \cdot min^{-1}$, and 9.9 (8.4–11.4) $beats \cdot min^{-1}$, respectively for each GOLD stage (fig. 1b). The p-value for trend was <0.001 in both analyses.

TABLE 1 Clinical characteristics of the 16 696 subjects included in the study

	GOLD stage					p-value
	No COPD	I	II	III	IV	
Subjects n	14051	516	1564	457	108	
Male n (%)	6251 (44.5)	313 (60.7)	866 (55.4)	261 (57.1)	75 (69.4)	<0.001
Age years	54±9	57±10	57±10	59±9	62±9	<0.001
Resting heart rate beats·min^{-1}	73.4±13	72.6±12	74.6±13	77.5±13	84.9±14	<0.001
Systolic blood pressure mmHg	137±22	138±22	141±23	141±22	144±20	<0.001
Body mass index kg·m^{-2}	25.5±4.2	24.4±3.2	25.1±4.2	25.1±4.8	24.6±5.1	0.894
FEV1 % pred	89±17	89±16	65± 8	42±6	24±5	<0.001
Sedentary physical activity	17.6	21.4	24.3	31.1	47.7	<0.001
Smoking status						
Never	21.9	15.6	10.9	7.3	7.5	<0.001
Former	19.2	19.9	12.9	15.4	34.9	<0.001
Current	58.9	64.5	76.2	77.3	57.5	<0.001
Daily alcohol consumption	24.3	32.5	33.6	34.4	38.3	<0.001
Cholesterol mmol·L^{-1}	6.1±1.2	6.0±1.2	6.0±1.2	6.0±1.1	5.9±1.2	0.009
Use of heart medication	9.0	7.8	10.1	15.0	16.8	<0.001
Previous coronary heart disease	2.2	1.7	3.0	2.8	3.7	0.219
Previous stroke	1.0	1.4	1.5	1.5	2.8	0.152
Previous cancer	4.1	2.9	5.4	5.9	8.3	0.004
Diabetes	3.1	1.8	4.2	5.4	10.6	<0.001

Data are presented as mean±SD or %, unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; % pred: % predicted.

In a subanalysis also including use of asthma or bronchitis medication, MRC class, high-sensitivity CRP, fibrinogen and use of statins in the full multivariate model the positive relationship between resting heart rate and COPD severity remained highly significant (p<0.001).

Resting heart rate and mortality

Resting heart rate was highly significantly associated with both cardiovascular and all-cause mortality in both uni- and multivariate models (table 2). There was no interaction between COPD severity and heart rate with

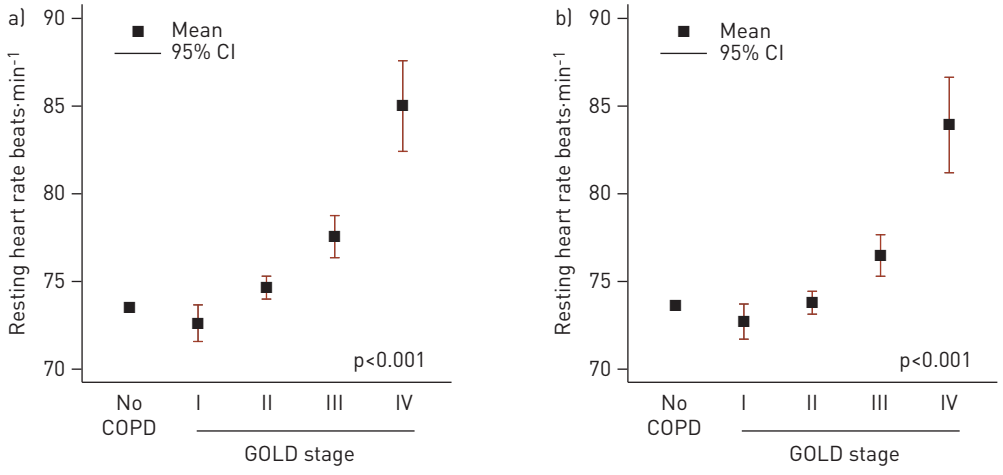

FIGURE 1 Resting heart rate and severity of chronic obstructive lung disease (COPD). Resting heart rate increase significantly with severity of COPD (p<0.001). a) Unadjusted analysis. b) Multivariate analysis adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol drinking habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischaemic heart disease, electrocardiographic evidence of ischaemic heart disease, previous stroke, previous diagnosis of any cancer, self-reported diabetes or fasting glucose >11.1 mmol·L^{-1}. Data are presented as mean with error bars representing 95% CI. No COPD n=14051, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I n=516, GOLD stage II n=1564, GOLD stage III n=457, GOLD stage IV n=108.

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TABLE 2 Resting heart rate, all-cause and cardiovascular mortality

	Resting heart rate beats·min^{-1}			
	<64	65–74	75–84	⩾85
All-cause mortality				
Univariate	1¶	1.11 (1.05–1.17)	1.30 (1.23–1.37)	1.51 (1.42–1.60)
Multivariate#	1¶	1.16 (1.10–1.22)	1.31 (1.24–1.38)	1.51 (1.43–1.60)
Cardiovascular mortality				
Univariate	1¶	1.08 (1.00–1.17)	1.34 (1.24–1.45)	1.57 (1.45–1.70)
Multivariate#	1¶	1.16 (1.07–1.25)	1.36 (1.26–1.48)	1.57 (1.45–1.71)

Data are presented as hazard ratio (95% CI). #: multivariate analysis adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol consumption habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischaemic heart disease, electrocardiographic evidence of ischaemic heart disease, previous stroke, previous diagnosis of any cancer, self-reported diabetes or fasting glucose >11.1 mmol·L^{-1}; ¶: reference.

regard to mortality. However, there was a significant interaction with smoking; elevated heart rate was associated with greater risk in current and former smokers. This has previously been discussed in detail [7].

GOLD stage, resting heart rate, and median life expectancy

Pulmonary function according to the GOLD staging was highly predictive of mortality. Median life expectancy (95% CI) was 78.8 (78.4–79.2) years in the no COPD group, 77.9 (75.6–79.5) years in GOLD stage I COPD, 73.4 (72.2–74.4) years in GOLD stage II COPD and 67.2 (65.2–68.9) years in GOLD stage III/IV COPD.

Figure 2 shows median life expectancy by GOLD class and resting heart rate. As shown, median life expectancy decreased with increase in resting heart rate across all GOLD stages. Median life expectancies (95% CI) in no COPD were 80.9 (80.2–81.6) years in subjects with resting heart rate <65 beats·min^{-1}, 79.7 (79.1–80.2) years in resting heart rates 65–74 beats·min^{-1}, 78.2 (77.6–79.0) years in resting heart rates 75–84 beats·min^{-1}, and 75.4 (74.5–76.3) years in resting heart rate ⩾85 beats·min^{-1}. In subjects with GOLD stage I COPD median life expectancies were 80.5 (77.9–84.2) years, 79.5 (74.4–82.8) years, 78.9 (74.7–81.4) years, and 70.7 (67.0–75.6) years, respectively. In GOLD stage II COPD median life expectancies were 76.2 (73.3–78.7), 74.1 (72.4–75.8), 73.1 (70.8–74.9), and 69.5 (67.2–71.6). In GOLD stage III/IV COPD median life expectancies were 70.4 (65.3–74.0), 68.2 (61.9–73.1), 68.0 (63.9–69.4), and 64.5 (62.7–67.7), respectively. Thus, the difference in median life expectancy between a subject with a resting heart rate <65 beats·min^{-1} compared to a subject with resting heart rate ⩾85 beats·min^{-1} was 5.5 years in subjects with no COPD, 9.8 years in subjects with stage I COPD, 6.7 years in subjects with stage II COPD and 5.9 years in subjects with stage III/IV COPD.

Risk reclassification, adding resting heart rate to pulmonary function

The addition of resting heart rate to models with pulmonary function alone significantly improved risk prediction.

In a model where pulmonary function was determined as GOLD stage, C-statistics for GOLD stage alone were 0.54 (0.53–0.56) *versus* 0.57 (0.55–0.60) ($p<0.001$) with GOLD stage and resting heart rate. The categorical NRI was 4.9% ($p=0.01$) (fig. 3) and the categoryless NRI was 23.0% ($p<0.0001$). In a model where pulmonary function was determined as FEV_1 % pred, C-statistics were 0.57 (0.54–0.59) *versus* 0.59 (0.56–0.61) with both FEV_1 % pred and resting heart rate ($p<0.001$). The categorical NRI was 7.8% ($p=0.002$) (fig. 4) and the categoryless NRI was 24.1% ($p<0.0001$).

Resting heart rate correctly reclassified subjects across all COPD stages, 76.4% were GOLD stage II, 19.7% GOLD stage III and 3.9% GOLD stage IV which was similar to the general distribution of COPD (77.9% GOLD stage II, 18.3% GOLD stage III and 3.8% GOLD stage IV). Resting heart rate especially improved the prediction of non-events indicating that subjects with lower resting heart rates had a better survival than expected on the basis of their level of FEV_1.

Discussion

Resting heart rate increases with severity of pulmonary dysfunction in COPD, and improves prediction of mortality above and beyond knowledge of pulmonary function alone. These findings raise the question whether heart rate could be a target for intervention in COPD.

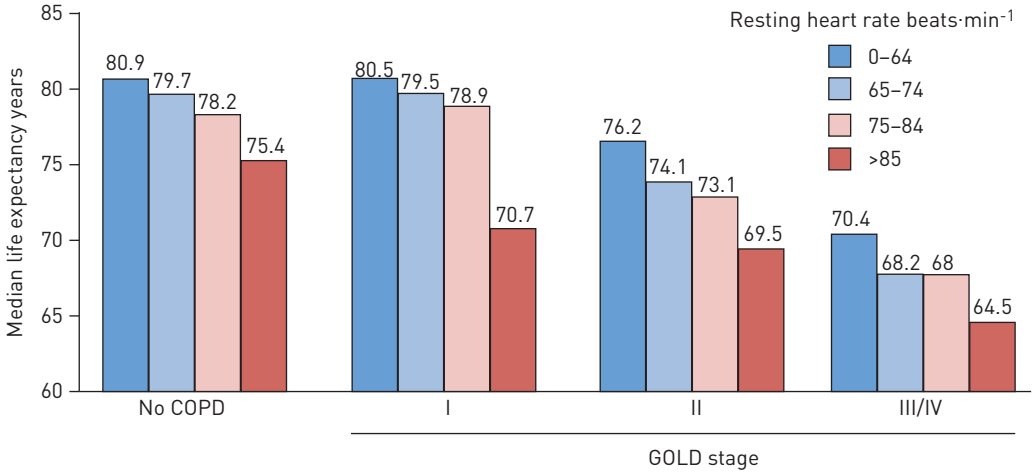

FIGURE 2 Life expectancy by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage and resting heart rate.

For example, in subjects with moderate COPD, resting heart rate predicts up to 10 years difference in median life expectancy between subjects with resting heart rate <65 and $\geqslant 85$ beats·min^{-1}; in fact, the difference between high and low resting heart rate within the same GOLD stage is of a greater magnitude than the differences in life expectancy between adjacent GOLD stages, thus, the difference in median life expectancies between mild COPD and moderate COPD was 4.5 years. Hence, resting heart rate improves the identification of subjects with COPD at risk. Monitoring resting heart rate can readily be implemented into clinical practice and day-to-day patient care.

Also, in terms of differences in absolute risk two important points can be inferred from our findings. First, in subjects within the same GOLD stage classification but with different resting heart rates an elevated resting heart rate is associated with poor prognosis and, in relation to absolute risk, the greater the severity of pulmonary dysfunction the greater is the difference in absolute risk between high and low heart rate categories. For example, in individuals without COPD the absolute mortality risk in a 10-year period is 17% in the low heart rate groups and 25% in the high heart rate groups and the absolute risk difference is, therefore, 8%. In comparison, participants with GOLD stage IV COPD have a poor prognosis and the corresponding absolute mortality risk during a 10-year period is 49% in the low resting heart rate group and

	Model with GOLD stage and resting heart rate				
Model with GOLD stage	<25%	25–35%	35–50%	≥50%	Total
Subjects without event					
<25%	0	0	0	0	0
25–35%	55	900	82	0	1037
35–50%	0	49	179	4	232
≥50%	0	0	1	36	37
Total	55	949	262	40	1306
Subjects with event					
<25%	0	0	0	0	0
25–35%	7	329	51	0	387
35–50%	0	25	110	0	135
≥50%	0	0	0	35	35
Total	7	354	161	35	557

FIGURE 3 Risk reclassification: Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage *versus* GOLD stage with resting heart rate. Resting heart rate improves the risk prediction when added to a model with GOLD stage alone. This is shown by the greater number of subjects in the blue squares compared with the number of subjects in the red squares for both non-events and events. White squares: subjects classified in the same risk category by both models; blue squares: subjects without events reclassified into a lower risk category and subjects with events reclassified into a higher risk category after inclusion of resting heart rate to the model with GOLD stage alone; red squares: subjects without events reclassified into a higher risk category and subjects with events reclassified into a lower risk category after inclusion of resting heart rate to the model with GOLD stage alone.

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	Model with FEV_1 % pred and resting heart rate				
Model with FEV_1 % pred	<25%	25–35%	35–50%	≥50%	Total
Subjects without event					
<25%	111	35	1	0	147
25–35%	117	613	60	1	791
35–50%	0	65	250	21	336
≥50%	0	0	10	22	32
Total	228	713	321	44	1306
Subjects with event					
<25%	25	20	0	0	45
25–35%	25	216	45	0	286
35–50%	0	36	144	15	195
≥50%	0	0	7	24	31
Total	50	272	196	39	557

FIGURE 4 Risk reclassification: forced expiratory volume in 1 s (FEV_1) % predicted *versus* FEV_1 % pred with resting heart rate. Resting heart rate improves the risk prediction when added to a model with FEV_1 % pred alone. This is shown by the greater number of subjects in the blue squares compared with the number of subjects in the red squares for both non-events and events. White squares: subjects classified in the same risk category by both models; blue squares: subjects without events reclassified into a lower risk category and subjects with events reclassified into a higher risk category after inclusion of resting heart rate to the model with FEV_1 % pred alone; red squares: subjects without events reclassified into a higher risk category and subjects with events reclassified into a lower risk category after inclusion of resting heart rate to the model with FEV_1 % pred alone.

72% in the high resting heart rate group, giving an increased absolute risk of mortality of 23%. Secondly, the proportion of subjects with high heart rate is far greater in GOLD stages III and IV and this implies that a far greater proportion of subjects with severe COPD are at risk compared with subjects with no or less pulmonary dysfunction.

The relationship between elevated heart rate and severity of COPD has never previously been established in a large-scale study. The most important issue is whether high resting heart rate is a feature of the pulmonary disease and, therefore, not a focus for a specific intervention, or whether increased heart rate plays an independent pathophysiological role and, therefore, might be a goal for intervention to improve the prognosis in COPD.

Resting heart rate has been shown to be a risk factor in both the general population [6, 7, 17–19] and in populations with cardiovascular disease [4, 8]. COPD and heart failure share many of the same features. Both are characterised by dyspnoea, fatigue, decreased stroke volume and increased heart rate. However, in contrast to the clinical classification of heart failure [20], heart rate has so far played no role in the risk stratification or management of patients with COPD.

Heart rate-reducing agents such as beta-blockers have, in cardiovascular clinical medicine, long proven beneficial effects on mortality and morbidity, but the effect of heart rate-reducing agents specifically for COPD is unexplored. Clinicians commonly avoid the use of beta-blockers in subjects with COPD [21]. However, a recent retrospective study of 6000 patients with COPD suggested that beta-blockers may have a beneficial effect on mortality [3]. New agents (I_f -inhibitors) with selective sinus node inhibition and heart rate-reducing properties without systemic effects have recently been introduced in heart failure and ischaemic heart disease [22, 23]. It is possible, that reducing heart rate in subjects with COPD could increase myocardial performance and thereby improve symptoms and prognosis. A clinical trial of heart rate reduction in COPD seems warranted at this point in time.

Several haemodynamic factors, such as hypoxia and decreased stroke volume, probably play a role in the relationship between high resting heart rate and COPD. Low arterial oxygen saturation leads to an increase in cardiac output [24]. Furthermore, pulmonary dysfunction in COPD is associated with an incremental decrease in left ventricular size and stroke volume [25, 26]. When stroke volume is decreased, cardiac output can be maintained by an increase in heart rate. COPD is additionally known to be associated with autonomic dysfunction resulting in decreased parasympathetic and increased sympathetic activity [27, 28]. Smoking is the leading cause of COPD. We have recently shown that former and current smokers are at increased risk of elevated heart rate compared to never-smokers [7]. These findings are in line with BARR *et al.* [25] who found a significant interaction between smoking status and stroke volume in subjects with pulmonary dysfunction; smokers were found to have lower ventricular dimensions compared to

nonsmokers. Vascular abnormalities with intimal hypertrophy, endothelial dysfunction, decreased vascular relaxation and, as a consequence, an increase in pulmonary pressure and myocardial impairment may play a role. This has been observed in both subjects with COPD as well as in smokers with normal pulmonary function [29]. However, this subject needs further investigation.

Study limitations

Resting heart rate was assessed from the ECG. It is possible that other assessments of heart rate, *e.g.* 24-hour ambulatory ECG, could provide more accurate heart rate measurements. However, the current findings can easily be translated into a normal clinical setting. Also, misclassification of resting heart rate from a single ECG would bias the results toward the null hypothesis.

A possible limitation may also be that diagnosis of asthma in our study was made by an affirmative answer to the question ''Do you have asthma?''. We have no data on reversibility of FEV_1 and, thus, some misclassification between asthma and COPD is possible. Yet, we do not think that this possibility affects our general findings regarding heart rate and mortality.

Bronchodilators are known to increase heart rate and could be an important confounder in this study; however, we found that adjusting for use of asthma or bronchitis medication in addition to other possible confounding factors did not change the association between elevated heart rate and severity of pulmonary dysfunction.

In epidemiological studies residual confounding factors can never be excluded. Inflammatory markers have previously been shown to be associated with subclinical disease [30–32]; including these markers of chronic low-grade inflammation in the multivariate adjustments did not change the results. The possible contribution from underlying subclinical disease may, therefore, have been minimised.

In conclusion, we demonstrate that resting heart rate increases with the severity of COPD. In multivariate analyses, resting heart rate is associated with both cardiovascular and all-cause mortality in subjects with COPD. High resting heart rate is associated with decreased median life expectancies across all stages of COPD and provides improved risk prediction above that of pulmonary function alone, measured either as GOLD stage or FEV_1 % pred.

Resting heart rate can easily, with minimal clinical training, and without cost be included in the clinical assessment of patients with COPD as a risk marker. Resting heart rate is a potentially modifiable risk factor. Clinical trials of heart rate lowering in COPD seem warranted.

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ORIGINAL ARTICLE

Elevated resting heart rate, physical fitness and all-cause mortality: a 16-year follow-up in the Copenhagen Male Study

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ABSTRACT

Objective To examine whether elevated resting heart rate (RHR) is an independent risk factor for mortality or a mere marker of physical fitness (VO_2Max).

Methods This was a prospective cohort study: the Copenhagen Male Study, a longitudinal study of healthy middle-aged employed men. Subjects with sinus rhythm and without known cardiovascular disease or diabetes were included. RHR was assessed from a resting ECG at study visit in 1985–1986. VO_2Max was determined by the Åstrand bicycle ergometer test in 1970–1971. Subjects were classified into categories according to level of RHR. Associations with mortality were studied in multivariate Cox models adjusted for physical fitness, leisure-time physical activity and conventional cardiovascular risk factors.

Results 2798 subjects were followed for 16 years. 1082 deaths occurred. RHR was inversely related to physical fitness ($p<0.001$). Overall, increasing RHR was highly associated with mortality in a graded manner after adjusting for physical fitness, leisure-time physical activity and other cardiovascular risk factors. Compared to men with RHR ≤50, those with RHR >90 had an HR (95% CI) of 3.06 (1.97 to 4.75). With RHR as a continuous variable, risk of mortality increased with 16% (10–22) per 10 beats per minute (bpm). There was a borderline interaction with smoking ($p=0.07$); risk per 10 bpm increase in RHR was 20% (12–27) in smokers, and 14% (4–24) in non-smokers.

Conclusions Elevated RHR is a risk factor for mortality independent of physical fitness, leisure-time physical activity and other major cardiovascular risk factors.

