ORIGINAL RESEARCH

Are Changes in Heart Rate Variability in Middle-Aged and Older People Normative or Caused by Pathological Conditions? Findings From a Large Population-Based Longitudinal Cohort Study

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***Background*—**No study to date has investigated longitudinal trajectories of cardiac autonomic modulation changes with aging; therefore, we lack evidence showing whether these changes occur naturally or are secondary to disease or medication use. This study tested whether heart rate variability (HRV) trajectories from middle to older age are largely normative or caused by pathological changes with aging in a large prospective cohort. We further assessed whether HRV changes were modified by socioeconomic status, ethnicity, or habitual physical activity.

***Methods and Results*—**This study involved 3176 men and 1238 women initially aged 44 to 69 years (1997–1999) from the UK Whitehall II population-based cohort. We evaluated time- and frequency-domain HRV measures of short-term recordings at 3 time points over a 10-year period. Random mixed models with time-varying covariates were applied. Cross-sectionally, HRV measures were lower for men than for women, for participants with cardiometabolic conditions, and for participants reporting use of medications other than beta blockers. Longitudinally, HRV measures decreased significantly with aging in both sexes, with faster decline in younger age groups. HRV trajectories were not explained by increased prevalence of cardiometabolic problems and/or medication use. In women, cardiometabolic problems were associated with faster decline in the standard deviation of all intervals between R waves with normal-to-normal conduction, in low-frequency HRV, and in low-frequency HRV in normalized units. Socioeconomic status, ethnicity, and habitual physical activity did not have significant effects on HRV trajectories.

***Conclusions*—**Our investigation showed a general pattern and timing of changes in indices of cardiac autonomic modulation from middle to older age. These changes seem likely to reflect the normal aging process rather than being secondary to cardiometabolic problems and medication use. **(*J Am Heart Assoc*. 2016;1:e002365 doi: 10.1161/JAHA.115.002365)**

Key Words: cardiac autonomic modulation • epidemiology • ethnicity • longitudinal trajectory • normative aging • socioeconomic status

A substantial amount of research has focused on biomarkers that identify people at higher risk of developing cardiovascular disease.[1] One indicator that seems to play a pivotal role is dysfunction of the autonomic nervous system. Specifically, increased sympathetic and/or decreased parasympathetic activity has been associated with increased risk for a number of cardiac outcomes such as sudden cardiac death, heart failure, ventricular arrhythmias, or hypertension.[2,3] Heart rate variability (HRV) is a valid noninvasive technique for estimating the characteristics of the autonomic nervous system and for quantifying modulation of the sympathetic and parasympathetic inputs.[4,5] Decreased HRV has been linked to increased mortality in cardiac patients[6,7] and increased risk of coronary heart disease and cardiac mortality in general populations.[8,9] Establishing the associations between HRV and coronary heart disease remains problematic because a number of cofactors may wholly or partially account for the increased risk of coronary heart disease among persons with decreased HRV. These factors include age, poor health, physical inactivity, and medication use as well as socioeconomic status (SES) and ethnicity.

HRV is believed to decline as people age, but a key scientific question is whether falls in HRV occur naturally with

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age as a result of the aging process itself or as a result of pathogenic processes and/or medication use. A number of studies have documented the normal changes in HRV that accompany aging[10–16] and HRV changes due to chronic diseases or health-related conditions.[17–21] These studies, however, have significant limitations including a reliance on cross-sectional data or lack of statistical adjustment for important factors. The evidence of age-related HRV changes is based primarily on cross-sectional studies of different age groups,[10,12–16] making it difficult to identify within-person change. Differences between age groups in cross-sectional studies could be related to selective survival among older people rather than genuine effects. A small number of longitudinal studies on age-related HRV changes have been conducted.[11,17–21] Of these, only a few are population based,[18–21] and others have relied on small samples of elderly participants.[12,13] No studies with large sample sizes have conducted >2 repeated HRV measurements. Medication use and/or the existence of prevalent cardiometabolic problems such as diabetes or stroke may be related to HRV changes over time. Consequently, the rate and temporal course of HRV changes are not well understood.

Cardiac autonomic modulation has been found to be significantly influenced by sex.[10,12,14,16] On average, women have been shown to have reduced sympathetic influence and enhanced parasympathetic influence on heart rate (HR) relative to men.[22] Over time, different ways of responding to health conditions and medication may influence the shape of HRV changes between men and women.

