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

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Abstract

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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.

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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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.³⁴ 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 1s (FEV₁) 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, FEV₁, 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 model¹⁸ (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 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 intra-class 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).

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 studies⁵⁶ 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 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 disease⁸ 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,³²² and a heritability of similar magnitude in subjects around age 40 years.³²³ 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 twins²⁴ 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 males²⁶; in contrast, other studies have found RHR to be associated with mortality only in elderly males²⁷ and elderly females.²⁸ The present findings are possibly due to longer follow-up and greater number of endpoints 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.¹⁵³⁰

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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.

Figure 1.

Cardiovascular disease pacemaker, etc., include previous cardiovascular disease, pacemaker, self-reported medicine (beta-blockers, adrenergic stimulants, 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.

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 where the twin with higher RHR died first/number of available pairs. bpm, beats per min; RHR, resting heart rate.

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
	45–65year	>65year	45–65year	>65year	45–65year	>65year
N	1469	623	1354	836	2823	1459
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)
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)
Deaths (%)	14.3	68.4	11.5	64.8	12.7	66.4
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)
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)
Diabetes (%)	2.4	4.5	1.5	4.7	2.0	4.6
Hypertension (%)	0.5	5.9	2.4	6.6	1.4	6.3
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)
Physical activity						
Light (%)	54	44	63	50	59	47
Moderate (%)	36	39	31	37	33	38
High (%)	10	17	6	13	8	15
Smoking						
Never smokers (%)	30	18	43	46	36	34
Ex-smokers (%)	30	39	18	25	24	31
Current smokers (%)	40	43	39	29	40	35

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.

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 to 1.46)	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 to 1.35)	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 to 2.12)	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 (0.86 to 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, FEV1, diabetes, hypertension, smoking, physical activity and zygosity.

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