INTRODUCTION

Elevated resting heart rate has been shown to be associated with mortality across several general population studies[1–3] and in patient populations.[4 5]

In healthy subjects, the main question is whether a high resting heart rate is an independent risk factor, a surrogate marker of subclinical disease states, or a marker of poor physical fitness. A number of studies have shown that resting heart rate is associated with circulating levels of inflammatory markers related to subclinical chronic disease states.[6–8] Resting heart rate is determined by the activity of the autonomic nervous system, levels of circulating hormones and cardiorespiratory fitness.[9 10] The association between a high level of cardiorespiratory fitness (physical fitness) and a low resting heart rate is well known[11] and physical fitness may therefore be an important confounding factor. Most general population studies have included information about self-reported physical activity.[12 13] However, the correlation between self-reported physical activity and objectively measured physical fitness is only poor to moderate.[14] The lack of objectively measured physical fitness in the current literature may have resulted in residual confounding and may have influenced the interpretation of previous findings.

In the present study, we investigated whether resting heart rate was predictive of mortality in a population of employed apparently healthy middle-aged men who previously had physical fitness determined by a bicycle ergometer test and were followed for 16 years.

METHODS

Population

The Copenhagen Male Study was set up in 1970–1971 as a prospective cardiovascular study of Caucasian middle-aged men employed at 14 large workplaces in Copenhagen.[15 16]

First examination, 1970–1971

Overall, 6125 men were invited to participate; 5249 men (87%) agreed. All men were interviewed by a physician (FG) about a previously completed questionnaire, and had a clinical examination including measurement of physical fitness (VO_2Max) using a bicycle ergometer.

Physical fitness was determined using a bicycle ergometer and Åstrand nomogram and estimated through information on heart rate and workload. Heart rate was measured during submaximal bicycle work in a steady state with the aid of a stopwatch and a stethoscope. The loads used were 100, 150 and 200 W. One, two, or in a few cases three different loads were used. The load chosen in each case was determined from the weight and age of the person or heart rate during the first minute of the test. The method used has previously been described in detail.[15]

Second examination, 1985–1986

In 1985–1986 a new baseline was established, which was used for the analyses in the present study together with information on VO_2Max measured in 1970–1971. All survivors from the 1970–1971 examination were traced through the Danish National Civil Registry. Between June 1985 and June 1986, 4505 men, except 34 subjects who emigrated and therefore were lost to follow-up, were

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invited to take part in this new study; 3387 men (75%) agreed to participate and gave informed consent. Their mean age was 63 years (range 53–75). We excluded 33 invalid questionnaires, leaving 3354 men for the analysis; within this group 319 men were excluded because of cardiovascular disease (angina pectoris, acute myocardial infarction, stroke and/or intermittent claudication); a further 34 men without sinus rhythm on ECG were excluded, as were 85 men with diabetes or glucosuria; in all, 2798 men with useful information on heart rate from ECG and measurement of VO_2Max from the first baseline in 1970–1971 were included (figure 1). At baseline in 1970–1971, the 1985–1986 non-responders were more likely to be older, smokers, have higher alcohol consumption and higher blood pressure (BP) than the responders. However, the difference in mean levels of physical fitness was small (32.1 vs 32.7 ml/kg/min).

All men were interviewed by a physician (HOH) about a previously completed questionnaire, and were examined with measurements of height, body weight, and BP; a fasting venous blood sample was taken for the determination of serum lipids, and a urine sample for determination of glucosuria.

A resting ECG was recorded at the 1985–1986 examination, using a three channel Mingograph-34 by taking 12 standard leads in a supine position. A skilled technician coded according to the Minnesota code. As mentioned, only subjects with sinus rhythm were included in the study.

Medical history, smoking habits, alcohol consumption and leisure-time physical activity were assessed from the questionnaire. The men classified themselves as never having smoked, being a previous smoker or being a current smoker. Current tobacco smoking was calculated from information about the number of cigarettes, cheroots or cigars, or the weight of pipe tobacco smoked daily. One cigarette was taken as equivalent to 1 g of tobacco, one cheroot as 3 g and one cigar as 4 g. As previously estimated by means of measurements of serum cotinine,

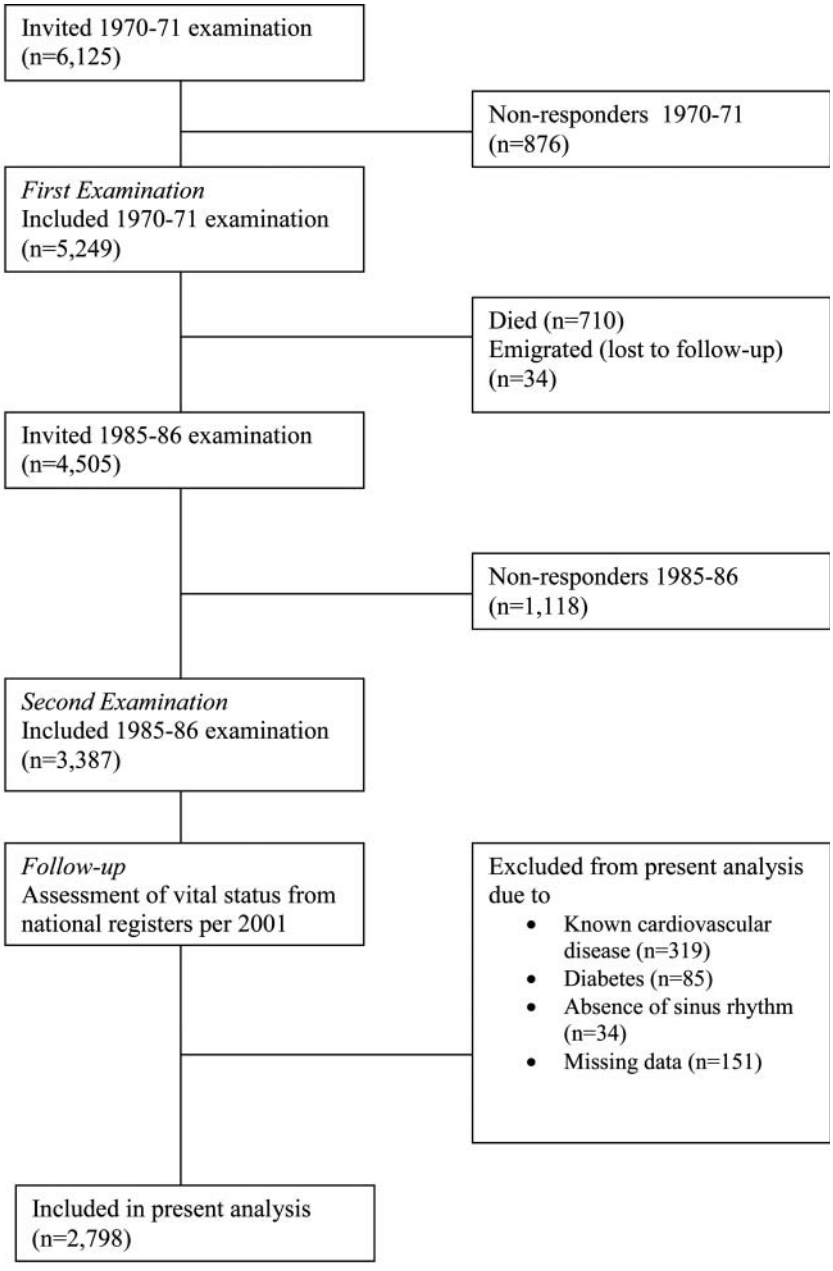

Figure 1 Flow-chart for the Copenhagen Male Study.

Heart rate, fitness and mortality

the validity of tobacco reporting was high.[17] Cumulative tobacco consumption (in pack-years) was calculated on the basis of information about mean total daily use of tobacco in grams multiplied by the time as a smoker in years divided by 20. In the multivariable analyses, cumulative tobacco consumption was included as a predictor/confounder.

The men were subdivided into five social classes, using a modification of a system by Svalastoga[18] based on the level of education and the job profile. Men in social class I were predominantly academics and well skilled administrators or executives; men in social class V were unskilled and semiskilled workers.

Body mass index (BMI) was calculated as weight in kg divided by height in m^2. Serum concentrations of total cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) were determined using enzymatic assays (Boehringer-Mannheim Biochemica, Mannheim, Germany).[19] Fasting lipids were measured only once in each subject. Definitions of high serum TG (≥1.70 mmol/l), low HDL-C (≤1.03 mmol/l), high systolic BP (>130 mm Hg) and high diastolic BP (>85 mm Hg) were based on criteria for definition of the metabolic syndrome according to the Adult Treatment Panel III.[20] Low density lipoprotein cholesterol (LDL-C) was calculated using the indirect method as developed by Friedewald.[21] Urine samples were examined for glucosuria using a glucose kinase method (Clinistix, Bayer, Leverkusen, Germany).

BP was measured on the right arm with the subject seated and after at least 10 min of rest, using a manometer developed by the London School of Hygiene and Tropical Medicine. Information on hypertension treatment was obtained from the questionnaire.

Ethics approval from the regional ethics committee was obtained for the second examination in 1985–1986; no approval was possible for the 1970–1971 examination since the ethics committee did not exist before 1980.

Follow-up, 2001

Information about vital status as of 31 December 2001 was collected through national registers for all subjects who had participated in both the 1970 examination and the 1985–1986 examination.

Statistical analyses

Basic statistical analyses, including trend tests, Kendall's τ B and test for linearity in analysis of variance, and regression analyses were performed. The population was divided into categories of resting heart rate. Relative risks were estimated by exp(β), where β is the hazard coefficient for the variable of interest in a Cox proportional hazards regression model, using the maximum likelihood ratio method and a backward stepwise elimination procedure.[22] Assumptions regarding the use of Cox proportional hazards were met by inspection of the log minus log function at the covariate mean.

First, we studied the correlation between physical fitness measured at the first examination and level of resting heart rate measured at the second examination. Second, we studied the relationship between resting heart rate and mortality in Cox models adjusting for: (1) age alone; (2) age and physical fitness (VO_2Max); (3) age, leisure-time physical activity, tobacco consumption and alcohol intake; (4) age, BMI, systolic and diastolic BP, serum TGs and serum total cholesterol; and (5) in a fully adjusted model including all potential confounders from analyses 1–4. Also, based on findings from a previous study showing an interaction with smoking status, resting heart rate and mortality,[23] we performed a subanalysis stratifying the population according to smoking status. A two-sided probability value of $p \leq 0.05$ was a priori taken as significant.

RESULTS

A total of 2798 subjects were included in the current study; 1082 men (38.7%) died during the 16 years of follow-up.

Table 1 shows baseline characteristics according to categories of resting heart rate. As shown, high resting heart rate was associated with lower physical fitness, and higher BP, total cholesterol, TGs and BMI. There was no difference in age or social class. Interestingly, subjects in the lowest resting heart rate categories were more likely to be smokers than in the higher resting heart rate categories.

Resting heart rate and physical fitness (VO_2Max)

There was a highly significant correlation between VO_2Max and resting heart rate ($R=-0.34$, $p<0.001$) (figure 2). Subjects with higher levels of physical fitness were more likely to have lower resting heart rates.

Resting heart rate and mortality

Overall, a high resting heart rate was a significant predictor of mortality. As shown in table 2, subjects with elevated resting heart rate were at significantly greater risk of mortality in all models (1–5). In the fully adjusted model, resting heart rate in the range 51–80 bpm was associated with about a 40–50% increase in risk, a resting heart rate in the range 81–90 bpm conferred a twofold increase in risk, and resting heart rates above 90 bpm risk conferred a threefold increase in risk compared to subjects in the lowest heart rate category (<50 bpm).

In a fully adjusted model with heart rate as a continuous variable, elevated heart rate was associated with an increased risk of 16% (10–22) per 10 bpm increase in resting heart rate.

There was a borderline significant interaction between resting heart rate, smoking status and mortality ($p=0.07$). In the fully adjusted model and with resting heart rate as a continuous variable, risk increased with 20% (12–27) in smokers, and 14% (4–24) in non-smokers per 10 bpm increase in resting heart rate.

DISCUSSION

In the present study of healthy middle-aged men, the main finding was that resting heart rate was a risk factor for mortality independent of physical fitness (VO_2Max) and other major potential confounders.

Resting heart rate as a risk factor for mortality has received considerable attention in recent years. However, a concern has been whether elevated resting heart rate is merely a surrogate marker of poor physical fitness, which in turn is associated with poor prognosis. A high level of physical fitness is a strong predictor of longevity[11] and is associated with lower heart rate, as also demonstrated in the present study. Level of physical fitness therefore plays a pivotal role in the study of resting heart rate. In a study from the Paris Prospective Study, resting heart rate was predictive of mortality and especially sudden death after adjusting for duration of exercise.[24] However, the main body of studies use self-reported levels of physical activity[22 25] or, in some cases, include no information.[26] In the current study, all subjects underwent a physical exercise test and estimation of VO_2Max as well as an assessment of leisure-time physical activity; we found that irrespective of level of physical fitness subjects with high resting heart rates fare worse than subjects with lower heart rates. This suggests that a high resting heart rate is not a mere marker of poor physical fitness but is an independent risk factor.

Table 1 Demographics

	Heart rate (bpm)						
n=222	≤50 n=1003	51–60 n=969	61–70 n=404	71–80 n=146	81–90 n=54	>90	p Value*
Resting heart rate (bpm)	47.2 (2.8)	56.0 (2.8)	65.0 (2.9)	74.2 (2.7)	84.7 (2.8)	100.6 (10.3)	
Lifestyle factors 1985–1986							
Leisure-time physical activity (%)							
Low	8.6	7.2	9.5	9.0	12.3	11.1	<0.001
Medium	30.9	33.9	38.0	41.8	52.1	55.6	
High	60.5	58.9	52.5	52.5	35.6	33.3	
Smoking (%)	71.9	58.8	52.8	49.9	42.1	42.6	<0.001
Pack-years	32.3 (23.1)	28.5 (25.3)	27.0 (26.2)	26.4 (23.3)	24.2 (23.0)	25.5 (23.1)	<0.001
Alcohol, beverages/week	15.0 (13.5)	15.5 (12.9)	16.0 (13.5)	15.5 (13.2)	16.9 (16.2)	16.7 (16.3)	0.20
Clinical and metabolic risk factors							
Systolic BP	114.9 (17.8)	117.7 (16.5)	120.6 (15.3)	125.3 (16.8)	130.8 (16.6)	132.7 (22.9)	<0.001
Systolic BP >130 (%)	20.3	20.9	26.6	35.9	53.4	48.1	<0.001
Diastolic BP	65.7 (10.5)	70.7 (10.8)	72.9 (10.9)	77.0 (12.9)	78.2 (11.6)	78.9 (11.7)	<0.001
Diastolic BP >85 (%)	5.4	9.5	12.2	20.5	28.8	31.5	<0.001
Hypertension (%)†	13.2	12.3	9.3	10.6	12.5	16.7	0.19
TG (mmol/l)	1.36 (0.67)	1.47 (0.87)	1.51 (0.80)	1.69 (1.54)	1.84 (1.69)	1.68 (1.08)	<0.001
TG (>1.70 mmol/l)	21.4	25.5	27.4	30.3	35.2	26.4	0.002
HDL-C (mmol/l)	1.34 (0.32)	1.36 (0.35)	1.37 (0.35)	1.35 (0.35)	1.39 (0.39)	1.48 (0.44)	0.09
HDL-C (<1.03 mmol/l)	17.1	16.5	14.5	14.1	17.8	14.8	0.28
Total cholesterol, mmol/l	6.36 (0.95)	6.47 (1.11)	6.55 (1.10)	6.53 (1.09)	6.53 (1.01)	6.67 (1.11)	0.02
LDL-C (mmol/l)	4.75 (0.96)	4.82 (1.09)	4.88 (1.08)	4.84 (1.05)	4.80 (0.99)	4.87 (1.11)	0.36
BMI (kg/m^2)	25.0 (3.0)	25.4 (3.2)	25.7 (3.3)	26.0 (3.8)	26.2 (3.6)	26.6 (3.7)	<0.001
Other characteristics							
Low social class (%)	48.6	51.5	48.1	48.3	59.6	62.3	0.71
Age (years)	62.8 (5.1)	62.4 (4.9)	62.6 (5.3)	62.7 (5.2)	63.9 (5.6)	63.3 (4.8)	0.03

Lifestyle and other characteristics according to resting heart rate group. Values presented are mean (SD) or frequency in per cent.
*p Values of trend test (Kendall's τ B) or test for linearity in analysis of variance.
†Defined as treatment due to hypertension.
BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides.

There were more smokers in the low heart rate categories than in the higher heart rate categories. Although the acute effects of smoking are tachycardia and increase in BP, healthy smokers are more likely to have lower BP than non-smokers; this has been shown in numerous studies,[27–29] and the same mechanisms may explain the observation in the present study. The possible mechanisms are at least twofold and probably pertinent to heart rate as well: first, it represents a counter-regulatory physiological response to the acute rise in BP and heart rate following smoking; and second, the healthy worker effect probably plays a role—smokers in the present study are healthier, leaner and more fit than non-smokers; they can 'endure' the smoking.

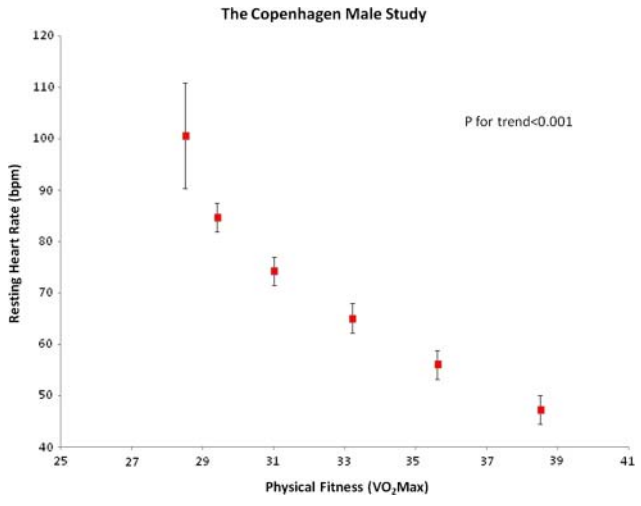

Figure 2 Relationship between physical fitness (VO_2Max) and resting heart rate (bpm).

Interestingly, we found a borderline significant interaction between resting heart rate, smoking and mortality, which suggests that high heart rate at any given resting heart rate level is associated with greater risk in smokers than in non-smokers. In a study from the Copenhagen City Heart Study,[23] resting heart rate was a stronger predictor of all-cause mortality among smokers than among non-smokers, which is in line with results from the present study. That this relationship can be found in two different large cohorts adds to the evidence that a true relationship may exist and not simply be a random association. Considering that the number of smokers globally is about 1 billion,[30] this is yet another argument for preventive measures against tobacco consumption and might have therapeutic implications in terms of heart rate monitoring and perhaps modification in smokers.

Several pathophysiological mechanisms have been proposed to explain the relationship between high resting heart rate and mortality.[31 32] Resting heart rate has been found to correlate with longevity in mammals. Levine[33] showed that the number of heart beats per lifetime is the same across different mammal species, indicating that basal metabolic effects may explain the effect of high resting heart rate on mortality. Smoking is known

Table 2 HRs (95% confidence limits) for all-cause mortality according levels of resting heart rate

	Heart rate (bpm)					
	≤50 n=222	51–60 n=1003	61–70 n=969	71–80 n=404	81–90 n=146	>90 n=54
Crude incidence (%)	30.5	36.6	38.1	40.6	54.8	66.7
HR, adjustment for						
(1) Age	1*	1.34 (1.03 to 1.73)	1.40 (1.08 to 1.81)	1.51 (1.13 to 2.00)	2.04 (1.47 to 2.82)	3.00 (2.00 to 4.50)
(2) Age+VO_2Max	1*	1.27 (0.97 to 1.65)	1.27 (0.98 to 1.66)	1.32 (0.99 to 1.78)	1.75 (1.25 to 2.45)	2.55 (1.68 to 3.86)
(3) Age+lifestyle†	1*	1.45 (1.11 to 1.90)	1.57 (1.20 to 2.05)	1.66 (1.24 to 2.23)	2.44 (1.46 to 2.90)	3.37 (2.23 to 5.09)
(4) Age+clinical factors‡	1*	1.40 (1.07 to 1.83)	1.47 (1.13 to 1.92)	1.58 (1.18 to 2.13)	2.06 (1.46 to 1.90)	3.11 (2.05 to 4.73)
(5) Age+all potential confounders§	1*	1.40 (1.06 to 1.85)	1.46 (1.10 to 1.93)	1.51 (1.11 to 2.06)	2.04 (1.43 to 2.92)	3.06 (1.97 to 4.75)

Cox proportional hazards regression analyses with forced entry of variables.
*Reference group.
†Leisure-time physical activity, cumulative tobacco consumption (cigarette equivalents), alcohol intake.
‡Body mass index (BMI), systolic blood pressure (BP), diastolic BP, serum triglycerides (TG), serum total cholesterol.
§Leisure time physical activity, VO_2Max, cumulative tobacco consumption (cigarette equivalents), alcohol intake, BMI, systolic BP, diastolic BP, high serum TG, total serum cholesterol, social class.

to promote inflammatory pathways and induce alterations in metabolism, vessel walls, haemostatics and impaired blood flow[34 35]; also, high heart rate may promote the development of atherosclerosis and plaque rupture through increase in cardiac work, decreased artery compliance and increase in arterial wall stress.[36] Altogether, these mechanisms could be related to the findings of this study. Studies investigating cause-specific mortality, be it mainly mortality from cardiovascular reasons, cancer or other disease entities, may further elucidate the relationship between elevated resting heart rate and longevity.