Another relevant factor that contributes to accelerated aging processes and development and prognosis of cardiovascular disease outcomes is SES.[23] It is well documented that persons from lower SES groups have higher risk of cardiovascular disease outcomes and reduced HRV and parasympathetic activity than persons from higher SES groups.[24,25] It remains unclear how the associations between SES and HRV change as people age. Similarly, ethnicity is associated with HRV levels. On average, people of white ethnic origin have been shown to have lower HRV than African Americans,[26] whereas studies of differences in HRV levels between people of South Asian and European origin have shown inconsistent results.[27,28] Evidence of ethnic differences in changes in HRV over time is limited. Finally, physical activity has been proposed as a further important determinant of HRV.[29] Maintenance of physical activity as part of the aging process may have a positive effect on the rate of change in HRV over time.

Using unique data from a large, longitudinal UK population-based cohort study with 3 measurements of short-term HRV over a 10-year period, we sought to test whether HRV changes were largely normative or caused by pathological changes with aging. We also examined whether changes in HRV over time varied systematically by SES, ethnicity, and habitual physical activity.

Methods

Sample

The Whitehall II cohort study is an ongoing longitudinal study of 10 308 civil servants (6895 men and 3413 women) based in London, United Kingdom.[30] All civil servants aged 35 to 55 years and employed in 20 London-based white collar civil service departments were invited to participate in this study, and recruitment took place from 1985 to 1988. Subsequent data collection alternated between postal questionnaires alone and postal questionnaires accompanied by clinical examination. HR and HRV were measured at the fifth (1997–1999), seventh (2002–2004), and ninth (2007–2009) phases of data collection. At phase 5, all study members known to be alive and resident in the United Kingdom were invited to attend a screening clinic. Although 6554 participants (1909 women) attended the clinic (67% of participants), HR was recorded for only 3365 participants because of staff availability. No HRV recordings were collected on 69 days during screening, accounting for the majority of missing HRV data at phase 5. Participants who did not undergo HRV recordings at phase 5 did not differ significantly from those who did with respect to age, sex, and employment grade.[24] To focus on the estimation of within-person change in HR and HRV levels, we restricted the analytical sample to the subset of participants with at least 2 HRV measurements. The analytical sample for this study comprised 4414 participants (3176 men) with at least 2 HRV measurements. The University College London Medical School committee on the ethics of human research approved the Whitehall II study. Informed consent was obtained at baseline and renewed at each contact. Whitehall II data, protocols, and other metadata are available to bona fide researchers for research purposes. Please refer to the Whitehall II data sharing policy (http://www.ucl.ac.uk/whitehallII/data-sharing).

Outcomes

Details on the assessment of HR and HRV in Whitehall II can be found elsewhere.[20,24] Briefly, 5-minute supine resting 12-lead ECGs were obtained after 5 minutes of rest. Different ECG recorders were used in the different phases. A Kardiosis device (Kardiosis Cardiologic Diagnostic Systems), a SEER MC recorder (GE Medical Systems), and a Getemed recorder (Getemed Teltow) were used at phases 5, 7, and 9, respectively. The sampling frequencies and outputs of the different devices were comparable. Five minutes of beat-to-beat HR data were sampled at 500 Hz frequency to obtain a

digitized sequence of R waves. Using an automatic algorithm,[31] ECG abnormalities including ectopic beats, right bundle-branch block, respiratory arrhythmia, blocked atrial extrasystole, and high-amplitude and wide T waves were identified, and normal QRS complexes suited for a reliable HRV analysis were detected. HRV was analyzed both in the time domain (standard deviation of all intervals between R waves with normal-to-normal conduction [SDNN]) and in the frequency domain using a Blackman-Tukey algorithm. Frequency-domain components were computed by integrating the power spectrum within 2 frequency bands: 0.04 to 0.15 Hz (low-frequency power [ms^2]) and 0.15 to 0.4 Hz (high-frequency power [ms^2]). Low-frequency power (low-frequency HRV [LF-HRV]) reflects both parasympathetic and sympathetic HR modulations; high frequency (high-frequency HRV [HF-HRV]) is an index of parasympathetic modulation of HR.[4,5] In addition, we used LF-HRV in normalized units (LFnu [%]), which was computed as LF/(LF+HF). To avoid redundancy, the HF-HRV in normalized units, being equal to 100% minus LFnu (%), was not analyzed. These ratio-based HRV measures have been proposed as indices of sympathovagal balance.[4,5]

Covariates

Age at phase 5 (1997–1999) was categorized into 4 groups (44–49, 50–54, 55–59, and 60–69 years). SES, assessed by the British civil service employment grade, was categorized into 3 groups in order of decreasing salary and work role: administrative (high), professional/executive (middle), and clerical/support (low). Ethnicity was defined according to the Office for National Statistics 1991 census categories, and participants were initially categorized into 4 ethnic groups: white European, South Asian, African Caribbean, and other. Numbers were too small to examine age- and sex-specific HR and HRV trajectories for nonwhite minority ethnic groups.