Methodological considerations

Possible study limitations should be considered. Since all subjects were employed and recruited from work places, there may have been a 'healthy worker' effect, resulting in the study population being healthier than would be seen in the general population. Also, there may have been a survivor selection bias. Since resting heart rate and VO_2Max were measured at different examinations, only subjects who survived to attend both examinations were included in the study. This may have biased the results towards the null hypothesis, making the observed HRs smaller than the true HRs.

Also, physical fitness may have changed between the first and the second examination. However, subjects were free of overt disease and survived to participate in the second examination; this makes it more likely that the subjects were healthier than the background population as a whole; second, all subjects with cardiovascular disease, diabetes or absence of sinus rhythm were excluded, suggesting that no major health-related event would have occurred to change general fitness levels substantially; third, a normal deterioration in general fitness over time would be the same in the entire study population and would therefore not affect the findings; and fourth, the correlation between physical fitness measured at the first examination and resting heart rate measured at the second examination supports that cardiorespiratory physical fitness was in general maintained between the two examinations. This is supported by the finding that the correlation between resting heart rate and physical fitness ($r=-0.34$) found in the present study was identical with the correlation between resting heart rate and physical fitness measured at the same point in time in a male population in the Tromsø Study.[14]

Heart rate shows diurnal variation, which may give some imprecision in the estimate of resting heart rate; however, misclassification of heart rate due to a single assessment would bias the results towards the null hypothesis and can therefore not explain our findings.

Finally, it should be mentioned that since the results presented here are based only on findings among healthy, middle-aged and elderly Caucasian men, our results may not necessarily apply to other population groups.

CONCLUSION

In the present study of 2798 healthy, middle-aged and elderly Caucasian men followed for 16 years, resting heart was a risk factor for mortality independent of physical fitness (VO_2Max) assessed by a bicycle ergometer, leisure-time physical activity and other conventional risk factors. These results suggest that in healthy subjects, elevated resting heart rate is not merely a marker of poor general fitness but an independent risk factor.

Contributors All authors have substantially contributed to the manuscript in terms of conception and design, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version.

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Competing interest None.

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Heart rate at discharge and long-term prognosis following percutaneous coronary intervention in stable and acute coronary syndromes — results from the BASKET PROVE trial☆,☆☆

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ABSTRACT

Background: Elevated heart rate (HR) is associated with mortality in a number of heart diseases. We examined the long-term prognostic significance of HR at discharge in a contemporary population of patients with stable angina (SAP), non-ST-segment elevation acute coronary syndromes (NSTE-ACS), and ST-segment elevation myocardial infarction (STEMI) revascularized with percutaneous coronary intervention (PCI).
Methods: Patients from the BASKET-PROVE trial, an 11-center randomized all-comers trial comparing bare-metal and drug-eluting stenting in large coronary vessels, were included. Discharge HR was determined from a resting ECG. Long-term outcomes (7 days to 2 years) were evaluated for all-cause mortality and cardiovascular death and non-fatal myocardial infarction.
Results: A total of 2029 patients with sinus rhythm were included, 722 (35.6%) SAP, 647 (31.9%) NSTE-ACS, and 660 (32.5%) STEMI. Elevated discharge HR was associated significantly with all-cause mortality: when compared to a reference of <60 beats per minute (bpm), the adjusted hazard ratios were (95% CI) 4.5 (1.5–13.5, $p = 0.006$) for 60–69 bpm, 3.8 (1.2–11.9, $p = 0.022$) for 70–79 bpm, 4.3 (1.2–15.6, $p = 0.025$) for 80–89 bpm, and 16.9 (5.2–55.0, $p < 0.001$) for >90 bpm. For cardiovascular death/myocardial infarction, a discharge HR >90 bpm was associated with a hazard ratio of 6.2 (2.5–15.5, $p < 0.001$) compared to a HR <60 bpm. No interaction was found for disease presentation, diabetes or betablocker use.
Conclusion: In patients revascularized with PCI for stable angina or acute coronary syndromes an elevated discharge HR was independently associated with poor prognosis. Conversely, a HR <60 bpm at discharge was associated with a good long-term prognosis irrespective of indication for PCI.

1. Introduction

Elevated heart rate has been shown to be a risk factor for mortality in both healthy subjects [1–6] and in patients with cardiovascular and pulmonary disease [7–9]. However, the relationship between heart rate and mortality in a contemporary "all-comer" population with both stable and acute coronary syndromes treated with percutaneous coronary intervention (PCI) remains undetermined.

Heart rate is a fundamental physiological parameter, and can easily be assessed in the clinical setting. In a study including patients across large registries and randomized clinical trials between 1975 and 1979 Diaz et al. [10] demonstrated how elevated heart rate at

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rest was predictive of long-term adverse outcomes. Also, in subjects with stable coronary artery disease and left ventricular dysfunction heart rate has been shown to be predictive of mortality [7]. In a more recent study, it was demonstrated that ST-segment elevation myocardial infarction (STEMI) patients with a high discharge heart rate were of increased risk of both cardiovascular and all-cause mortality following primary PCI [11]. However, the prognostic significance of heart rate in a contemporary population undergoing PCI for stable angina pectoris (SAP), non-ST-segment elevation acute coronary syndromes (NSTE-ACS) and ST-elevation myocardial infarction (STEMI) is undetermined. We studied the relationship between heart rate after treatment with PCI and risk of death or cardiovascular death and non-fatal myocardial infarction in patients from the randomized BASKET PROVE trial [12].

2. Methods

2.1. Study population

BASKET-PROVE was a multicenter randomized investigator-driven clinical trial of 1st generation sirolimus-eluting stent (Cypher Select®, Cordis), a bare-metal (cobalt–chromium) stent (Vision®, Abbott Vascular), versus a 2nd generation everolimus-eluting stent (Xience V®, Abbott Vascular). Financial support was given by the Basel Cardiovascular Research Foundation, the Swiss National Foundation for Research and the Swiss Heart Foundation. Patients were included at 11 participating centers in Switzerland, Denmark, Austria and Italy between March 5, 2007, and May 15, 2008. Patients were all-comers with stable or acute coronary heart disease (categorized as SAP, NSTE-ACS, or STEMI) treated with PCI and in need of stenting in vessels ≥3.0 mm in diameter. Exclusion criteria were cardiogenic shock, in-stent restenosis, stent thrombosis, unprotected left main coronary disease, planned surgery within 12 months, a need for oral anticoagulation, increased risk of bleeding, and suspected non-compliance with long-term antiplatelet therapy. The protocol was approved by the ethics committee at each center and each patient gave written informed consent. The study design of BASKET-PROVE has previously been described in detail [12].

2.2. Follow-up

Clinical follow-up was performed at 24 months. Follow-up angiography and revascularization were performed only if clinically indicated. Data on all patients were collected by local investigators, recorded on electronic case report forms, and transmitted over the Internet to a central database at the University of Basel. A central monitoring team verified all submitted information.

2.3. Patients

2314 patients were included in the BASKET PROVE trial, hereof, 738 STEMI patients, 754 NSTE-ACS, and 822 with stable angina pectoris. In the present study, heart rate was determined as the latest ECG recording before discharge or an event; in few cases heart rate and rhythm was determined from a printout of the cardiac telemetry. In all cases, rate and rhythm was determined by a medical professional at each of the 11 participating centers. Heart rate was available in 2086 patients. In the present study subjects with absence of sinus rhythm or presence of implantable devices were excluded (n = 25). Also, subjects dying or lost to follow-up within the first 7 days were excluded (n = 38), leaving 2029 patients for the present analysis.

2.4. Main outcomes

The main outcomes were all-cause mortality and a composite endpoint of cardiovascular death and non-fatal myocardial infarction, as defined in the original BASKET PROVE trial [12]. Follow-up was determined as 7 days to 2 years of follow-up thereby excluding the possibility of acute disease affecting the association between heart rate at discharge and long-term outcome.

2.5. Statistics

All analyses were performed with STATA 12.1 (STATACorp LP, TX USA). For baseline demographics the population was divided into clinically meaningful categories of discharge heart rate; categorical variables were analyzed with the χ^2-test and continuous variables with ANOVA. The association between heart rate and outcome was analyzed in Cox proportional hazards models, and the proportional hazards assumption was tested using log–log Kaplan–Meier- and Cox adjusted survival estimates plotted against time. The proportionality assumption was found to be met when analyzing discharge heart rate and outcome for the patients surviving the first week of inclusion. Significant predictors were included in the multivariate models and a backward elimination analysis with a significance level of 0.1 was performed to test the variables in the final model. These predictors were age, sex, heart failure at admission, indication for PCI (SAP, NSTE-ACS, and STEMI), and use of angiotensin-converting-enzyme (ACE)-inhibitors or angiotensin II receptor blockers (ARBs) at discharge. Relevant analyses for interaction were performed before inclusion in the models. There was no interaction between heart rate, indication for PCI and events which allowed for combining all three groups for analyses. The association between heart rate and the primary endpoints was analyzed and reported in models with heart rate as a categorical variable (<60, 60–69, 70–79, 80–89, >90 bpm), and as a continuous variable. A p-value <0.05 was considered statistically significant.

3. Results

2029 patients with sinus rhythm at discharge were included in the present study. Indication for PCI was in 722 (35.6%) SAP, 647 (31.9%) NSTE-ACS, and 660 (32.5%) STEMI.

Baseline demographics are shown in Table 1. Subjects with elevated discharge heart rates were more likely to have diabetes, have hypertension, and to have been treated for STEMI. There was no difference in presence of clinically diagnosed heart failure at admission or diseased LAD, whereas subjects who previously had undergone revascularization were more prevalent in the lowest heart rate categories.

There was no difference in the use of discharge medications, particularly betablocker therapy, between heart rate categories, except for the use of ACE-inhibitors or ARBs which was more prevalent in the high heart rate categories, see Table 2.

Table 1
Demographics. bpm: beats per minute.

	<60 bpm	60–69 bpm	70–79 bpm	80–89 bpm	>90	p
No. (%)	564 (27.8%)	689 (34.0%)	463 (22.8%)	215 (10.6%)	98 (4.8%)	
Age, mean (SD)	63.0 (10.6)	62.5 (10.4)	63.3 (11.0)	63.8 (11.4)	63.7 (10.7)	0.52
Male, no. (%)	481 (85.3%)	531 (77.2)	315 (68.0%)	144 (67.0%)	74 (76.0%)	<0.001
Indication for PCI:						<0.001
Stable angina, no. (%)	238 (42.2%)	263 (38.2%)	136 (29.4%)	61 (28.4%)	24 (24.5%)	
NSTEMI/UAP, no. (%)	181 (32.1%)	221 (32.1%)	153 (33.1%)	64 (29.8%)	28 (28.6%)	
STEMI, no. (%)	145 (25.7)	205 (29.8%)	174 (37.6%)	90 (41.9%)	46 (46.9%)	
Diabetes, no. (%)	67 (11.9%)	99 (14.4%)	83 (17.9%)	39 (18.1%)	26 (26.5%)	0.001
Hypertension, no. (%)	319 (56.6%)	435 (63.1%)	298 (64.4%)	139 (64.7%)	70 (71.4%)	0.012
Smoking:						0.96
Never, no. (%)	205 (36.4%)	257 (37.3%)	161 (34.8%)	80 (37.2%)	37 (37.8%)	
Former, no. (%)	182 (32.3%)	205 (29.8%)	143 (30.9%)	61 (28.4%)	29 (29.6%)	
Current, no. (%)	177 (31.4%)	227 (33.0%)	159 (34.3%)	74 (34.4%)	32 (32.7%)	
Left anterior descending disease, no. (%)	356 (63.1%)	448 (65.0%)	298 (64.4%)	150 (69.8%)	65 (66.3%)	0.53
Left circumflex disease, no. (%)	205 (36.4%)	250 (36.3%)	183 (39.5%)	67 (31.2%)	41 (41.8%)	0.23
Right coronary disease, no. (%)	298 (52.8%)	357 (51.8%)	252 (54.4%)	109 (50.7%)	45 (45.9%)	0.59
Heart failure, no. (%)	21 (3.7%)	34 (4.9%)	25 (5.4%)	10 (4.7%)	7 (7.3%)	0.55
Prev. revasc., no. (%)	93 (16.5%)	100 (14.5%)	54 (11.7%)	16 (7.4%)	7 (7.1%)	0.003

Table 2
Discharge medication according to heart rate.

	<60 bpm	60–69 bpm	70–79 bpm	80–89 bpm	>90	p
Betablockers, no. (%)	441 (79.5%)	538 (79.1%)	359 (78.9%)	156 (73.9%)	76 (78.4%)	0.54
Calcium inhib, no. (%)	76 (13.5%)	82 (11.9%)	49 (10.6%)	28 (13.0%)	6 (6.1%)	0.24
ACE-inhib/ARB, no. (%)	295 (52.3%)	412 (59.9%)	312 (67.4%)	150 (69.8%)	77 (78.6%)	<0.001
Statins, no. (%)	520 (93.0%)	648 (94.5%)	438 (94.8%)	198 (93.0%)	90 (93.8%)	0.71
ASA, no. (%)	562 (99.7%)	688 (99.6)	462 (99.8%)	215 (100%)	98 (100%)	0.84
Clopidogrel, no. (%)	564 (100%)	688 (99.9)	463 (100%)	215 (100%)	98 (100%)	0.75
Nitroglycerine, no. (%)	51 (9.1%)	51 (7.5%)	31 (6.7%)	8 (3.7%)	7 (7.1%)	0.14

3.1. Heart rate and all-cause mortality

The association between discharge heart rate and mortality is shown in Fig. 1. Elevated heart rate was highly predictive of mortality (log rank, $p < 0.001$).

In a multivariate model, adjusted for age, sex, heart failure at admission, indication for PCI, and use of ACE-inhibitors or ARBs at discharge, a heart rate above 90 bpm compared to the reference value of 60 bpm was significantly and independently associated with increased long-term mortality, see Table 3.

There was a graded increase in mortality with increased heart rate; patients with a heart rate between 60 bpm and 89 bpm had a 4-fold increase in mortality compared to patients in the lowest heart rate category (<60 bpm). Patients discharged with a heart rate above 90 bpm had a 17-fold increase in mortality compared to patients below 60 bpm (Table 3). In a sensitivity analysis, the risk associated with heart rate above 90 bpm was 4.0 (1.8–8.2, $p < 0.001$) when using the 60–89 bpm groups as reference (not shown in table).

With heart rate as a continuous variable all-cause mortality increased 4.1% ($p < 0.001$) pr. every 1 bpm increase in heart rate after multivariate adjustments.

3.2. Heart rate and cardiovascular death and non-fatal myocardial infarction

The association between heart rate and cardiovascular death and non-fatal myocardial infarction is shown in Fig. 2, (log rank, $p < 0.001$).

Patients discharged with a heart rate above 90 bpm had a 6-fold increase in risk of cardiovascular death and non-fatal myocardial infarction after adjusting for age, sex, heart failure at admission, indication for PCI, and use of ACE-inhibitors or ARBs at discharge when compared to patients in the lowest heart rate category, see Table 4.

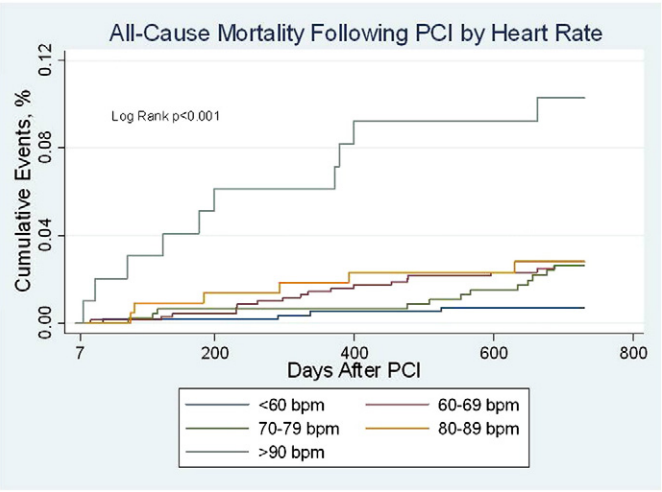

Fig. 1. Heart rate and all-cause mortality. Discharge heart rate is associated with long-term mortality following PCI. Patients with events or lost to follow-up within 7 days of follow-up were excluded.

Heart rates from below 90 bpm were not predictive of the long-term outcome of cardiovascular death and myocardial infarction. With heart rate as a continuous variable, the risk of cardiovascular death and myocardial infarction increased with 2.9% pr. every 1 bpm increase in heart rate.

Additional analyses for interaction were performed; there was no interaction between heart rate at discharge, outcomes, and use of betablockers, or between heart rate at discharge, outcomes, and diabetes (all $p > 0.05$).

4. Discussion

In a contemporary population of patients with both stable and acute coronary disease who have been revascularized with PCI, the current study demonstrates that elevated heart rate is an independent and graded predictor of long-term prognosis. Hence, patients discharged with a heart rate above 90 bpm had an almost 17-fold increase in risk for mortality during two years of follow-up, and patients with a heart rate between 60–89 bpm had a 4-fold increase in mortality compared to patients with heart rate below 60 bpm. For every bpm increase in heart rate, the long-term risk of mortality increased with 4%. For cardiovascular death and non-fatal myocardial infarction, the risk of events was 6-times greater in patients with a heart rate above 90 bpm compared to patients with lower heart rates, and a 1 bpm increase in heart rate conveyed an increase in risk of almost 3%.

Heart rate as a prognostic marker and potential modifiable risk factor has received much attention in recent years [7,13–15]; heart rate is a physiological, fundamental, and prognostic parameter that is very easy to measure and monitor, and may be subject to therapeutic intervention in coronary artery disease [7].

Heart rate has been shown to be associated with adverse outcomes in different populations with confirmed or suspected coronary artery disease [11,16–20] However, our study is the first to investigate the relationship between heart rate at discharge and long-term outcome in a contemporary population of patients undergoing percutaneous coronary revascularization therapy for stable coronary artery disease as well as ACS (NSTE-ACS and STEMI). In terms of clinical application, our study suggests, that patients discharged with an elevated heart rate following PCI for any indication should receive special attention, and heart rate may be considered a possible therapeutic target following discharge and during cardiac rehabilitation.

In terms of all-cause mortality, a discharge heart rate below 60 bpm was associated with a low event rate (0.7%) and with a good prognosis irrespective of indication, whereas a heart rate of more than 90 bpm was associated with a much higher event rate (10.2%) and a poor prognosis. It is worth noticing, that being discharged with a heart rate below 60 bpm or above 90 bpm is by no means a rare case but represents 27.8% and 4.8% of the population, respectively. Interestingly, none of the 145 STEMI patients with a heart rate below 60 bpm, comprising 22% of the STEMI population, died during the 7 days to 2 years follow-up period.

In this context and in terms of information to patients following PCI, it is therefore just as important to note, that whereas an elevated heart rate is a marker of poor prognosis and increased risk of mortality, a low heart rate at discharge is an indicator of a very good prognosis.

Table 3
Heart rate and all-cause mortality. Hazard ratios and 95% confidence intervals. There is an increased risk of mortality with an increase in discharge heart rate.

All-cause mortality from 7 days to 2 years			
Heart rate/bpm	No. patients	Adjusted hazard ratio[a] (95% CI)	p-Value
<60 bpm	564	1[b]	
60–69 bpm	689	4.5 (1.5–13.5)	0.006
70–79 bpm	463	3.8 (1.2–11.9)	0.022
80–89 bpm	215	4.3 (1.2–15.6)	0.025
>90 bpm	98	16.9 (5.2–55.0)	<0.001
Heart rate increase by 1 bpm	2029	1.041 (1.020–1.063)	<0.001

[a] Adjusted for age, sex, heart failure at admission, indication for PCI, and use of ACE-inhibitors/ARBs at discharge.
[b] Reference.

Table 4
Heart Rate and Cardiovascular Death and Non-Fatal Myocardial Infarction. There is an increased risk of cardiovascular events with an increase in discharge heart rate.

Cardiovascular death and non-fatal myocardial infarction from 7 days to 2 years			
Heart rate/bpm	No. patients	Adjusted hazard ratio[a] (95% CI)	p-Value
<60 bpm	564	1[b]	
60–69 bpm	689	1.4 (0.6–3.0)	0.45
70–79 bpm	463	1.2 (0.5–3.0)	0.69
80–89 bpm	215	0.9 (0.2–3.4)	0.89
>90	98	6.2 (2.5–15.5)	<0.001
Heart rate increase by 1 bpm	2029	1.029 (1.0–1.05)	0.011

[a] Adjusted for age, sex, heart failure at admission, indication for PCI, and use of ACE-inhibitors/ARBs at discharge.
[b] Reference.

The mechanisms explaining the deleterious effects of elevated heart rate may be through an increase in myocardial oxygen consumption [21], increased formation of atherosclerosis and risk of plaque rupture [22] and increase in the risk of ventricular arrhythmias [23]. Also, diastolic filling and distal coronary perfusion can be compromised by increased heart rate [8]. Patients with diabetes may be particularly likely to have high heart rates as a result of autonomic neuropathy, however no interaction was found between diabetes, heart rate and outcome, suggesting that a high or low heart rate in subjects with diabetes confers the same risk as in nondiabetic patients. Also, it is interesting that no interaction was found between the use of betablockers at discharge, heart rate and outcome, since this indicates, that prognosis is just as good whether heart rate is therapeutically lowered with betablockers or if heart rate is physiologically low. It is therefore possible that discharge heart rate should be a target for therapeutic intervention following PCI — be it through cardiac rehabilitation [24], sinus node inhibition [25], increased use of betablockers, or other forms of heart rate modification. However, studies specifically investigating heart rate modification in this group of patients are needed.

4.1. Limitations

A potential limitation is the relative low number of events in the BASKET PROVE trial as seen in this contemporary "all-comer" trial. In spite of this, heart rate at discharge was a highly significant predictor of mortality even after multivariate adjustments. In the present trial, there was no information on angiographically determined LVEF in all patients, however, our multivariate analysis included information about known heart failure at admission and use of ACE-inhibitors or ARBs at discharge as a proxy for heart failure at discharge and these factors did not change the association between elevated heart rate and events. Furthermore, patients in cardiogenic shock were excluded from the BASKET-PROVE trial, and patients dying or lost to follow-up within the first 7 days were excluded in order to minimize the possibility that acute mortality could affect the relationship between elevated heart rate and long-term prognosis. Although confounding can never be excluded from an observational study our results therefore suggest that elevated heart rate at discharge is an independent risk factor for long-term mortality and cardiovascular events. Other limitations relate to the subgroup of disease presentation which has to be interpreted with appropriate caution.

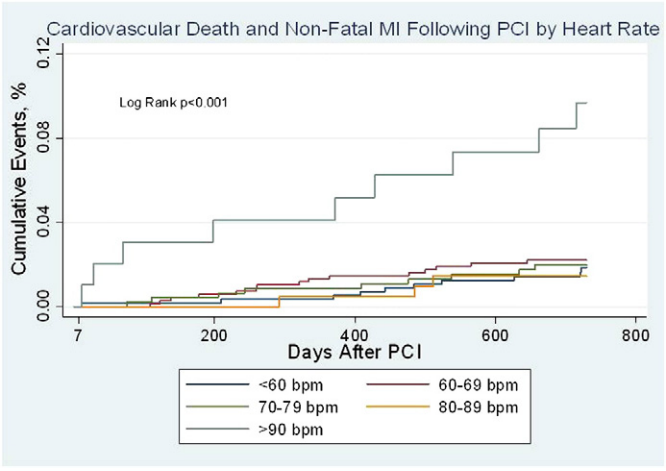

Fig. 2. Heart rate and cardiovascular death and non-fatal myocardial infarction. Discharge heart rate is associated with long-term cardiovascular events following PCI. Patients with events or lost to follow-up within 7 days of follow-up were excluded.

5. Conclusion

Elevated heart rate at discharge was associated with long-term all-cause mortality as well as cardiovascular deaths and non-fatal myocardial infarction in "all-comer" patients undergoing PCI irrespective of disease presentation, i.e. stable angina pectoris, NSTE-ACS, and STEMI. Thus, all-cause mortality was increased 17-fold in patients with a discharge heart rate above 90 bpm compared to patients with a heart rate below 60 bpm and risk of mortality increased 4% for every 1 bpm increase in heart rate. A discharge heart rate below 60 bpm was associated with a very good long-term prognosis following PCI irrespective of indication. Therefore, elevated discharge heart rate following PCI is an easily accessible independent risk factor for adverse events that should be assessed, and possibly modified.

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Heart rate at admission is a predictor of in-hospital mortality in patients with acute coronary syndromes: Results from 58 European hospitals: The European Hospital Benchmarking by Outcomes in acute coronary syndrome Processes study

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Abstract

Aims: The purpose of this study was to investigate the relationship between heart rate at admission and in-hospital mortality in patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS).

Methods: Consecutive ACS patients admitted in 2008–2010 across 58 hospitals in six participant countries of the European Hospital Benchmarking by Outcomes in ACS Processes (EURHOBOP) project (Finland, France, Germany, Greece, Portugal and Spain). Cardiogenic shock patients were excluded. Associations between heart rate at admission in categories of 10 beats per min (bpm) and in-hospital mortality were estimated by logistic regression in crude models and adjusting for age, sex, obesity, smoking, hypertension, diabetes, known heart failure, renal failure, previous stroke and ischaemic heart disease. In total 10,374 patients were included.

Results: In both STEMI and NSTE-ACS patients, a U-shaped relationship between admission heart rate and in-hospital mortality was found. The lowest risk was observed for heart rates between 70–79 bpm in STEMI and 60–69 bpm in NSTE-ACS; risk of mortality progressively increased with lower or higher heart rates. In multivariable models, the relationship persisted but was significant only for heart rates >80 bpm. A similar relationship was present in both patients with or without diabetes, above or below age 75 years, and irrespective of the presence of atrial fibrillation or use of beta-blockers.

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Conclusion: Heart rate at admission is significantly associated with in-hospital mortality in patients with both STEMI and NSTE-ACS. ACS patients with admission heart rate above 80 bpm are at highest risk of in-hospital mortality.

Keywords
Heart rate, acute coronary syndrome, non-ST-segment elevation acute coronary syndrome, ST-segment elevation myocardial infarction, mortality

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Introduction

Heart rate is a basic vital parameter which is assessed at admission in every patient admitted with an acute coronary syndrome (ACS).

Heart rate at rest has been shown to be predictive of adverse outcomes in both general populations[1–3] and patient populations[4–6] across several prognostic studies, and heart rate at discharge has been shown to be a predictor of long-term outcomes in patients with coronary artery disease.[7,8]

In the acute setting, admission heart rate has been shown to be predictive of mortality across several previous studies; in the US Global Registry of Acute Coronary Events (GRACE) registry,[9] admission heart rate was shown to be one of the eight most important predictors of in-hospital mortality, and in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) population of US patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS)[10] there was also an association between heart rate and prognosis.

Nonetheless, data on the association between admission heart rate and outcome in a contemporary population of patients with both NSTE-ACS and ST-segment elevation myocardial infarction (STEMI) admitted to European hospitals is scarce.

In the present study we therefore examined the relationship between heart rate at admission and in-hospital mortality in patients with ACS admitted across the 58 hospitals from six participant countries of the European Hospital Benchmarking by Outcomes in ACS Processes (EURHOBOP) collaboration.

Methods

The EURHOBOP project is a collaborative, multicentre and multinational retrospective study of patients hospitalised with a final diagnosis of ACS, consecutively discharged from 70 hospitals in seven Western European countries (Finland, France, Germany, Greece, Italy, Portugal and Spain) between 2008–2010. The study has previously been described.[11] In brief, in each country, 8–10 centres selected to represent the distribution of university, regional and private hospitals within the country's healthcare system were included. Each centre contributed to the study with at least 200 consecutive patients. The inclusion criteria were a discharge diagnosis of myocardial infarction, with or without ST-segment elevation, or unstable angina (International Classification of Diseases, 10th revision: I21.0–I21.9 and I20.0). The current analysis only considers data from six European countries (Finland, France, Germany, Greece, Portugal and Spain) including 58 hospitals. Italian patients were excluded due to the lack of information on heart rate at admission.

Patient and hospital data were collected by trained medical record extractors using a standardised data collection form. To ensure quality of data collection all investigators underwent specific training. The main source of information was the discharge letter, however information on emergency room records and laboratory information systems was also accessed, whenever available. For each case, the investigators collected demographic, clinical, biological and electrocardiographic data from the medical records. The study protocol, including a detailed description of variable collection and definitions, is available at http://www.eurhobop.eu/files/EURHOBOP%20Data%20Extraction%20Procedures%20FINAL.pdf.

Data analysis

The type of ACS was defined according to electrocardiogram (ECG) findings at admission in agreement with current European guidelines.[12,13] Patients who were not classifiable into type of ACS or with missing data on that variable were excluded from the analysis. The outcome of interest was defined as death of any cause during hospitalisation. Heart rate at admission was extracted from the files as a continuous variable and categorised into 10-beat wide intervals. Patients with cardiogenic shock were excluded.[10]

To compare socio-demographic characteristics, invasive procedures during hospitalisation and outcomes with respect to different heart rate categories, Kruskal-Wallis tests and Pearson chi-square tests were used for continuous variables and categorical variables, respectively.

Unconditional logistic regression was used to estimate the odds ratios (ORs) for the association between in-hospital mortality and heart rate. In addition to the crude OR, we computed OR adjusting for age, sex and prior clinical history

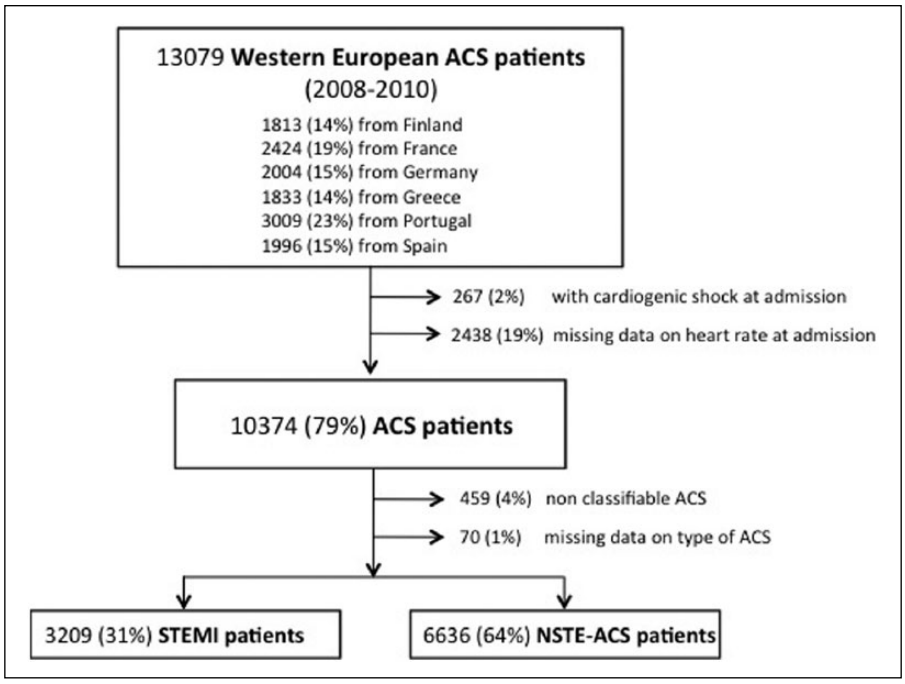


Figure 1. Flowchart illustrating the sample selection for the present analysis, by type of acute coronary syndrome (ACS). NSTE-ACS: non-ST-segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction.

of obesity, smoking, diabetes, coronary heart disease, known heart failure, stroke and renal failure. Please consult the Supplementary Material data for detailed description of statistics. A p-value<0.05 was considered statistically significant.

Ethics

The study was approved by the Internal Review Boards of the institutions enrolled.

Results

Sample characteristics

A total of 10,374 ACS patients without cardiogenic shock at admission and with information about heart rate at admission were included, 3209 (31%) STEMI patients, 6636 (64%) NSTE-ACS patients, and 529 with non-classifiable ACS or with missing data on the type of ACS (Figure 1). Overall, the median length of hospitalisation was six days (interquartile range (IQR) 3–8): six days (IQR 4–8) in STEMI patients and five days (IQR 3–8) in NSTE-ACS. A total of 199 (6.2%) of the STEMI patients and 175 (2.6%) of the NSTE-ACS patients died during the index hospitalisation.

In the STEMI population, patients with the lowest and highest heart rates were slightly older and with a higher proportion of women compared to patients in the intermediate heart rate categories. The same pattern was observed for diabetes, known heart failure, previous stroke and renal failure. There was no association between admission heart rate and obesity, hypertension, or previous Coronary artery disease (CAD) in STEMI patients. Details for admission data, procedures, and outcomes in STEMI patients are available in Table 1.

In the NSTE-ACS population, patients in the lower or higher heart rate categories tended to be older; there were relatively more women in the higher heart rate categories. In terms of comorbidities NSTE-ACS patients with CAD tended to have lower heart rates, whereas known heart failure was more frequent in patients with higher admission heart rates. Stroke and renal failure were more prevalent in the higher heart rate categories. There were no differences between admission heart rate and obesity, hypertension, and smoking. Details of admission data, procedures and outcomes in NSTE-ACS patients are available in Table 2.

Admission heart rate and in-hospital mortality

STEMI. The association between admission heart rate and mortality in STEMI patients is displayed in Figure 2. As shown, there was a U-shaped relationship between admission heart rate and in-hospital mortality; in STEMI patients, heart rates between 70–79 bpm were associated with the lowest risk. Heart rate <40 bpm was associated with a 4.3-fold increased risk and admission heart rate categories >80 bpm with a 2.2 to 5.3-fold increased risk of mortality. In the adjusted model the U-shape persisted, although only heart rates >80 bpm remained significantly associated with increased risk compared to the reference group.

Table 1. Socio-demographic, prior clinical history, admission data, invasive procedures and outcomes during hospitalisation in the ST-segment elevation myocardial infarction (STEMI) patients of the European Hospital Benchmarking by Outcomes in ACS Processes (EURHOBOP) cohort by admission heart rate.

	All patients	Admission heart rate (bpm)										
	n (%)	<40 *n* (%)	40–49 *n* (%)	50–59 *n* (%)	60–69 *n* (%)	70–79 *n* (%)	80–89 *n* (%)	90–99 *n* (%)	100–109 *n* (%)	110–119 *n* (%)	⩾120 *n* (%)	*p*-value
STEMI patients	*n*=3209	*n*=31	*n*=127	*n*=313	*n*=638	*n*=720	*n*=632	*n*=335	*n*=203	*n*=91	*n*=119	
Age (years)	64.8±13.8[a]	71.2±12.3[a]	65.6±13.4[a]	64.8±12.8[a]	63.2±13.8[a]	63.2±13.4[a]	64.7±13.8[a]	63.7±13.6[a]	66.0±14.1[a]	65.8±14.9[a]	68.8±14.0[a]	<0.001
Male sex	2364 (73.7)	20 (64.5)	88 (69.3)	240 (76.7)	495 (77.6)	532 (73.9)	469 (74.2)	244 (72.8)	132 (65.0)	63 (69.2)	81 (68.1)	0.018
Prior clinical history												
Obesity	553 (17.2)	6 (19.4)	14 (11.0)	46 (14.7)	104 (16.3)	128 (17.8)	120 (19.0)	58 (17.3)	48 (23.6)	10 (11.0)	19 (16.0)	0.083
Diabetes mellitus	702 (21.9)	16 (51.6)	23 (18.1)	45 (14.4)	104 (16.3)	145 (20.1)	141 (22.3)	94 (28.1)	62 (30.5)	34 (37.4)	38 (31.9)	<0.001
Hypertension	1724 (53.7)	15 (48.4)	66 (52.0)	157 (50.2)	328 (51.4)	394 (54.7)	343 (54.3)	181 (54.0)	117 (57.6)	59 (64.8)	64 (53.8)	0.381
Current smoking	1252 (39.0)	9 (29.0)	49 (38.6)	125 (39.9)	256 (40.1)	313 (43.5)	236 (37.3)	139 (41.5)	64 (31.5)	31 (34.1)	30 (25.2)	0.003
Coronary heart disease[b]	490 (15.3)	8 (25.8)	18 (14.2)	56 (17.9)	106 (16.6)	102 (14.2)	93 (14.7)	43 (12.8)	29 (14.3)	18 (19.8)	17 (14.3)	0.404
Heart failure	96 (3.0)	2 (6.4)	1 (0.8)	6 (1.9)	8 (1.2)	19 (2.6)	19 (3.0)	12 (3.6)	16 (7.9)	5 (5.5)	8 (6.7)	<0.001
Stroke	130 (4.0)	2 (6.4)	4 (3.2)	9 (2.9)	16 (2.5)	32 (4.4)	21 (3.3)	16 (4.8)	9 (4.4)	9 (9.9)	12 (10.1)	0.002
Renal failure	318 (9.9)	12 (38.7)	16 (12.6)	27 (8.6)	49 (7.7)	53 (7.4)	52 (8.2)	35 (10.4)	37 (18.2)	17 (18.7)	20 (16.8)	<0.001
Admission data												
Acute pulmonary oedema	101 (3.2)	1 (3.2)	2 (1.6)	1 (0.3)	3 (0.5)	15 (2.1)	17 (2.7)	17 (5.1)	16 (7.9)	16 (17.6)	13 (10.9)	<0.001
Systolic blood pressure (mm Hg)	133.7±27.8[a]	103.4±34.0[a]	120.1±26.2[a]	127.8±26.6[a]	132.9±25.6[a]	134.0±25.4[a]	135.4±25.1[a]	137.0±27.2[a]	140.6±30.3[a]	134.0±30.8[a]	128.2±35.7[a]	<0.001
Initial creatinine (mg/dl)	1.00 (0.80–1.20)[c]	1.46 (1.00–2.00)[c]	1.00 (0.85–1.30)[c]	1.00 (0.82–1.20)[c]	0.99 (0.80–1.17)[c]	0.96 (0.80–1.12)[c]	0.99 (0.80–1.16)[c]	1.00 (0.87–1.20)[c]	1.00 (0.84–1.20)[c]	1.08 (0.90–1.39)[c]	1.10 (0.80–1.37)[c]	<0.001
Initial haemoglobin (g/dl)	13.9 (12.6–15.0)[c]	12.5 (10.9–13.9)[c]	13.7 (12.4–14.9)[c]	13.9 (12.8–14.9)[c]	13.9 (12.6–14.9)[c]	14.1 (12.7–15.1)[c]	14.0 (12.5–15.2)[c]	14.0 (12.8–15.2)[c]	13.8 (12.3–14.9)[c]	13.9 (12.8–14.9)[c]	13.9 (12.5–15.1)[c]	0.017
Invasive procedures during hospitalisation												
Coronary angiography	2725 (84.9)	24 (77.4)	110 (86.6)	270 (86.3)	554 (86.8)	638 (88.6)	536 (84.8)	278 (83.0)	160 (78.8)	68 (74.7)	87 (73.1)	<0.001
Percutaneous coronary intervention	2372 (73.9)	22 (71.0)	105 (82.7)	240 (76.7)	477 (74.8)	558 (77.5)	463 (73.3)	250 (74.6)	129 (63.6)	58 (63.7)	70 (58.8)	<0.001
Thrombolysis	707 (22.0)	5 (16.1)	27 (21.3)	83 (26.5)	138 (21.6)	164 (22.8)	150 (23.7)	69 (20.6)	36 (17.7)	15 (16.5)	20 (16.8)	0.225
Coronary artery bypass grafting	71 (2.2)	0 (0.0)	1 (0.8)	3 (1.0)	12 (1.9)	21 (2.9)	16 (2.5)	8 (2.4)	4 (2.0)	3 (3.3)	3 (2.5)	0.628
Hospital outcomes												
Days of hospitalisation	6 (4–8)[c]	6 (3–9)[c]	5 (4–8)[c]	5 (4–7)[c]	5 (3–8)[c]	15 (4–7)[c]	6 (3–8)[c]	6 (4–9)[c]	6 (4–9)[c]	7 (4–10)[c]	6 (3–10)[c]	0.005
Mortality	199 (6.2)	4 (12.9)	7 (5.5)	16 (5.1)	25 (3.3)	24 (3.3)	44 (7.0)	25 (7.5)	25 (12.3)	14 (15.4)	15 (12.6)	<0.001

ACS: acute coronary syndrome; bpm: beats per min.

[a]Mean±standard variation.

[b]Previous history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting.

[c]Median (interquartile range).

Table 2. Socio-demographic, prior clinical history, admission data, invasive procedures and outcomes during hospitalisation in the non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients of the European Hospital Benchmarking by Outcomes in ACS Processes (EURHOBOP) cohort by admission heart rate.