Physical activity was categorized according to whether participants adhered to the World Health Organization (WHO) physical activity guidelines of at least 1 hour of vigorous activity 3 times or 2.5 hours of moderate activity 5 times per week.[32] These guidelines are widely used and have been quantitatively validated for cardiovascular outcomes.[33] Habitual physical activity over the 10-year period was categorized as hardly ever (once or less through follow-up), sometimes (in 2 phases), or always (in all 3 follow-up phases) meeting the WHO guidelines. Cardiometabolic problems at each phase were assessed as the presence of any of the following chronic disease or health-related conditions: diagnosed coronary heart disease including heart failure,[9,34] stroke,[35] hypertension,[18,20] diabetes,[19,29] and obesity.[20] These factors were chosen as covariates based on systematic literature review as likely to profoundly influence HRV. At each screening, participants provided details of current medications taken in the previous 14 days (generic name, brand name, or both). Prescribed medication included all drugs taken in the previous 14 days that were prescribed by a doctor such as analgesics, antihyperlipidemic agents, antidiabetic agents, psychotropic agents, and antibiotics. We distinguished between beta blockers (British National Formulary codes, chapter 2.4) and other prescribed medications because previous studies have shown the former to have a beneficial effect on HRV levels.[36] Other cardiovascular and central nervous system–related medications have been shown to decrease or have no effect on HRV levels.[17,18]

Statistical Analysis

Analyses were performed in Stata 13.1 (StataCorp). All tests of statistical significance were based on 2-tailed probability ($P<0.05$). SDNN, LF-HRV, and HF-HRV were transformed by natural logarithm because their distributions were skewed. Outliers (mean±3 SD) were trimmed to 3 SD from the mean prior to transformation. Age-adjusted arithmetic and geometric means and 95% CIs were calculated for the subset of 1658 participants with complete HR and HRV measurements at each phase of data collection. For this subset of participants, the change in HR between the first and third measurements was defined as HR at phase 9 minus HR at phase 5, scaled to a time difference of 10 years. For HRV measurements, change over time was calculated using the log-transformed values. Back transformation was applied to present the percentage change over the 10-year period. Spearman rank correlation coefficient was used to examine the correlations between the HR and HRV measures at phase 5.

Two sets of linear mixed models were used to estimate change in HR and HRV over 10-year follow-up. This method of estimation uses all available data over follow-up, takes into account the intraindividual correlation between repeated measurements, and can handle missing data. The intercept was fitted as a random effect, allowing participants to have different HRV values at baseline.[37]

The first set of models was used to examine age-specific HRV trajectories without adjusting for any covariates. The dependent variable was the 3 repeated measurements of HR and HRV, and the independent variables were time (exact time in years between phases, included as a continuous variable, divided by 10 to yield estimates of change over 10 years), age at phase 5 (included as a categorical variable), and interaction between time and age (thereby enabling the rate of change to vary by age at baseline). Previous studies have suggested sex differences in autonomic nervous system functioning. Interaction terms suggested sex difference in the association between age and HR trajectories ($P=0.074$), leading us to stratify all analyses by sex. In the second set of models, 5 key

covariates (cardiometabolic problems, medication use [other than beta blockers] versus those not on medication, SES, ethnicity, and adherence to WHO physical activity guidelines) were included to explore their temporal association with HR and HRV. The following 3 age-adjusted coefficients were of interest, using cardiometabolic condition incidence as an example: (1) The coefficient for time represented the 10-year change in HR or HRV for participants in the reference category (ie, no cardio-metabolic condition), (2) the coefficient for cardiometabolic condition represented the difference in HR or HRV between the no cardiometabolic condition and cardiometabolic condition groups at baseline (phase 5), and (3) the coefficient for the interaction between time and cardiometabolic condition represented the difference in the 10-year rate of change between participants with and without cardiometabolic condition. As we focused on medications associated with potential decreases in HRV, we excluded participants using beta blockers in primary analyses. In secondary analyses, we focused specifically on the rates of change in HR and HRV for the participants who reported use of beta blockers at any phase over the 10-year period. Sensitivity analyses were also run focusing specifically on a subset of "healthy" participants, namely, those who were free of a cardiometabolic condition and had no reported medication use over the 10-year period.