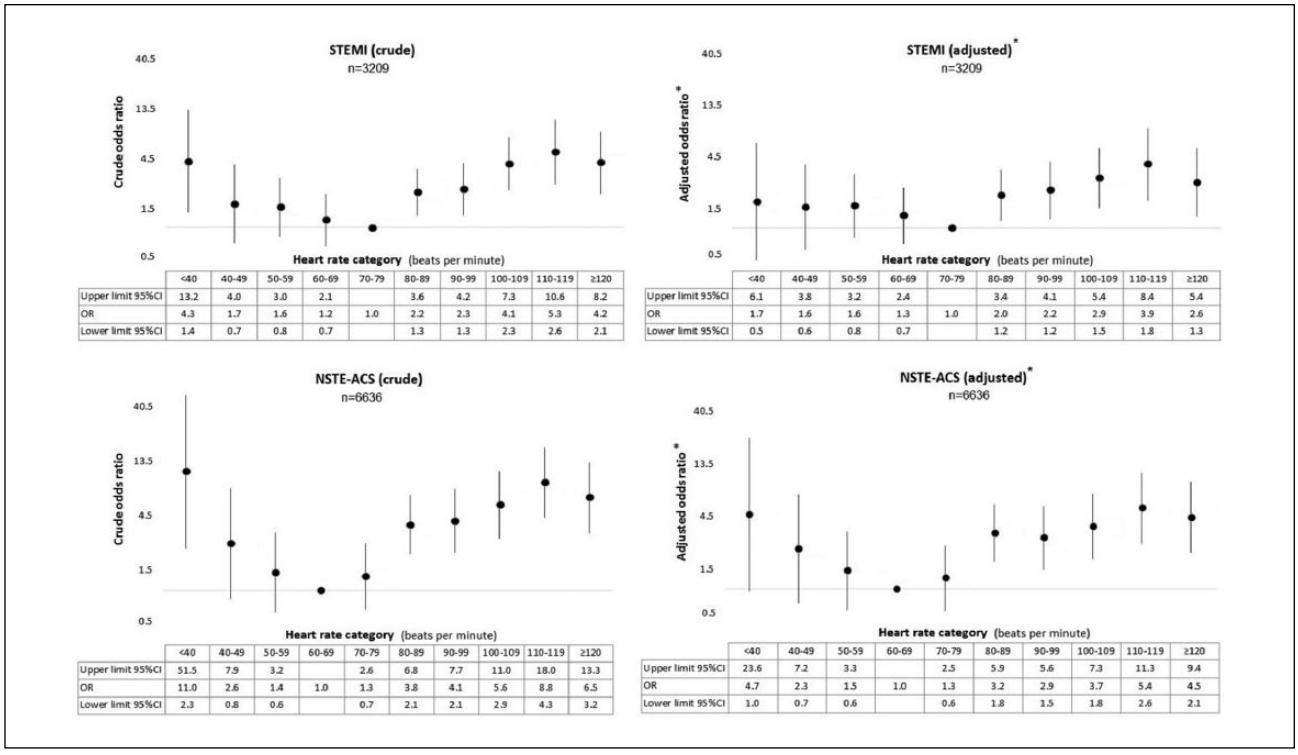
	All patients	Admission heart rate (bpm)										
	n (%)	<40 *n* (%)	40–49 *n* (%)	50–59 *n* (%)	60–69 *n* (%)	70–79 *n* (%)	80–89 *n* (%)	90–99 *n* (%)	100–109 *n* (%)	110–119 n (%)	⩾120 *n* (%)	*p*-value
NSTE-ACS patients	(*n*=6636)	(*n*=20)	(*n*=157)	(*n*=695)	(*n*=1494)	(*n*=1585)	(*n*=1171)	(*n*=658)	(*n*=390)	(*n*=207)	(*n*=259)	
Age (years)	68.4±12.7[a]	75.4±12.4[a]	69.1±11.7[a]	67.3±11.7[a]	67.6±12.2[a]	67.4±12.6[a]	68.1±13.0[a]	69.1±13.4[a]	70.9±12.8[a]	70.6±12.2[a]	68.8±12.8[a]	<0.001
Male sex	4544 (68.5)	14 (70.0)	118 (75.2)	525 (75.5)	1096 (73.4)	1064 (67.1)	782 (66.8)	418 (63.5)	245 (62.8)	127 (61.4)	155 (59.8)	<0.001
Prior clinical history												
Obesity	1320 (19.9)	3 (15.0)	20 (12.7)	118 (17.0)	320 (21.4)	322 (20.3)	227 (19.4)	134 (20.4)	81 (20.8)	47 (22.7)	48 (18.5)	0.153
Diabetes mellitus	2072 (31.2)	4 (20.0)	36 (22.9)	158 (22.7)	415 (27.8)	469 (29.6)	384 (32.8)	252 (38.3)	164 (42.0)	89 (43.0)	101 (39.0)	<0.001
Hypertension	4430 (66.8)	14 (70.0)	95 (60.5)	434 (62.4)	1002 (67.1)	1055 (66.6)	781 (66.7)	458 (69.6)	276 (70.8)	144 (69.6)	171 (66.0)	0.096
Current smoking	1611 (24.3)	5 (25.0)	26 (16.6)	168 (24.2)	363 (24.3)	420 (26.5)	281 (24.0)	162 (24.6)	82 (21.0)	42 (20.2)	62 (23.9)	0.142
Coronary heart disease[b]	2575 (38.8)	4 (20.0)	71 (45.2)	323 (46.5)	644 (43.1)	589 (37.2)	433 (37.0)	193 (29.3)	142 (36.4)	75 (36.2)	101 (39.0)	<0.001
Heart failure	555 (8.4)	2 (10.0)	9 (5.7)	36 (5.2)	91 (6.1)	110 (6.9)	105 (9.0)	68 (10.3)	58 (14.9)	36 (17.4)	40 (15.4)	<0.001
Stroke	553 (8.3)	5 (25.0)	9 (5.7)	58 (8.4)	108 (7.2)	114 (7.2)	93 (7.9)	67 (10.2)	49 (12.6)	25 (12.1)	25 (9.6)	<0.001
Renal failure	1093 (16.5)	9 (45.0)	21 (13.4)	81 (11.6)	181 (12.1)	231 (14.6)	208 (17.8)	137 (20.8)	98 (25.1)	60 (29.0)	67 (25.9)	<0.001
Admission data												
Acute pulmonary oedema	379 (5.7)	3 (15.0)	6 (3.8)	11 (1.6)	30 (2.0)	51 (3.2)	62 (5.3)	65 (9.9)	50 (12.8)	42 (20.3)	59 (22.8)	<0.001
Systolic blood pressure (mm Hg)	140.9±27.2[a]	143.8±36.5[a]	135.8±26.6[a]	137.0±26.0[a]	140.9±24.5[a]	142.6±25.6[a]	141.4±26.2[a]	144.1±28.7[a]	140.3±29.2[a]	143.9±31.9[a]	135.3±37.1[a]	<0.001
Initial creatinine (mg/dl)	1.00 (0.86–1.29)[c]	1.21 (1.00–1.65)[c]	1.00 (0.83–1.30)[c]	1.00 (0.87–1.20)[c]	1.00 (0.84–1.20)[c]	1.00 (0.83–1.20)[c]	1.00 (0.85–1.30)[c]	1.03 (0.86–1.30)[c]	1.10 (0.87–1.40)[c]	1.13 (0.90–1.50)[c]	1.12 (0.94–1.50)[c]	<0.001
Initial haemoglobin (g/dl)	13.6 (12.1–14.8)[c]	12.4 (11.4–14.3)[c]	13.6 (12.4–14.6)[c]	13.8 (12.6–14.9)[c]	13.8 (12.5–14.8)[c]	13.6 (12.2–14.8)[c]	13.6 (12.0–14.8)[c]	13.3 (11.6–14.8)[c]	13.1 (11.5–14.6)[c]	12.8 (10.9–14.6)[c]	13.4 (12.2–14.9)[c]	<0.001
Invasive procedures during hospitalisation												
Coronary angiography	4824 (72.7)	15 (75.0)	117 (74.5)	558 (80.3)	1162 (77.8)	1201 (75.8)	839 (71.6)	427 (64.9)	232 (59.5)	120 (58.0)	153 (59.1)	<0.001
Percutaneous coronary intervention	3078 (46.4)	11 (55.0)	72 (45.9)	364 (52.4)	739 (49.5)	812 (51.2)	546 (46.6)	246 (37.4)	136 (34.9)	65 (31.4)	87 (33.6)	<0.001
Coronary artery bypass grafting	213 (3.2)	1 (5.0)	2 (1.3)	27 (3.9)	53 (3.6)	51 (3.2)	33 (2.8)	22 (3.3)	14 (3.6)	8 (3.9)	2 (0.8)	0.375
Hospital outcomes												
Days of hospitalisation	5 (3–8)[c]	7 (4–12)[c]	5 (3–7)[c]	4 (3–7)[c]	5 (3–7)[c]	5 (3–8)[c]	5 (3–8)[c]	6 (4–9)[c]	6 (4–10)[c]	7 (3–10)[c]	7 (4–10)[c]	<0.001
Mortality	175 (2.6)	2 (10.0)	4 (2.6)	10 (1.4)	15 (1.0)	21 (1.3)	43 (3.7)	26 (4.0)	21 (5.4)	17 (8.2)	16 (6.2)	<0.001

ACS: acute coronary syndrome; bpm: beats per min.

[a]Mean±standard variation.

[b]Previous history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting.

[c]Median (interquartile range).



STEMI (crude)	<40	40-49	50-59	60-69	70-79	80-89	90-99	100-109	110-119	≥120
Upper limit 95%CI	13.2	4.0	3.0	2.1		3.6	4.2	7.3	10.6	8.2
OR	4.3	1.7	1.6	1.2	1.0	2.2	2.3	4.1	5.3	4.2
Lower limit 95%CI	1.4	0.7	0.8	0.7		1.3	1.3	2.3	2.6	2.1

STEMI (adjusted)*	<40	40-49	50-59	60-69	70-79	80-89	90-99	100-109	110-119	≥120
Upper limit 95%CI	6.1	3.8	3.2	2.4		3.4	4.1	5.4	8.4	5.4
OR	1.7	1.6	1.6	1.3	1.0	2.0	2.2	2.9	3.9	2.6
Lower limit 95%CI	0.5	0.6	0.8	0.7		1.2	1.2	1.5	1.8	1.3

NSTE-ACS (crude)	<40	40-49	50-59	60-69	70-79	80-89	90-99	100-109	110-119	≥120
Upper limit 95%CI	51.5	7.9	3.2		2.6	6.8	7.7	11.0	18.0	13.3
OR	11.0	2.6	1.4	1.0	1.3	3.8	4.1	5.6	8.8	6.5
Lower limit 95%CI	2.3	0.8	0.6		0.7	2.1	2.1	2.9	4.3	3.2

NSTE-ACS (adjusted)*	<40	40-49	50-59	60-69	70-79	80-89	90-99	100-109	110-119	≥120
Upper limit 95%CI	23.6	7.2	3.3		2.5	5.9	5.6	7.3	11.3	9.4
OR	4.7	2.3	1.5	1.0	1.3	3.2	2.9	3.7	5.4	4.5
Lower limit 95%CI	1.0	0.7	0.6		0.6	1.8	1.5	1.8	2.6	2.1

Figure 2. Association between admission heart rate and in-hospital mortality across 58 European Hospitals in patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS). *Adjusted for age, sex and prior clinical history of obesity, smoking, hypertension, diabetes, coronary heart disease, heart failure, stroke and renal failure. CI: confidence interval; OR: odds ratio.

NSTE-ACS. For NSTE-ACS, an admission heart rate of 60–69 was associated with the lowest risk (Figure 2); a heart rate <40 bpm was associated with an 11-fold increased risk and heart rate categories >80 bpm with a 3.8 to 8.8-fold increased risk of mortality. As with the STEMI population, the U-shaped relationship persisted but was attenuated for the low heart rates in the multivariable models. Again, heart rates >80 bpm were significantly associated with mortality after multivariable adjustments.

Admission heart rate, in-hospital mortality, by sex, in the elderly and in patients with diabetes. Additional analyses were performed and are shown in the data in the Supplementary Material, Figures 1–4. When stratifying into men and women, the U-shaped relationship was observed in men for both STEMI and NSTE-ACS, and for women for NSTE-ACS, but not in women with STEMI; here, a positive association with admission heart rate was observed (Supplementary Material, Figure 1) with a low heart rate being associated with the lowest risk, however, there were no patients in the <40 bpm heart rate category.

To examine if the relationship was observed also in the elderly patients, the population was stratified into two groups, above or below 75 years (Supplementary Material, Figure 2); as shown, the U-shaped relationship between admission heart rate and in-hospital mortality was observed in the elderly and younger patients alike.

Also, in both patients with diabetes and without diabetes the U-shape persisted, see the results in the Supplementary Material, Figure 3.

Admission heart rate, in-hospital mortality, atrial fibrillation and use of beta-blockers. Information about presence of atrial fibrillation during hospitalisation was available only in patients admitted in Portugal encompassing a total of 3009 patients (1021 STEMI, 1765 NSTE-ACS, 223 with non-classifiable or missing type of ACS). The U-shape observed across all countries was also observed in the Portuguese data alone. The effect of atrial fibrillation was examined by excluding patients with atrial fibrillation (n=280), resulting in no change in the overall association between admission heart rate and in-hospital mortality; if anything, the association was stronger. Further adjustment for the use of beta-blockers (n=1713 (57%)) was included, however, no change in the association between heart rate and mortality was observed. The analyses are shown in the data in the Supplementary Material, Figure 4.

Discussion

In the present study of 10,000 patients admitted with an ACS across 58 Western European hospitals we found that heart rates at admission in patients with both STEMI and NSTE-ACS are highly associated with in-hospital mortality.

The association between admission heart rate and in-hospital mortality is U-shaped with the lowest and highest heart rates conferring the greatest risk. In NSTE-ACS, the risk of death in patients with bradycardia is increased by up to 11-fold and heart rates >80 bpm are associated with up to almost nine-fold increased risk of mortality compared to the reference heart rate category of 60–69 bpm. In STEMI patients, the risk of mortality is increased up to five-fold in patients with admission heart rates below or above the reference heart rate category of 70–79 bpm. When adjusting for confounding factors, a heart rate above 80 bpm remains associated with increased risk of in-hospital mortality in both STEMI and NSTE-ACS patients whereas bradycardia is no longer significantly associated with risk of mortality. Altogether, these findings suggest that ACS patients with high heart rates at admission are at increased risk of in-hospital mortality.

Heart rate is one of the first and most readily available physiological parameters in ACS patients and is obtainable within the first few minutes of a patient being admitted to the emergency room. In the acute setting, information about heart rate is therefore available much earlier than any other clinical and paraclinical information, such as troponin, and often even before other ECG changes occur. Furthermore, heart rate is very easy to obtain and there are no difficulties in interpretation or analysis. Heart rate at admission is therefore a fundamental and obvious biomarker to assess in the clinical setting, and to study prognostically.

Heart rate in both the acute and non-acute setting has been studied previously. Heart rate at rest has been shown to be predictive of ischaemic heart disease and mortality in several prospective studies of general populations.[1–3,13,14] In patients from the Coronary Artery Surgery Study (CASS) registry[16] with suspected or proven coronary artery disease, elevated resting heart rate was found to be predictive of adverse events during 14 years of follow-up. In a more recent study of 3300 patients undergoing coronary angiography,[17] heart rate at rest was associated with both total mortality and cardiovascular outcome, and in the Effects of Ivabradine in Patients With Stable Coronary Artery Disease and Left Ventricular Systolic Dysfunction (BEAUTIFUL) trial a heart rate at rest >70 bpm was associated with increased risk.[6] Furthermore, discharge heart rate of patients admitted with ACS has been studied in recent populations following percutaneous coronary intervention for STEMI[7] and for both NSTE-ACS and STEMI,[8] and in both populations an increased discharge heart rate was associated with long-term mortality.

Admission heart rate in ACS has been studied in previous populations in both pre-thrombolytic and thrombolytic eras; Madsen et al.[18] and Hjalmarson et al.[19] found high heart rate to be associated with increased risk, and Designi et al.[20] showed similar findings, however treatment of ACS has changed dramatically since these studies were conducted. Admission heart rate has also been studied in a relatively more recent cohort; in the CRUSADE cohort of NSTE-ACS patients only included in the USA from 2001–2005, a U-shaped relationship was found between admission heart rate and in-hospital mortality.[10] In the present study of a contemporary population of both STEMI and NSTE-ACS patients included across 58 European hospitals, we also found a U-shaped relationship in both NSTE-ACS and STEMI patients. In the multivariable analyses, the overall relationship persisted but was significant only for admission heart rates above 80 bpm. Furthermore, we found the relationship to be present in both the elderly population and the diabetes population, as well as in both men and women. The relationship between admission heart rate and mortality therefore seems to be a robust and clinically relevant marker of prognosis, also in a contemporary population of patients treated at European hospitals.

In light of the present findings, we suggest that a heart rate >80 bpm in patients admitted with ACS, irrespective of type of ACS, should be considered a marker of adverse events during hospitalisation. In the GRACE score model,[9] increasing admission heart rates from a baseline of ⩽50 bpm is considered to be associated with increased risk; in our present study, however, the crude results suggest that an admission heart rate ⩽50 bpm should not be considered to be a low-risk heart rate, and secondly, the cut-off value for a high-risk heart rate should be considered to be 80 bpm and above.

In the present cohort of patients with ACS, heart rate may possibly be both a marker of risk and potentially also related to the pathophysiological mechanism. Patients with ACS admitted with a very low heart rate may have bradycardia due to conduction defects such as high-grade atrioventricular block although we have no information about this; we found that both patients presenting with NSTE-ACS or STEMI and heart rate <40 bpm were at high risk of in-hospital mortality (OR 11.0 and 4.3 – relative to their respective reference heart rate category),[21] however, the data are difficult to interpret due to the low number of patients and events in the lowest heart rate group. Also, the relationship with in-hospital mortality did not remain significant after multivariable adjustments, indicating that the patients in the <40 bpm group were more comorbid compared to the others heart rate groups which is supported by their lower blood pressure, haemoglobin and worse kidney function at admission. These patients may therefore have been in a state of 'pre-cardiogenic shock' explaining the relationship seen in the crude model. Conventionally, tachycardia is defined as >100 bpm, although this has been debated,[22,23] and the present study supports a lower cut-off in patients admitted with ACS. We found admission heart rates >80 bpm to be associated with a highly increased risk of in-hospital mortality, and these findings were robust to multivariable adjustments. Furthermore, we show that this relationship is similar when stratified according to, age, diabetes and presence of atrial fibrillation or use of beta-blockers. Here, it is important to note that cardiogenic shock patients were excluded, so other mechanisms must be in play. These may include decreased

diastolic filling time, increased myocardial oxygen consumption, and increased susceptibility to development of malignant arrhythmias with increase in heart rate.[24,25]

Potential study limitations should be considered. Firstly, although all 58 participating centres adhered to European guidelines, the available means for therapeutic intervention were not uniform across participating countries, and in-hospital mortality therefore varied between countries. This is likely explained by regional differences in the organisation of healthcare systems and geographical distances to invasive centres. This has been discussed in detail elsewhere.[11] However, inclusion of country or participant centre in the multivariable analyses did not change the association. Finally, only in-hospital events are available in the EURHOBOP cohort, and long-term follow-up could therefore not be assessed.

In conclusion, we examined the relationship between admission heart rate and in-hospital mortality in 10,374 consecutive ACS patients admitted from 2008–2010 across 58 European hospitals in six participant countries of the EURHOBOP collaboration. There was a U-shaped relationship between mortality and admission heart rate in both NSTE-ACS and STEMI patients in that heart rates above 80 bpm and below 40 bpm were associated with increased risk. In STEMI, patients with admission heart rate between 70–79 bpm were at lowest risk, and in NSTE-ACS patients in the 60–69 bpm range were at lowest risk. After multivariable adjustments the association with bradycardia was attenuated. An admission heart rate above 80 bpm was associated with a greatly increased risk of in-hospital mortality in both patients with STEMI and NSTE-ACS, and the relationship was present irrespective of beta-blocker use, presence of atrial fibrillation, in both men and women, in patients with and without diabetes, and in the younger and elderly patient alike.

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Conflict of interest

D Farmakis reports personal fees from Servier, outside the submitted work; J Ferrières reports grants from Amgen and Merck, educational activities with Astra Zeneca and Sanofi, also outside the submitted work. All other authors have nothing to declare.

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Heart rate at admission is a predictor of in-hospital mortality in patients with acute coronary syndromes

– Results from 58 European hospitals: *The EURHOBOP study*

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SUPPLEMENTAL DATA

Data analysis

Type of ACS was defined according to ECG findings at admission in agreement with current European guidelines[12,13]. Patients who were not classifiable into type of ACS or with missing data on that variable were excluded from the analysis. Outcome of interest was defined as death of any cause during hospitalization. Heart rate at admission was extracted from the files as a continuous variable and categorized into 10-beat wide intervals. Patients with cardiogenic shock were excluded[10].

To compare demographic characteristics, data collected at admission, invasive procedures during hospitalization and outcomes with respect to different heart rate categories, Kruskal-Wallis tests and Pearson chi-square tests were used for continuous variables and categorical variables, respectively. Two different approaches were used to deal with missing data: 1) for previous medical history, acute pulmonary edema at admission, invasive procedures during hospitalization and hospital outcomes we assumed that the information would be reported in the files if those conditions occurred, and in case of no reference to them, we assumed they did not occur; 2) for all the other variables, we omitted cases with missing data from that specific analysis.

Unconditional logistic regression was used to estimate the odds ratios (OR) for the association between in-hospital mortality and heart rate. In addition to the crude OR, we computed OR adjusting for variables that are likely to confound the association between mortality and heart rate. The variables included in the multivariable regression model were age, sex and prior clinical history of obesity, smoking, diabetes, coronary heart disease, known heart failure, stroke and renal failure. A random intercept for participant center was considered in hierarchical mixed models with country alone, hospital alone and also two levels for hospital and country, but since this approach did not lead to different results regarding the effect of heart rate, we present only the final logistic regression models. Several additional analyses were performed, including stratification of the population according to sex, age above or below 75 years and diabetes vs non-diabetes. Information about presence of atrial fibrillation and use of beta-blockers was available only in patients from Portugal; due to the smaller sample size of one country alone, patients with STEMI and NSTE-ACS were pooled in this analysis which therefore also included patients with non-classifiable ACS or with missing information about type of ACS. A p-value<0.05 was considered statistically significant.

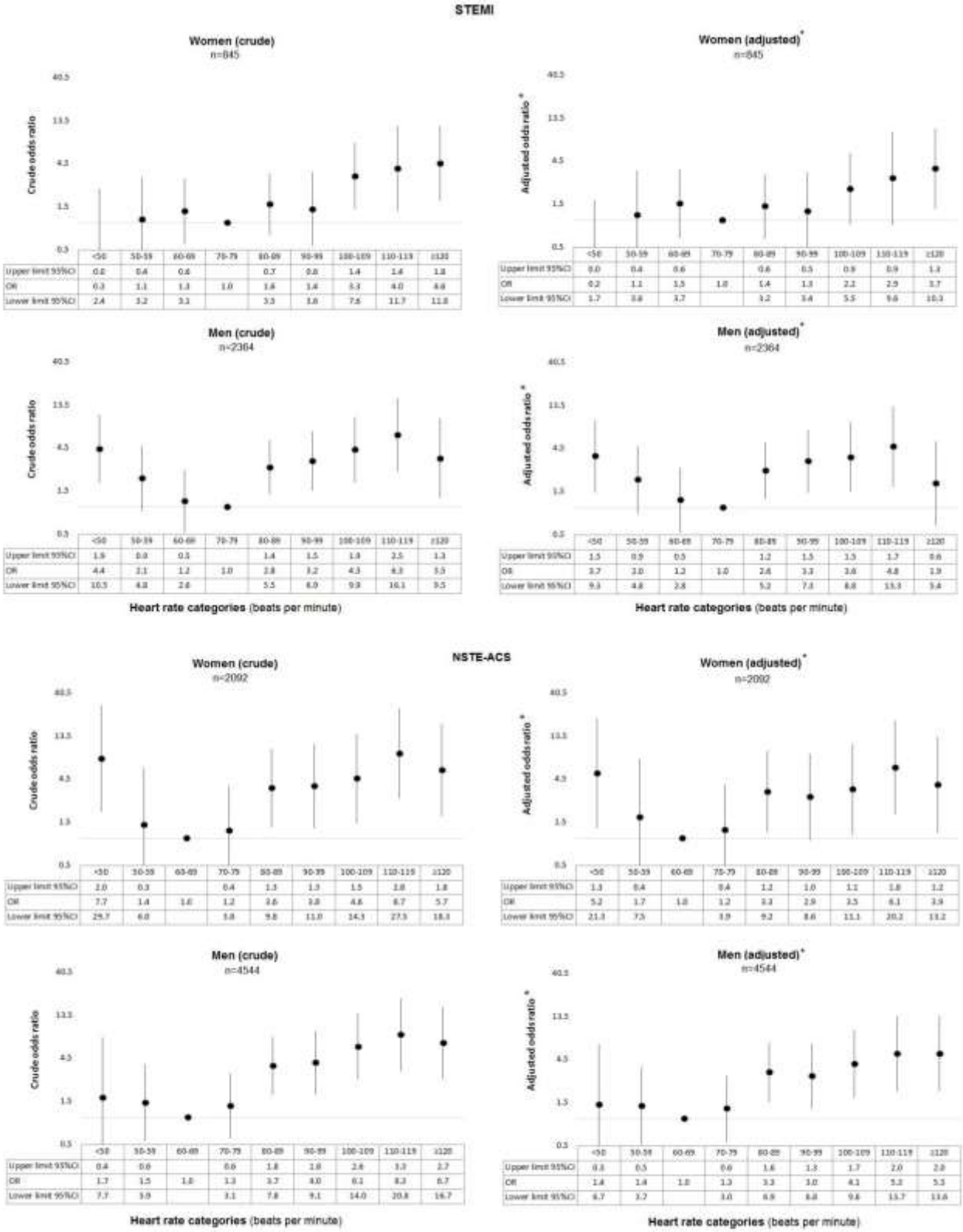
Figure S1: Association between admission heart rate and in-hospital mortality across 58 European Hospitals in patients with STEMI and NSTE-ACS, stratified by sex.

Figure S2: Association between admission heart rate and in-hospital mortality across 58 European Hospitals in patients with STEMI and NSTE-AC, stratified into above or below 75 years.

Figure S3: Association between admission heart rate and in-hospital mortality across 58 European Hospitals in patients with STEMI and NSTE-ACS, stratified into diabetes or no diabetes.

Figure S4: Association between admission heart rate and in-hospital mortality in patients with ACS in Portugal, overall, after excluding patients with atrial fibrillation and adjusting additionally for use of beta-blockers.

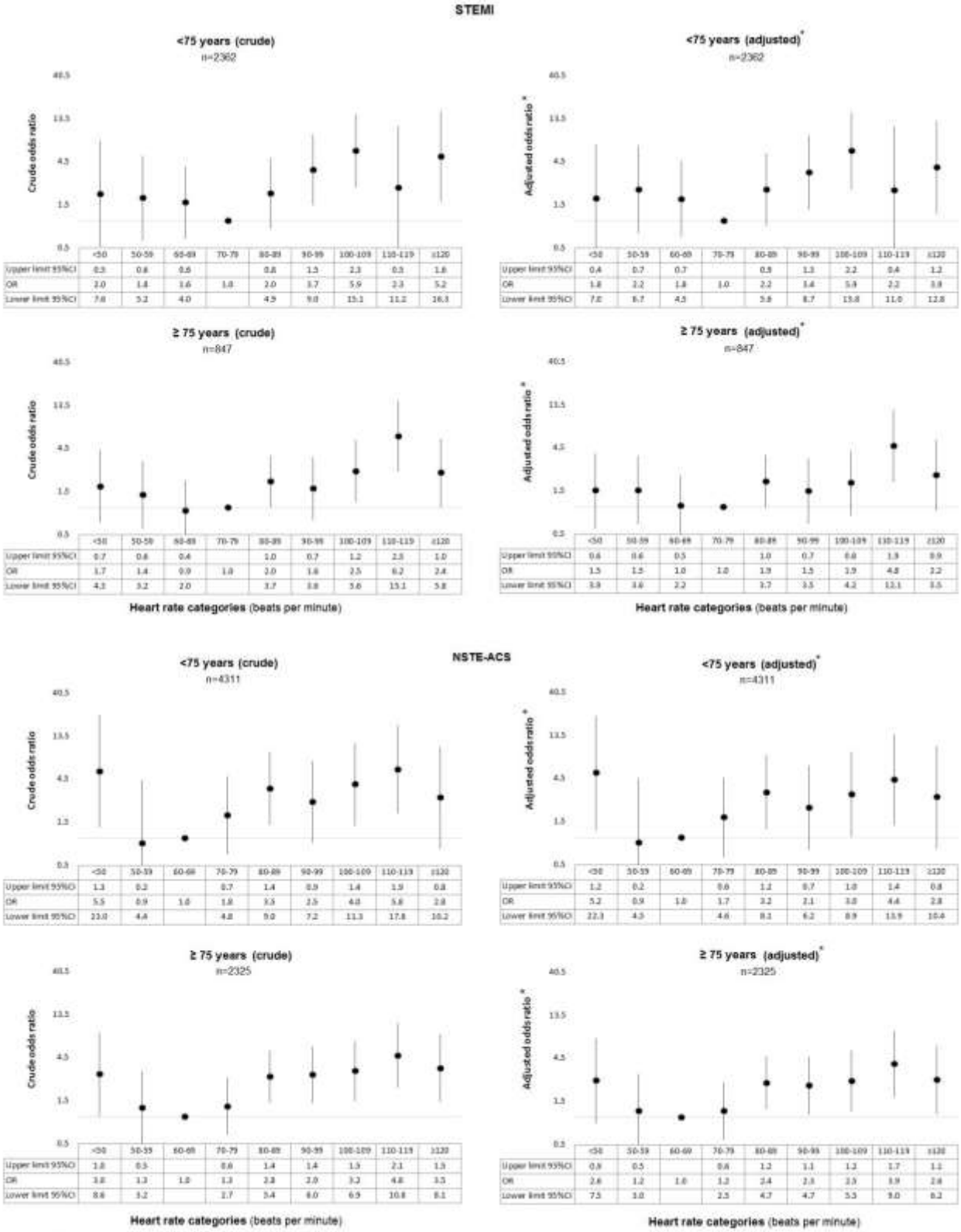
Figure S1



* Adjusted for age, sex and prior clinical history of obesity, smoking, hypertension, diabetes, coronary heart disease, heart failure, stroke and renal failure

CI – Confidence interval; NSTE-ACS – Non-ST-Segment Elevation Acute Coronary Syndrome; OR – Odds ratio; STEMI – ST-segment elevation myocardial infarction

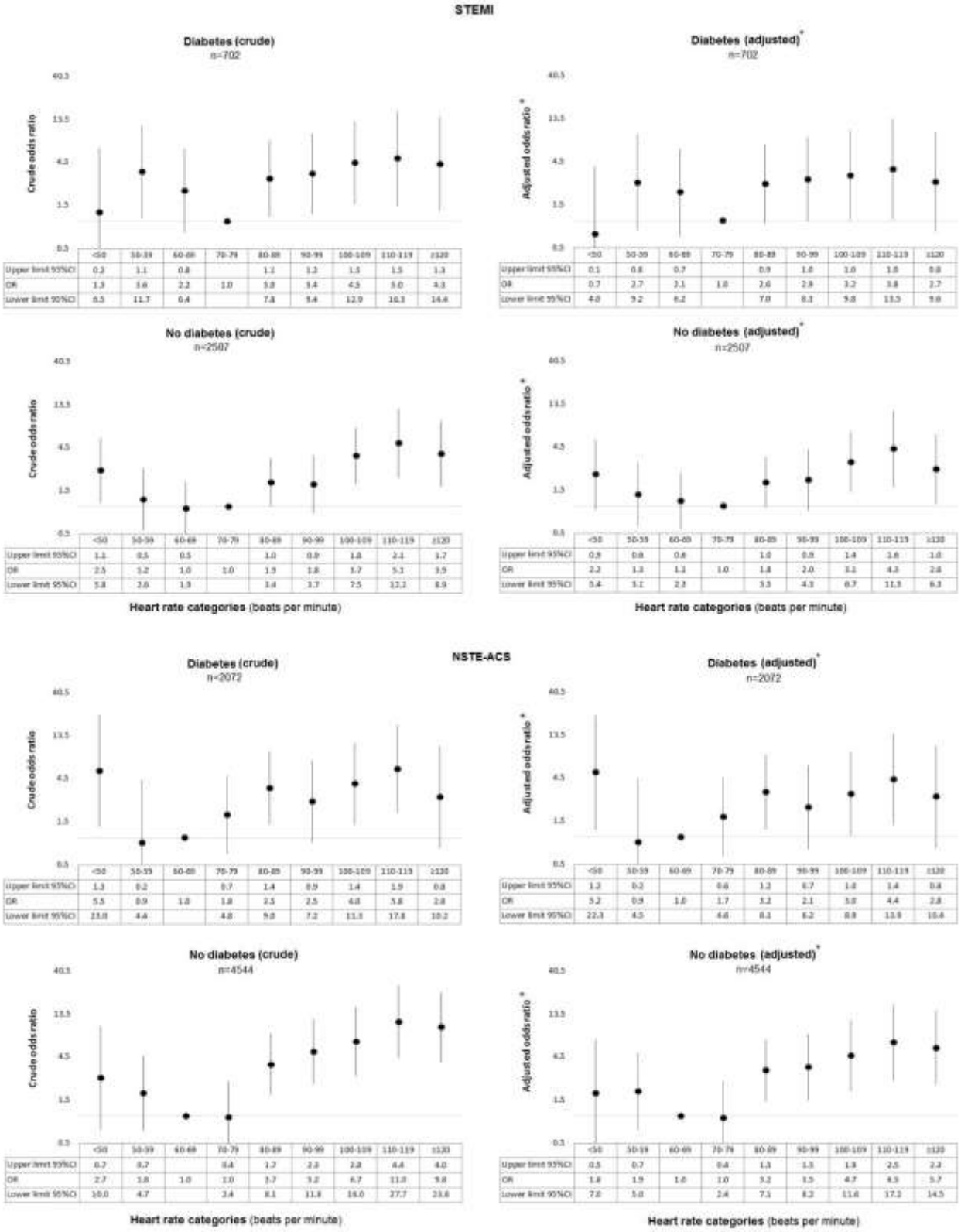
Figure S2



* Adjusted for age, sex and prior clinical history of obesity, smoking, hypertension, diabetes, coronary heart disease, heart failure, stroke and renal failure

CI – Confidence interval; NSTE-ACS – Non-ST-Segment Elevation Acute Coronary Syndrome; OR – Odds ratio; STEMI – ST-segment elevation myocardial infarction

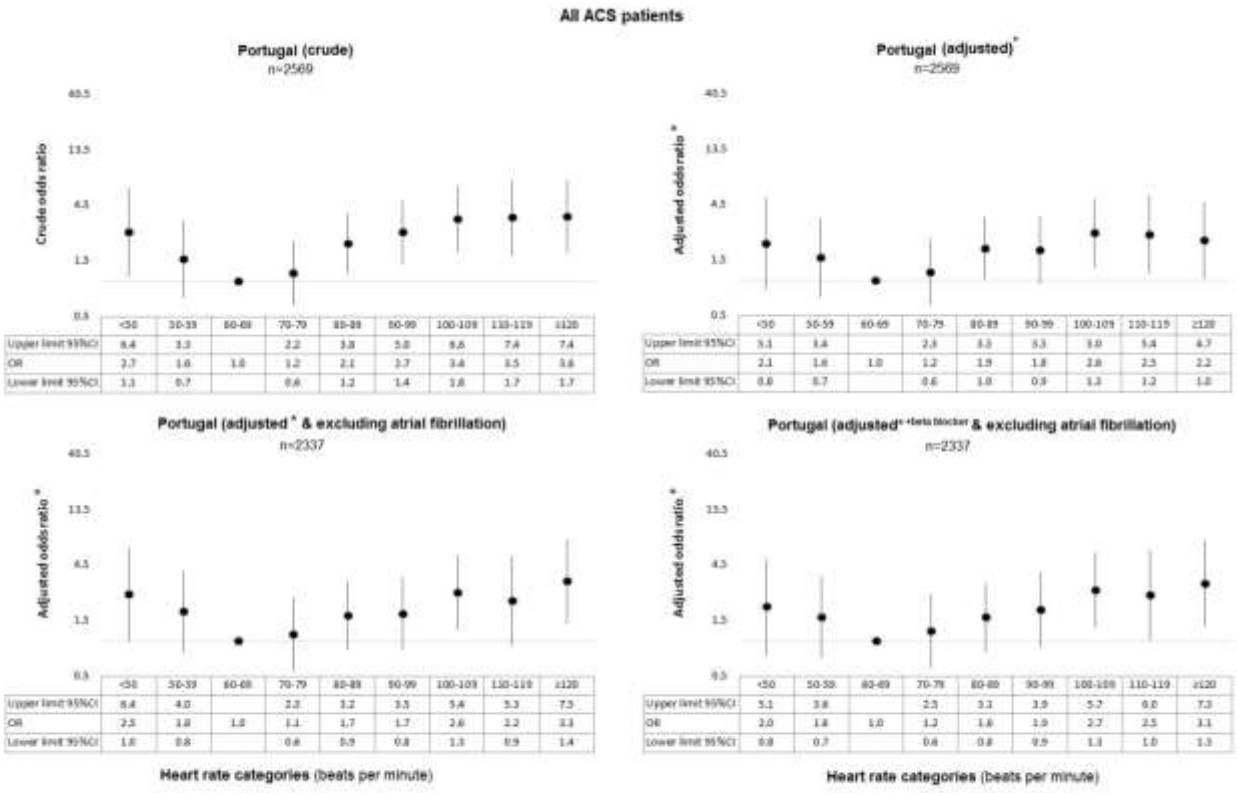
Figure S3



* Adjusted for age, sex and prior clinical history of obesity, smoking, hypertension, diabetes, coronary heart disease, heart failure, stroke and renal failure

CI – Confidence interval; NSTE-ACS – Non-ST-Segment Elevation Acute Coronary Syndrome; OR – Odds ratio; STEMI – ST-segment elevation myocardial infarction

Figure S4



* Adjusted for age, sex and prior clinical history of obesity, smoking, hypertension, diabetes, coronary heart disease, heart failure, stroke and renal failure

ACS = Non-ST-Segment Elevation Acute Coronary Syndrome; CI = Confidence interval; OR = Odds ratio

ORIGINAL RESEARCH ARTICLE

Heritability of resting heart rate and association with mortality in middle-aged and elderly twins

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ABSTRACT

Objective Resting heart rate (RHR) possibly has a hereditary component and is associated with longevity. We used the classical biometric twin study design to investigate the heritability of RHR in a population of middle-aged and elderly twins and, furthermore, studied the association between RHR and mortality.

Methods In total, 4282 twins without cardiovascular disease were included from the Danish Twin Registry, hereof 1233 twin pairs and 1816 'single twins' (twins with a non-participating co-twin); mean age 61.7 (SD 11.1) years; 1334 (31.2%) twins died during median 16.3 (IQR 13.8–16.5) years of follow-up assessed through Danish national registers. RHR was assessed by palpating radial pulse.

Results Within pair correlations for RHR adjusted for sex and age were 0.23 (95% CI 0.14 to 0.32) and 0.10 (0.03 to 0.17) for RHR in monozygotic (MZ) and dizygotic (DZ) twin pairs, respectively. Overall, heritability estimates were 0.23 (95% CI 0.15 to 0.30); 0.27 (0.15 to 0.38) for males and 0.17 (0.06 to 0.28) for females. In multivariable models adjusting for age, gender, body mass index, diabetes, hypertension, pulmonary function, smoking, physical activity and zygosity, RHR was significantly associated with mortality (eg, RHR >90 vs 61–70 beats per min: all-cause HR 1.56 (95% CI 1.21 to 2.03); cardiovascular 2.19 (1.30 to 3.67). Intrapair twin comparison revealed that the twin with the higher RHR was significantly more likely to die first and the probability increased with increase in intrapair difference in RHR.

Conclusions RHR is a trait with a genetic influence in middle-aged and elderly twins free of cardiovascular disease. RHR is independently associated with longevity even when familial factors are controlled for in a twin design.

INTRODUCTION

Resting heart rate (RHR) is a fundamental physiological parameter associated with longevity and may be a heritable trait. Genome-wide association studies (GWAS) have so far found several genetic loci that are significantly associated with RHR. However, when combining the GWAS identified heart rate-increasing alleles, only a few percentages of the variance in heart rate is explained.[1] Using the classical twin design, the relative contribution of genetic and environmental factors can be determined. Examination of twins from early infancy to the age of 7 years has shown that RHR in monozygotic (MZ) twins are significantly more correlated than in dizygotic (DZ) twins indicating that variation in RHR in children has a significant genetic component of magnitudes between 0.22 and 0.50.[2] In adolescents, twins' RHR also showed a substantial heritability of 0.68, which was of similar magnitude in twins with a mean age of 44–47 years.[3 4] The heritability of RHR in older age groups, however, is not well characterised.

A high heart rate has been shown to be associated with cardiovascular and all-cause mortality in general populations[5–7] and in various patient populations from patients with chronic obstructive pulmonary disease,[8] cardiovascular disease,[9] to patients with diabetes.[10] Studies specifically investigating elderly subjects have shown RHR to be associated with short-term mortality in subjects aged 65 years or older followed for up to 6 years,[11] but the long-term relationship between RHR and mortality in this age-group is unknown.