Results

Of the 10 308 participants at phase 1 (1985–1988), 306 died and 752 dropped out of the study before the start of HR and HRV data collection at phase 5 (1997–1999). Of the 9250 remaining participants, HR and HRV measures were obtained from 3365, 4095, and 5624 participants at phases 5, 7, and 9, respectively. A total of 6410 participated in ≥1 of the 3 HR and HRV assessments over 10 years; 4414 had ≥2 assessments of HR and HRV over the 10-year follow-up. Two-thirds (2756) of the 4414 participants in the analytical sample contributed 2 waves of HR and HRV data, and 1658 (37.6%) contributed all 3 waves. The analytical sample was composed of more men than women (70.8% versus 59.9%; $P<0.001$) and persons from the high employment grade (43.2% versus 35.1%; $P<0.001$). In participants with only 1 measure, the mean estimates of HR and LF-HRV were slightly higher and lower, respectively, for both sexes at phase 5 compared with the main analysis. Table S1A compares the characteristics at phase 5 for participants with 1 HR and HRV assessment versus ≥2 assessments. Compared with participants with 1 assessment, the analytical sample was composed of more men than women (72.0% versus 68.4%; $P=0.004$), more persons in the youngest age category (22.9% versus 20.3% aged 44–49 years at phase 5; $P<0.001$), and persons from the high employment grade (45.1% versus 38.6%; $P<0.001$). The difference in the prevalence of cardiometabolic conditions was not statistically significant.

Table 1 presents the descriptive characteristics of the analytical sample at phases 5, 7, and 9 by age, civil service grade, ethnicity, presence of cardiometabolic problems, medication use, and adherence to WHO physical activity guidelines. The majority of participants were of white European origin. Table S1B presents the Spearman rank correlation coefficients between HR and HRV at phase 5. Strong positive correlations were found between all HRV measures except for LFnu, ranging from 0.74 (LF-HRV and HF-HRV) to 0.90 (LF-HRV and SDNN). Correlations between HRV and HR were negative and lower in magnitude: $r=-0.47$ for SDNN, $r=-0.37$ for LF-HRV, and $r=-0.42$ for HF-HRV.

Table 2 presents the age-adjusted means at phases 5, 7, and 9 for the subset of 1658 participants with HR and HRV measurements at all 3 phases. Average levels of HR, SDNN, and LF- and HF-HRV decreased consistently for men but increased for women from phase 5 to 7. These HRV measures, however, declined significantly for both sexes over the 10-year follow-up. HF-HRV, for example, decreased by 30.6% for men and 32.8% for women over the 10-year period. LFnu did not change significantly over the 10-year period.

Table 3 presents the results from the mixed models that estimated associations between age at baseline and HR and HRV trajectories. Age-specific rates of change over the 10-year follow-up estimated from each model are presented in Table 4. Results indicated significant decreases in SDNN, LF-HRV, HF-HRV, and HR; however, the interaction terms between age at baseline and time showed significant differences in the rate of decline in LF-HRV for women, in HF-HRV for men and for women, and in LFnu for men. Younger participants at baseline experienced faster decline in HF-HRV than their older counterparts ($P=0.001$ and $P=0.020$ for the time×age interaction term for men and for women, respectively). Change in HF-HRV for men aged ≥60 years at baseline, for example, was −13% over 10 years compared with −52% for men aged 44 to 49 years (see Table 4). In the case of LFnu, older men at baseline (aged 54–59 and ≥60 years) experienced decreases in LFnu compared with no change in the youngest men (aged 44–49 years). Declines in HR and SDNN for women showed marginally significant differences in the rate of change across age groups ($P=0.063$ and $P=0.060$) (Table 3).