In the present study, we investigated the heritability of RHR and its association with cardiovascular and all-cause mortality in 4282 middle-aged and elderly twins without known cardiovascular disease followed for a median of 16 years. The twin design enables us to make intrapair comparisons of RHR and subsequent survival, hereby controlling for familial, genetic and environmental confounding.

METHODS

Study population

The individuals in this study were identified among 7023 twins who participated in one of two population-based nationwide cohorts: The Longitudinal Study of Aging Danish Twins (LSADT; third wave) and the Middle Age Danish Twin study (MADT). Both studies were ascertained through the nationwide Danish Twin Registry (DTR).[12] LSADT is a cohort sequential study of Danish same-sex twins aged 70 years and older and was initiated in 1995 with follow-up every second year through 2005.[13] Data in this study are for the third wave in 1999, as this was the only wave in which RHR was measured. The MADT study included twins born between 1931 and 1952 and were first assessed in 1998.[14] The participation rates were 69.9% in the third wave of LSADT (n=2709) and 83.1% in MADT (n=4314). Each survey comprises multidimensional interviews conducted by trained interviewers. All participants provided informed consent and the Danish Scientific Ethical

Committees approved both studies which complied with the Helsinki Declaration.

Follow-up and data linkage

Since 1968, all Danish residents have been assigned a unique central registration number (CPR number). Population-based registries in Denmark offer unique possibilities for studies on long-term occurrence of cardiovascular outcomes and mortality as well as discharge records. Exact dates of death were ascertained from the Danish Civil Registration System and causes of death through the Danish Cause of Death Registry. Causes of death have been coded according to the International Classification of Diseases Tenth Edition (ICD-10) codes.

Exclusion criteria

Individual participants with known cardiovascular disease before the survey were excluded. Information about cardiovascular disease and pacemakers was collected from the Danish National Patient Registry. Cardiovascular disease was defined by ICD-8 and ICD-10 codes (400-438 and I20-I99, DZ950, respectively). Self-reported medicine use (beta-blockers, adrenergic stimulators and calcium-channel inhibitors) also leads to exclusion as well as self-reported coronary thrombosis, angina pectoris, arrhythmia, prescription-treated hypertension and 'general heart trouble'. To exclude the presence of undiagnosed bradycardia or tachyarrhythmia, participants with very low (<40 beats per min (bpm)) or very high (>120 bpm) RHR were excluded.

Resting heart rate

RHR was measured, as recommended,[15] by palpating the radial pulse for 30 s and multiplying by 2 to obtain the number of bpm. RHR was measured with the participant in a sitting position after a written questionnaire had been completed by the participant (>100 items in the questionnaire).

Covariates/confounders/mediators in the survival analyses

Diabetes was defined by ICD-8 as 249-250 and by ICD-10 as E10-11 or self-reported during interview. Hypertension was defined as use of medication with Anatomical Therapeutic Chemical Classification (ATC) C02, C03, C08 and C09 obtained from the interview.

Forced expiratory volume in 1 s (FEV_1) was measured during the study visit. Self-reported data included medicine use, smoking, physical activity, height (cm) and weight (kg). Smoking was categorised as never, previous or current. The questions on physical activity were not identical in LSADT and MADT, thus physical activity was categorised as light, moderate or high based on self-reported walking, biking and other physical activity.

Outcomes

The main outcome, heritability, was determined as described below. Endpoints for the survival analyses included: (1) death from any cause and (2) cardiovascular death (ICD-10 I20-99).

Statistical analysis

Descriptive analyses

Median RHR, status (alive/dead at end of follow-up) and age at death are tabulated by sex. Unpaired t-test was used to test for differences between genders.

Twin similarity

Intra-class correlations were calculated for RHR and adjusted for gender and age, and heritability analyses were performed using standard biometric methods.[16] It is assumed that twins are exposed to shared and unique environmental factors, which are independent of zygosity. Correlations in the genetic component differ between MZ twin pairs (one for both additive and dominant genetic components) and DZ twin pairs (0.5 for additive and 0.25 for dominant). Hence, higher correlation between MZ twin pairs as compared with DZ twin pairs reflects genetic influences. The classical twin model decomposes total phenotypic variance into additive genetic (A), shared family environment (C) dominant genetic (D) and unique environment (E) components.[16] We used the free R package mets to fit and compare five models (ACE, ADE, AE, CE and E) to see which model was the best fit of data. The model with the lowest Akaike Information Criterion represents the best balance of goodness of fit and parsimony. Considering the large age span of the participants, we stratified participants into two age groups: 45–65 and >65 years, a cut-off which has previously been used to study RHR in the elderly.[11] All models were adjusted for sex and age when fitted.

Survival analyses

Survival analyses using Cox proportional hazard models were performed to study the association between RHR and mortality from all-cause and cardiovascular death, computing crude and adjusted HRs for intrapair comparison using the stratified Cox model with pair-specific baseline hazard functions, thereby exploiting the paired structure of the data which is in analogy to conditional logistic regression in case of complete follow-up.[17] Participants were categorised according to RHR (40–50, 51–60, 61–70, 71–80, 81–90, 91–120), with the largest group as reference (61–70 bpm). Analyses included the following covariates: (1) age at interview and gender; (2) age at interview, gender and body mass index (BMI) and (3) age at interview, gender, BMI, diabetes, hypertension, FEV_1, smoking, physical activity and zygosity. Follow-up extended from date of interview until 1 June 2015 or death, whatever came first. The proportional hazards assumption was assessed graphically and found to be met. Estimated HR curves of RHR relative to the hazard of RHR with best mortality were performed using a smoothing method based on splines to introduce flexibility into the Cox model[18] (see online supplementary data).

Survival analysis—intrapair difference in RHR

Finally, among pairs in which at least one member had died during follow-up, we calculated the proportion of pairs in which the co-twin with the higher RHR died first (null hypothesis was 50%). Participants were divided according to intrapair difference in RHR with increasing intrapair difference (≥1 bpm, ≥5 bpm, ≥10 bpm, ≥15 bpm, ≥20 bpm).

Data were analysed using STATA V.13.1 and R V.3.1.3 with R package mets V.1.1.0 and R package smooth HR V.1.0.2.

RESULTS

Descriptive analyses

There were 7023 participants of which 6374 (90.8%) had data on RHR, 31 were excluded due to missing information on zygosity and 2014 due to known heart disease or use of cardiac medication, leaving 4282 individuals for further analyses (males: n=2092; females: n=2190), figure 1. There were 1233 twin pairs and 1816 'single twins' (twins with a non-participating co-twin). Of these 479 were MZ pairs, 431 same-sex DZ pairs (ssDZ) and 323 opposite-sex DZ pairs (osDZ). A total of 1334 (31.2%) of the 4282 participants had died by 1 June 2015. Median RHR was virtually constant over age. Overall, males had a lower RHR than females (70 bpm (IQR

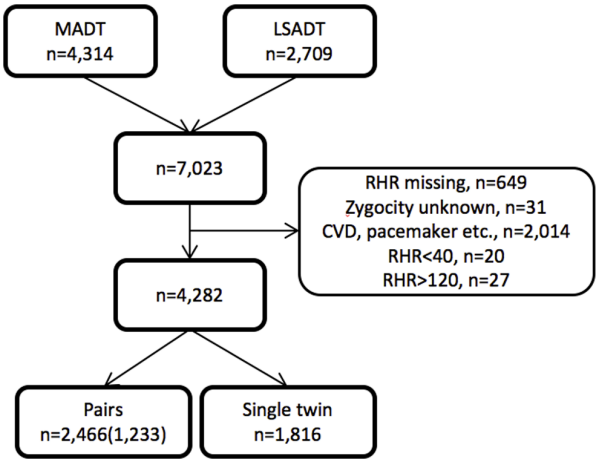

Figure 1 Cardiovascular disease pacemaker, etc,: include previous cardiovascular disease, pacemaker, self-reported medicine (beta-blockers, adrenergic stimulators, and calcium channel inhibitors) and self-reported conditions: coronary thrombosis, angina pectoris, arrhythmia, prescription-treated hypertension and 'general heart trouble'. LSADT: The Longitudinal Study of Aging Danish Twins (third wave); MADT, The Middle Age Danish Twin study; RHR, resting heart rate.

64 to 78) and 72 bpm (IQR 66 to 78), respectively; p<0.001), and females had a higher age of death than males (82.7±10.8 years vs 78.6±10.5 years; p<0.001). Online supplementary figure 1 shows RHR for males and females with 95% confidence bands. An RHR below 60 bpm was found in 16.2% of males and 12.5% of females. Table 1 displays the median RHR, status, age of death of males, females and combined.

Twin similarity

Intraclass correlation coefficients and heritability

The intraclass correlation coefficients (ie, within-pair correlation) adjusted for sex and age for RHR were 0.23 (95% CI 0.14 to 0.32) for MZ twin pairs and 0.10 (0.03 to 0.17) in DZ twin pairs (table 2). For ssDZ and osDZ twin pairs, the intraclass correlation coefficients were 0.07 (95% CI 0.00 to 0.16) and 0.14 (95% CI 0.03 to 0.25), respectively. When stratifying into age groups, no significant changes are observed. Table 2 gives the results for the genetic modelling for males, females and both genders. Among both males and females, a combined AE model showed the best fit in terms of AIC. All the models showed moderate genetic influence on RHR with an overall heritability of 0.23 (95% CI 0.15 to 0.30) for both genders, 0.27 (0.15 to 0.38) for males and 0.17 (0.06 to 0.28) for females. Heritability in age groups ranged from 0.17 (0.01 to 0.33; >65 years) to 0.24 (0.15 to 0.32; 45–65 years). The highest heritability estimate was found in males >65 years (0.42 (95% CI 0.14 to 0.69)) and the lowest in females >65 years (0.07 (0 to 0.27)).

Survival analyses

Among participants, 31.2% died during follow-up and 6.6% died of cardiovascular disease. Median follow-up time was 16.3 (IQR 13.8 to 16.5) years.

Risk increased with increasing RHR (table 3 and online supplementary table 1, stratified by gender). Multivariable adjustments left risk estimates virtually unchanged. A Wald test showed a significant interaction between RHR and gender (p=0.018). The HR curves by RHR confirmed that males and females may differ in RHR optimal for survival (shown in online supplementary figure 2). The curves showed a reference value of 40 bpm optimal for survival for males, adjusted by age at measurement, with increase in risk as RHR increased. For females, the corresponding reference value was 66 bpm and indicated a 'J-shaped' risk pattern of increased HRs at lower RHR and increased HRs at higher RHR.

Cox regression stratified by twin pair, that is, controlling for intrapair similarity (see online supplementary table 2), did not change the overall association. When performing Cox regression stratified by twin pair including only MZ twins, a significantly higher mortality was observed in groups with RHR of 81–90 and 90–120 bpm compared with the reference group (see online supplementary table 3).

Table 1 Median resting heart rate (median (IQR)), alive/dead at end of follow-up and mean age at death—males, females and both

	Male		Female		All		All
	45–65 year	>65 year	45–65 year	>65 year	45–65 year	>65 year	
N	1469	623	1354	836	2823	1459	4282
Mean Age (SD)	54.9 (5.4)	74.0 (6.4)	55.0 (5.4)	75.4 (6.9)	54.9 (5.4)	74.8 (6.7)	61.7 (11.1)
Median Age (IQR)	54.5 (50.3 to 59.3)	73.6 (7.6 to 78.0)	54.7 (50.1 to 59.6)	74.6 (70.8 to 80.2)	54.6 (50.2 to 59.5)	74.2 (70.4 to 79.0)	59.6 (52.5 to 70.6)
Deaths (%)	14.3	68.4	11.5	64.8	12.7	66.4	31.2
Median RHR (IQR)	70 (64 to 78)	70 (64 to 78)	72 (64 to 78)	72 (66 to 78)	72 (64 to 78)	72 (64 to 78)	72 (64 to 78)
Mean BMI (SD)	25.8 (3.1)	25.2 (3.3)	24.0 (3.1)	23.7 (3.8)	24.9 (3.5)	24.3 (3.7)	24.7 (3.6)
Diabetes (%)	2.4	4.5	1.5	4.7	2.0	4.6	2.9
Hypertension (%)	0.5	5.9	2.4	6.6	1.4	6.3	3.1
Mean FEV_1 (SD)	3.4 (0.7)	2.4 (0.5)	2.5 (0.5)	1.8 (0.5)	3.0 (0.8)	2.0 (0.7)	2.7 (0.9)
Physical activity							
Light (%)	54	44	63	50	59	47	55
Moderate (%)	36	39	31	37	33	38	35
High (%)	10	17	6	13	8	15	10
Smoking							
Never smokers (%)	30	18	43	46	36	34	35
Ex-smokers (%)	30	39	18	25	24	31	26
Current smokers (%)	40	43	39	29	40	35	38

FEV1, forced expiratory volume in 1 s; BMI, body mass index; RHR, resting heart rate.

Table 2 Intrapair ICC and heritability (from AE model) of RHR

	Pairs	ICC*		Pairs	Heritability†
All ages					
MZ	479	0.23 (0.14 to 0.32)	All	1233	0.23 (0.15 to 0.30)
DZ	754	0.10 (0.03 to 0.17)	Male	467	0.27 (0.15 to 0.38)
ssDZ	431	0.07 (0 to 0.16)	Female	443	0.17 (0.06 to 0.28)
osDZ	323	0.14 (0.03 to 0.25)			
45–65 year					
MZ	370	0.24 (0.14 to 0.34)	All	982	0.24 (0.15 to 0.32)
DZ	612	0.10 (0.02 to 0.18)	Male	374	0.23 (0.11 to 0.36)
ssDZ	324	0.06 (0 to 0.16)	Female	320	0.22 (0.08 to 0.35)
osDZ	288	0.16 (0.04 to 0.27)			
>65 year					
MZ	109	0.16 (0 to 0.34)	All	251	0.17 (0.01 to 0.33)
DZ	142	0.11 (0 to 0.27)	Male	93	0.42 (0.14 to 0.69)
ssDZ	107	0.12 (0 to 0.30)	Female	123	0.07 (0 to 0.27)
osDZ	35	0.09 (0 to 0.41)			

*ICC of resting heart rate adjusted for sex and age, †Heritability from AE model.
DZ, dizygotic; ICC, intraclass correlation; MZ, monozygotic; osDZ, opposite-sex dizygotic; RHR, resting heart rate; ssDZ, same-sex dizygotic.

Intrapair difference in RHR and mortality in twins

Out of the total number of 1233 complete twin pairs, there were 391 pairs in which at least one twin had died during follow-up, and 302 of these pairs were same-sex twins. Fifteen pairs were excluded as they had the exact same RHR, leaving 287 pairs for analysis. The analysis is shown in figure 2, displaying a clear 'dose–response' relationship and suggests that an increased intrapair difference in RHR was associated with a higher probability that the co-twin with the higher RHR would die first. In 160 of the 287 (55.7%) same-sex pairs with a difference in RHR of ≥1 bpm, the twin with the higher RHR died first, and in 38 of the 51 (74.5%) same-sex pairs with a difference of ≥20 bpm, the twin with higher RHR died first.

DISCUSSION

In the present study of 4282 middle-aged and elderly twins free from cardiovascular disease at inclusion and followed for a median of 16 years, the main findings were as follows: first, in the middle-aged and elderly persons, RHR is a trait with a significant heritability; second, the higher the RHR the greater the risk of all-cause and cardiovascular mortality; third, as an extension of this result, we found a clear dose–response relationship which showed that the greater the intrapair difference in RHR the more likely that the twin with the higher RHR died first.

RHR as a possible risk factor for adverse events has received increasing attention in recent years and has been investigated in both observational studies[5 6] and randomised clinical trials.[19] Levine demonstrated that there is a linear, inverse semilogarithmic relation between RHR and life expectancy across the animal kingdom, and that the number of heart beats per lifetime is nearly constant across species.[20] It would be reasonable to think that if a certain RHR characterises an individual species, then there must be a certain degree of heritability in RHR, also in humans.

In a large GWAS, combining 46 loci associated with RHR, only 2.5% of the variance of RHR was explained.[1] Here, a genetically predicted RHR increase of 5 bpm increased the risk

Table 3 Cox regression* adjusted for within-pair difference. HR of mortality according to RHR. Time extends from time of RHR measurement† to death or 1 June 2015

Risk factor	n	Events	Crude HR	Adj‡ HR	Adj§ HR	Adj¶ HR
Mortality						
40–50	64	20	0.94 (0.60 to 1.48)	0.94 (0.60 to 1.48)	0.89 (0.56 to 1.42)	0.76 (0.44 to 1.31)
51–60	548	160	1.23 (1.03 to 1.48)	1.22 (1.02 to 1.46)	1.21 (1.01 to1.46)	1.35 (1.10 to 1.66)
61–70	1512	419	1 (ref)	1 (ref)	1 (ref)	1 (ref)
71–80	1444	456	1.10 (0.97 to 1.26)	1.18 (1.04 to 1.35)	1.18 (1.03 to1.35)	1.13 (0.97 to 1.32)
81–90	475	178	1.71 (1.43 to 2.03)	1.78 (1.49 to 2.12)	1.77 (1.49 to2.12)	1.61 (1.31 to 1.98)
90–120	239	101	1.64 (1.32 to 2.04)	1.86 (1.50 to 2.31)	1.85 (1.48 to 2.30)	1.56 (1.21 to 2.03)
CVD death						
40–50	64	5	1.17 (0.47 to 2.88)	1.13 (0.45 to 2.79)	1.13 (0.46 to 2.81)	1.10 (0.39 to 3.11)
51–60	548	37	1.54 (1.04 to 2.27)	1.53 (1.03 to 2.26)	1.54 (1.04 to 2.28)	1.65 (1.05 to 2.60)
61–70	1512	80	1 (ref)	1 (ref)	1 (ref)	1 (ref)
71–80	1444	98	1.22 (0.91 to 1.64)	1.27 (0.94 to 1.71)	1.28 (0.95 to 1.73)	1.22 (0.87 to 1.72)
81–90	475	39	2.00 (1.37 to 2.94)	2.07 (1.41 to 3.03)	2.03 (1.38 to 2.99)	1.40 (0.86to 2.27)
90–120	239	25	2.14 (1.36 to 3.35)	2.30 (1.46 to 3.61)	2.32 (1.48 to 3.65)	2.19 (1.30 to 3.67)

*Stratified Cox model with pair-specific baseline hazard functions,[17] †Adjustments were made for all covariates at time of interview, ‡Adjusted for gender and age at interview, §Adjusted for gender, age at interview and BMI, ¶Adjusted for gender, age at interview, BMI, FEV_1, diabetes, hypertension, smoking, physical activity and zygosity.
BMI, body mass index; FEV1, forced expiratory volume in 1 s; RHR, resting heart rate.

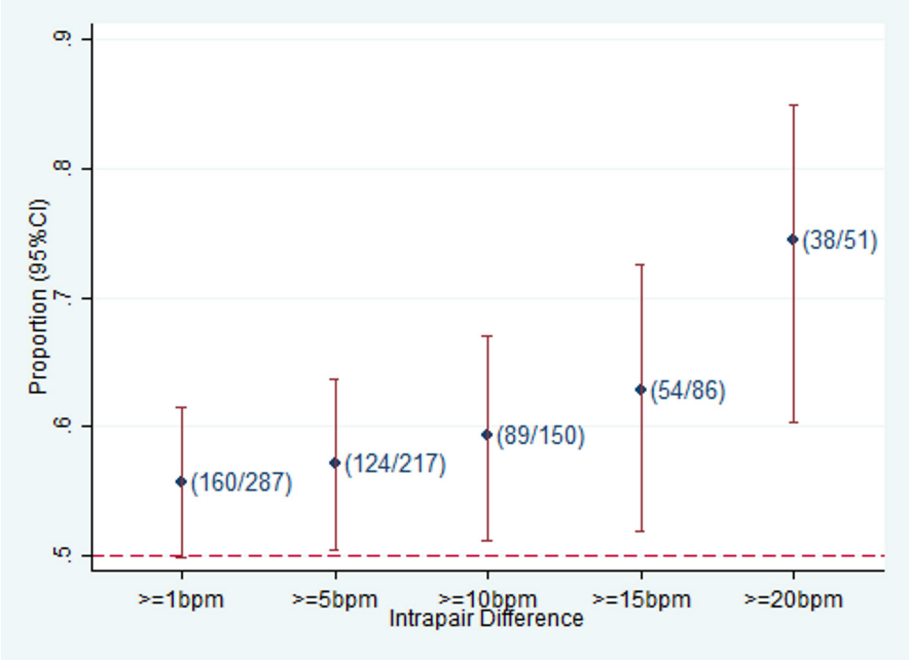

Figure 2 Proportion of pairs in which the co-twin with the higher RHR died first, according to the intrapair difference in RHR with increasing intrapair difference (≥0, ≥5, ≥10, ≥15 and ≥20 bpm). Numbers in brackets show the number of same-sex pairs were the twin with higher RHR died first/number of available pairs. bpm, beats per min; RHR, resting heart rate.

of mortality by 20%. This finding is within the same magnitude as the findings from The Copenhagen City Heart Study,[6] where crude analyses showed an increased risk of 15% per 10 bpm. RHR is a modifiable trait influenced by environmental factors such as fitness,[7] diabetes,[10] chronic obstructive pulmonary disease[8] and medication. For instance, in a population of patient with diabetes, 3 months of exercise lowered RHR, in average, by 7 bpm.[21] Also, heart rate-modifying drugs play a central role in clinical medicine. However, although RHR is subject to individual differences in health behaviour and life circumstances, a significant degree of the variance of RHR, ranging from weak to moderate, is explained by genetic factors, as shown in the present study, even in the elderly individuals.

Previous studies have found a significant heritability of 0.40–0.66 in twins aged 15 to 20 years,[3 22] and a heritability of similar magnitude in subjects around age 40 years.[3 23] In the present study, we studied individuals above 45 years with a mean age of 62 years with an equal distribution of males and females. Here, there was a slightly lower, but highly significant, overall heritability of 0.23 for the whole population, 0.27 for males and 0.17 for females with no clear age pattern. Our study demonstrates that genetic influences, which can vary or be stable by age, are present. The findings points towards a stable heritability, which is also seen for a number of ageing-related traits in studies of twins[24] in the latter half of the lifespan.

Our study indicates that RHR is a trait with a life-long twin similarity, which is in line with other phenotypes, demonstrating that when twins grow old, they do not grow apart on central ageing phenotypes.[24]

RHR was significantly associated with both cardiovascular and all-cause mortality. In males, a low heart rate was associated with a decreased risk of adverse events without a lower limit and with a stepwise increase in risk with increase in RHR. For females, our results indicated a 'J-shaped' relationship with a trend towards increased risk of mortality at very low RHR. This could be due to clinically undiagnosed conduction delay or block. The present findings are generally in line with other population studies finding an increased risk of mortality with increase in RHR.[25] Studies on RHR in the elderly, however, are not all consistent; Perk *et al* found RHR to be associated with mortality in elderly females but not in males[26]; in contrast, other studies have found RHR to be associated with mortality only in elderly males[27] and elderly females.[28] The present findings are possibly due to longer follow-up and greater number of endpoints

Key messages

What is already known on this subject?
Resting heart has been shown to be associated with longevity and may have a hereditary determinant.

What might this study add?
In the present study, we show that resting heart rate (RHR) is a trait with a life-long heritability. Also, elevated RHR is associated with increased risk of all-cause and cardiovascular mortality. The greater the intrapair difference in RHR the more likely that the twin with the higher RHR dies first, demonstrating that the association between RHR and mortality persists even after controlling for familial factors.

How might this impact on clinical practice?
RHR is a clinical variable that is very easy to measure, can be obtained with only minimal training and without any advanced equipment. Although there is currently not yet a specific cut-off for what is considered to be a high RHR, we recommend that RHR should be part of the routine assessment in primary prevention, and that individuals with an elevated heart rate should receive particular attention from the primary care physician, initially by way of risk factor assessment and through lifestyle modification.

compared with these studies. We extended these findings by showing that the twin with the higher heart rate was more likely to die first. This intrapair comparison design provides an opportunity to take into account the unobserved familial confounding exploiting that twins share their childhood environment and are matched partly (DZ) or fully (MZ) on genetic makeup. Hence, intrapair comparisons of exposure discordant twin pairs (difference in RHR) will per design be controlling for these familial factors.[29] To our knowledge, this methodology has not previously been used in studies of RHR.

Possible study limitations should be addressed. First, in the present study, RHR was assessed by palpating the pulse. While this is in line with recommendations,[15] the presence of an undiagnosed arrhythmia could not be detected. Second, there may have been a healthy survivor bias since all subjects survived into their middle age or older and were all without known heart disease. The 'true' risk estimate of RHR may therefore have been underestimated. In terms of the heritability estimates, this may have skewed the population towards twins with lower heart rates. Lastly, the present population was primarily of Scandinavian descent, and the results may therefore not be applicable to other populations.

In conclusion, we found that in middle-aged and elderly individuals free of cardiovascular disease, RHR is a trait with a lifelong heritability. Also, elevated RHR is associated with increased risk of all-cause and cardiovascular mortality, and the greater the intrapair difference in RHR the more likely the twin with the higher RHR is to die first, demonstrating that the association persists even after controlling for familial factors. RHR is a clinical variable that is very easy to measure. Although there is currently not yet a specific cut-off for what is considered to be a high RHR, we recommend that RHR should be part of the routine assessment in primary prevention, and that individuals with an elevated heart rate should receive particular attention from the primary care physician, initially by way of risk factor assessment and through lifestyle modification.[15 30]

Correction notice This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

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Contributors MTJ made substantial contributions to the conception, analysis, interpretation of the data, drafting the work and revising it critically for important intellectual content, performed final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. MW made substantial contributions to the analysis, interpretation of the data, drafting the work and revising it critically for important intellectual content, performed final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. SG and JH made substantial contributions to the analysis, interpretation of the data and revising it critically for important intellectual content, performed final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. GBJ made substantial contributions to the conception, interpretation of the data and revising it critically for important intellectual content, performed final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. KC made substantial contributions to the conception, acquisition, analysis, interpretation of the data and revising it critically for important intellectual content, performed final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

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Heritability of Resting Heart Rate and Association with Mortality in Middle-Aged and Elderly Twins

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SUPPLEMENTARY DATA

Supplementary table 1 Cox Regression. Hazard Ratios (HR) of Mortality According to Resting Heart Rate. Male and Female.

Time extends from time of RHR measurement to death or June 1st 2015.

Male						
Risk Factor	n	Events	Crude HR	Adj.* HR	Adj.** HR	Adj.*** HR
Mortality						
40-50	41	12	0.74 (0.42-1.33)	0.78 (0.43-1.39)	0.79 (0.44-1.41)	0.82 (0.40-1.68)
51-60	297	75	0.96 (0.74-1.25)	0.91 (0.70-1.19)	0.91 (0.70-1.19)	1.01 (0.75-1.36)
61-70	773	220	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
71-80	671	212	1.08 (0.89-1.31)	1.12 (0.93-1.36)	1.12 (0.93-1.35)	1.07 (0.86-1.34)
81-90	209	73	1.56 (1.19-2.03)	1.60 (1.22-2.08)	1.58 (1.21-2.07)	1.53 (1.11-2.10)
90-120	101	44	1.94 (1.40-2.68)	2.06 (1.49-2.85)	2.06 (1.49-2.85)	1.51 (0.99-2.31)
CVD Death						
40-50	41	3	0.97 (0.30-3.15)	0.99 (0.31-3.20)	1.02 (0.32-3.31)	1.37 (0.32-5.80)
51-60	297	10	0.68 (0.34-1.35)	0.66 (0.33-1.33)	0.67 (0.34-1.34)	0.64 (0.28-1.46)
61-70	773	42	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
71-80	671	43	1.14 (0.75-1.75)	1.16 (0.76-1.78)	1.17 (0.76-1.79)	1.08 (0.65-1.78)
81-90	209	21	2.37 (1.40-4.01)	2.40 (1.42-4.06)	2.36 (1.39-3.99)	1.89 (0.97-3.71)
90-120	101	6	1.40 (0.59-3.30)	1.42 (0.61-3.36)	1.42 (0.60-3.34)	1.32 (0.49-3.53)

Female						
Risk Factor	n	Events	Crude HR	Adj.* HR	Adj.** HR	Adj.*** HR
Mortality						
40-50	23	8	1.10 (0.54-2.24)	1.33 (0.65-2.69)	1.20 (0.57-2.57)	0.76 (0.32-1.80)
51-60	251	85	1.53 (1.18-1.97)	1.69 (1.31-2.18)	1.67 (1.30-2.16)	1.84 (1.37-2.46)
61-70	739	199	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
71-80	773	244	1.16 (0.96-1.40)	1.24 (1.03-1.50)	1.23 (1.02-1.49)	1.18 (0.95-1.47)
81-90	266	105	1.95 (1.54-2.47)	1.95 (1.54-2.47)	1.94 (1.53-2.46)	1.69 (1.28-2.23)
90-120	138	57	1.62 (1.21-2.18)	1.77 (1.32-2.38)	1.74 (1.29-2.34)	1.52 (1.09-2.14)
CVD Death						
40-50	23	2	1.36 (0.33-5.65)	1.56 (0.37-6.51)	1.63 (0.39-6.82)	1.59 (0.31-8.08)
51-60	251	27	2.66 (1.62-4.35)	2.85 (1.74-4.69)	2.91 (1.77-4.80)	3.26 (1.84-5.80)
61-70	739	38	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
71-80	773	55	1.31 (0.86-1.99)	1.38 (0.91-2.09)	1.39 (0.91-2.12)	1.37 (0.85-2.21)
81-90	266	18	1.82 (1.04-3.20)	1.82 (1.04-3.20)	1.75 (0.98-3.11)	1.09 (0.53-2.26)
90-120	138	19	2.85 (1.64-4.96)	2.98 (1.71-5.19)	3.01 (1.72-5.25)	2.55 (1.34-4.84)

*: Adjusted for gender and age at interview.

**: Adjusted for gender, age at interview and BMI.

***: Adjusted for gender, age interview, BMI, FEV_1, diabetes, hypertension, smoking, physical activity and zygosity.

Supplementary table 2 Matched pair Cox Regression (pair-specific baseline hazard function). Hazard Ratios (HR) of Mortality According to Resting Heart Rate. Time extends from time of RHR measurement to death or June 1st 2015.

Risk Factor	n	Events	Crude HR	Adj.* HR	Adj.** HR	Adj.*** HR
Mortality						
40-50	64	20	0.70 (0.17-2.97)	0.67 (0.16-2.84)	0.68 (0.16-2.89)	0.27 (0.03-2.36)
51-60	548	160	1.62 (1.02-2.58)	1.64 (1.03-2.61)	1.59 (1.00-2.55)	1.55 (0.87-2.77)
61-70	1,512	419	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
71-80	1,444	456	1.51 (1.07-2.13)	1.55 (1.10-2.20)	1.51 (1.07-2.15)	1.44 (0.91-2.26)
81-90	475	178	2.06 (1.29-3.30)	2.15 (1.34-3.47)	2.10 (1.30-3.39)	1.93 (1.02-3.64)
90-120	239	101	2.92 (1.44-5.95)	3.04 (1.48-6.23)	2.92 (1.42-6.02)	2.70 (1.02-7.13)
CVD Death						
40-50	64	5	3.36 (0.28-40.89)	2.55 (0.20-32.51)	2.78 (0.21-37.07)	1.49 (0.05-40.50)
51-60	548	37	2.08 (0.72-6.06)	1.93 (0.65-5.72)	1.93 (0.65-5.73)	1.15 (0.27-4.84)
61-70	1,512	80	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
71-80	1,444	98	2.13 (0.91-4.98)	2.31 (0.97-5.48)	2.25 (0.94-5.39)	2.53 (0.61-10.54)
81-90	475	39	2.22 (0.67-7.41)	2.10 (0.62-7.10)	2.08 (0.61-7.05)	0.83 (0.09-7.57)
90-120	239	25	5.11 (0.98-26.54)	6.01 (1.08-33.40)	5.73 (1.01-32.33)	2.22 (0.28-17.85)

*: Adjusted for gender and age at interview.
**: Adjusted for gender, age at interview and BMI.
***: Adjusted for gender, age interview, BMI, FEV_1, diabetes, hypertension, smoking, physical activity and zygosity.

Supplementary table 3 Matched pair Cox Regression (pair-specific baseline hazard function) for monozygotic twins. Hazard Ratios (HR) of Mortality According to Resting Heart Rate. Time extends from time of RHR measurement to death or June 1st 2015.

Risk Factor	**n**	**Events**	**Crude HR**	**Adj.* HR**	**Adj.** HR**	**Adj.*** HR**
Mortality						
40-50	10	0	-	-	-	-
51-60	120	26	1.44(0.67-3.08)	1.45(0.68-3.12)	1.41(0.65-3.02)	0.83(0.33-2.1)
61-70	360	64	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
71-80	330	68	1.25(0.73-2.15)	1.24(0.72-2.13)	1.23(0.71-2.12)	1.44(0.65-3.21)
81-90	89	27	2.89(1.2-6.98)	3.05(1.25-7.45)	2.91(1.18-7.19)	4.03(1.08-14.96)
90-120	49	14	3.26(0.88-12.03)	3.49(0.94-12.99)	4.03(1.05-15.42)	4.42(0.61-32.19)

*: Adjusted for gender and age at interview.
**: Adjusted for gender, age at interview and BMI.
***: Adjusted for gender, age interview, BMI, FEV_1, diabetes, hypertension, smoking, physical activity and zygosity.

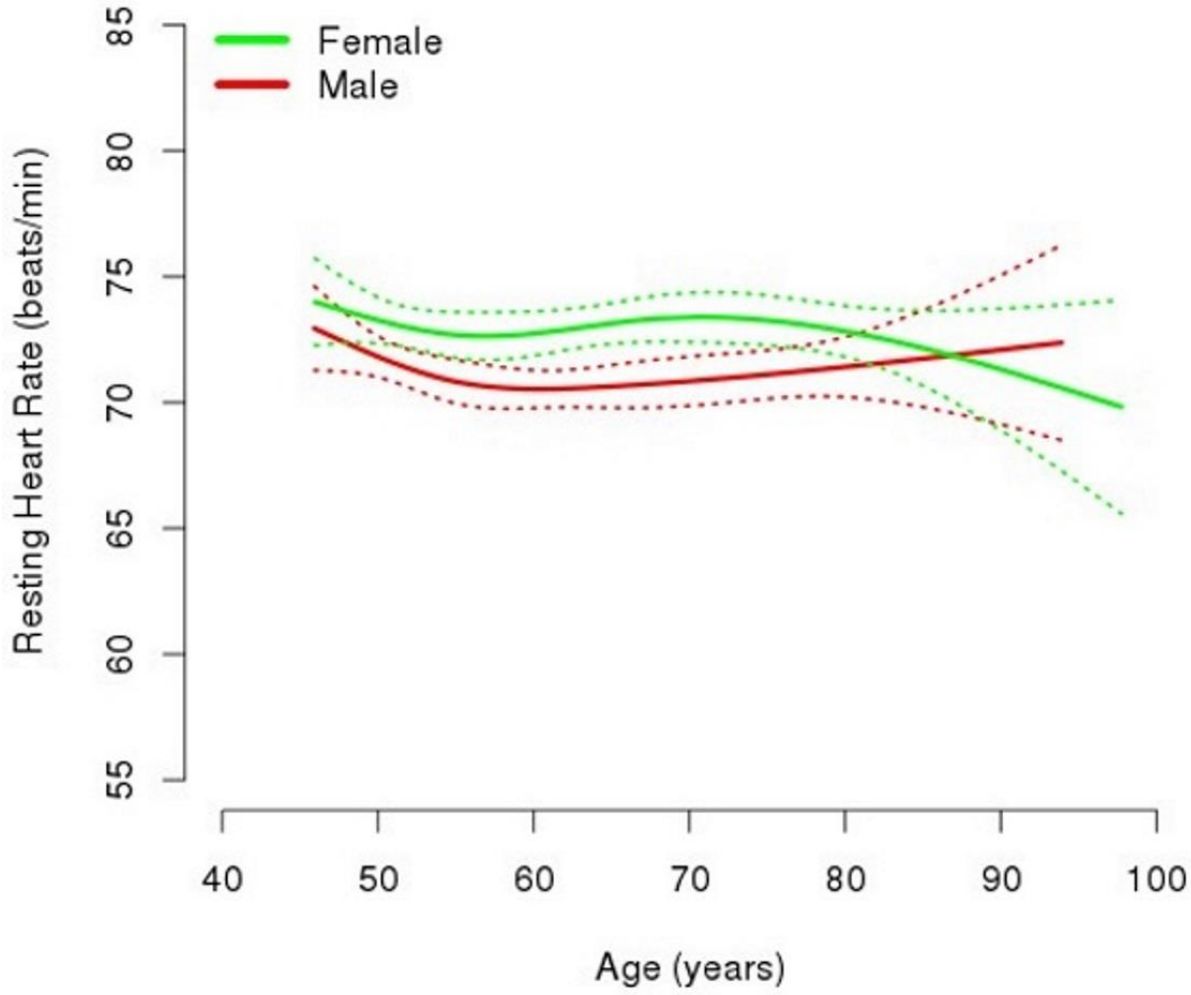

Figure 1: RHR for males and females with 95% confidence bands

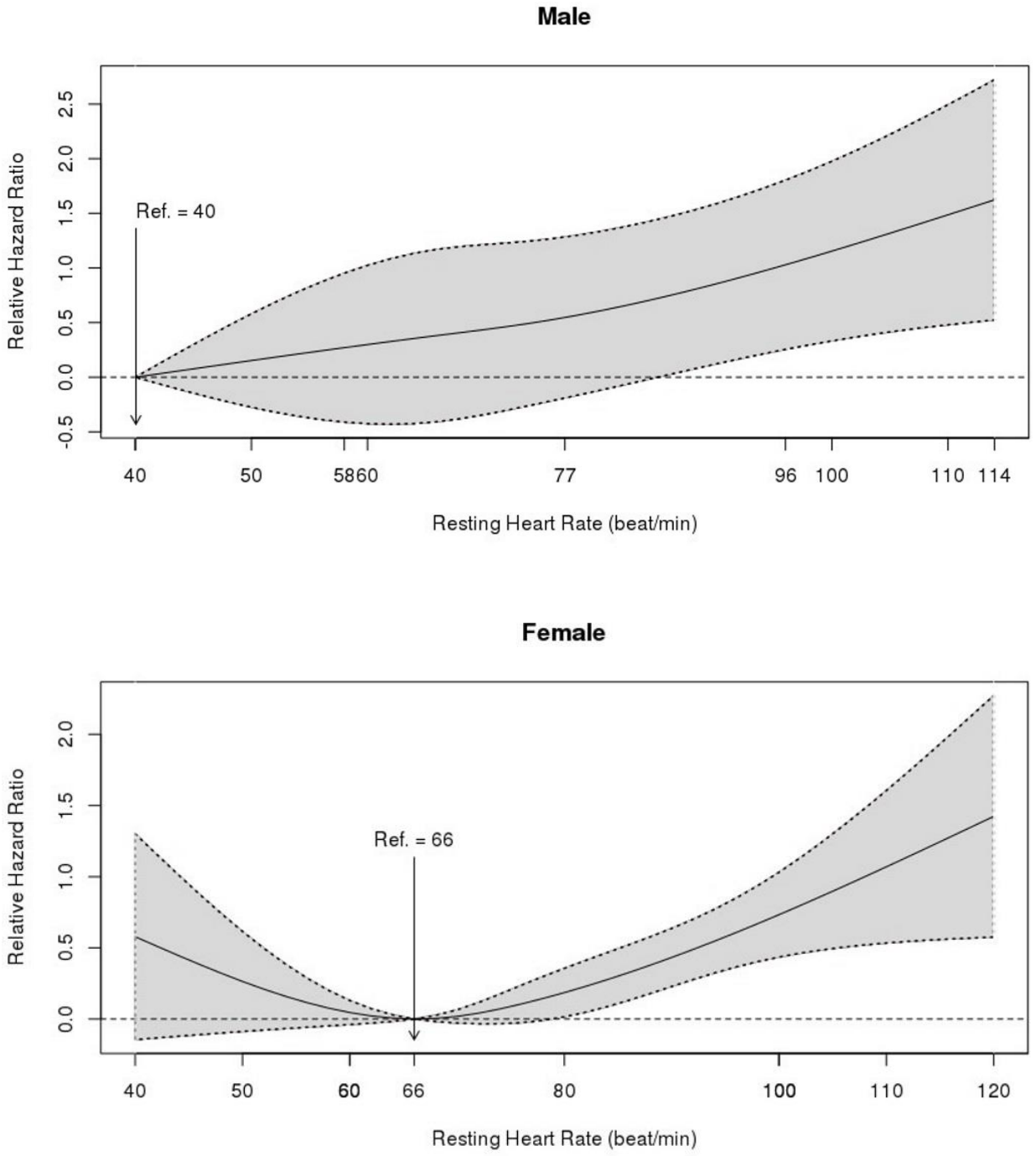

Figure 2 . Estimated hazard ratio curve by RHR (the hazard of RHR relative to the hazard of RHR with best mortality). A smoothing method based on splines was used to introduce flexibility into the Cox model and plotted the spline-based HR curve with a RHR reference value as the value of the predictor with the best mortality