Table 5 presents results from the mixed-models analysis undertaken to assess associations among cardiometabolic condition, medication use (other than beta blockers), and HR and HRV trajectories. At baseline, cardiometabolic condition was significantly associated with lower values of SDNN, LF-HRV, and HF-HRV for both sexes and lower values of LFnu for men. For men, cardiometabolic condition had no significant

Table 1. Descriptive Characteristics of Analytical Sample by Data Collection Phase and Sex

	Phase 5 (1997–1999)		Phase 7 (2002–2004)		Phase 9 (2007–2009)	
	Men	Women	Men	Women	Men	Women
n	1962	756	2648	1066	2940	1114
Age, y						
44–49, n (%)	457 (23.3)	166 (22.0)	608 (23.0)	224 (21.0)	692 (23.5)	257 (23.1)
50–54, n (%)	600 (30.6)	196 (25.9)	803 (30.3)	303 (28.4)	917 (31.2)	330 (29.6)
55–59, n (%)	395 (20.1)	160 (21.2)	566 (21.4)	248 (23.3)	615 (20.9)	257 (23.1)
60–69, n (%)	510 (26.0)	234 (31.0)	671 (25.3)	291 (27.3)	716 (24.4)	270 (24.2)
Civil service grade						
High, n (%)	1080 (55.5)	134 (18.0)	1360 (52.9)	243 (23.4)	1547 (54.1)	254 (23.4)
Medium, n (%)	776 (39.9)	360 (48.3)	1094 (42.6)	484 (46.7)	1201 (42.0)	517 (47.7)
Low, n (%)	89 (4.6)	252 (33.8)	115 (4.5)	310 (29.9)	114 (4.0)	313 (28.9)
Ethnicity						
White, n (%)	1850 (94.3)	643 (85.1)	2476 (93.5)	911 (85.6)	2760 (93.9)	953 (85.6)
South Asian, n (%)	80 (4.1)	55 (7.3)	118 (4.5)	80 (7.5)	120 (4.1)	78 (7.0)
African Caribbean, n (%)	22 (1.1)	48 (6.4)	38 (1.5)	60 (5.6)	40 (1.4)	66 (5.9)
Other, n (%)	9 (0.5)	9 (1.2)	12 (0.5)	4 (1.3)	16 (0.6)	16 (1.5)
Cardiometabolic c., n (%)*	852 (43.4)	348 (46.0)	1326 (50.1)	591 (55.4)	1666 (56.7)	672 (60.3)
CHD, n (%)	239 (12.2)	130 (17.2)	401 (15.1)	202 (19.0)	536 (18.2)	229 (20.6)
Medication use, n (%)	685 (35.2)	414 (55.1)	1340 (50.9)	677 (63.7)	2311 (78.7)	934 (83.9)
CVD medication, n (%)	267 (13.7)	109 (14.5)	710 (27.0)	297 (27.9)	1525 (51.9)	543 (48.8)
Beta blockers, n (%)	76 (3.9)	41 (5.5)	226 (8.6)	90 (8.5)	278 (9.5)	86 (7.7)
CNS medication, n (%)	51 (2.6)	37 (4.9)	102 (3.9)	62 (5.8)	142 (4.8)	95 (8.5)
Antidepressants, n (%)	35 (1.8)	30 (4.0)	69 (2.6)	45 (4.2)	102 (3.5)	71 (6.4)
Adherence to WHO physical activity recommendations						
Hardly ever, n (%)	1302 (74.3)	539 (83.2)	1766 (74.9)	776 (83.5)	2002 (74.7)	841 (83.5)
Sometimes, n (%)	270 (15.4)	66 (10.2)	353 (15.0)	92 (9.9)	412 (15.4)	99 (9.8)
Always, n (%)	180 (10.3)	43 (6.6)	239 (10.1)	61 (6.6)	266 (9.9)	67 (6.7)

Whitehall II study participants with ≥2 assessments of heart rate and heart rate variability over 10-year follow-up. CHD indicates coronary heart disease; CNS, central nervous system; CVD, cardiovascular disease; WHO, World Health Organization.

*Presence of any of the following cardiometabolic conditions: diagnosed CHD, stroke, heart failure, diabetes, obesity, and hypertension. Habitual physical activity over the 10-year period was categorized as hardly ever (once or less through follow-up), sometimes (in 2 phases), or always (in all 3 follow-up phases) meeting the WHO guidelines.

effect on the rate of decline in HRV measures. For women, cardiometabolic condition was associated with faster rates of decline in SDNN, LF-HRV, and LFnu. At baseline, reported use of prescribed medication (other than beta blockers) was associated with significantly lower values of SDNN, LF-HRV, and HF-HRV for men and for women and with higher values of HR for men. Differences in the rate of change in HR and HRV by medication group were not significant for either sex. The dynamics of HR and HRV change over time by cardiometabolic condition and reported medication use (other than beta blockers) are presented in Figures 1 and 2, respectively.

In secondary analyses, reported use of beta blockers at baseline was associated with significantly lower values of HR, LF-HRV, and LFnu for men and for women and significantly higher values of HF-HRV for women. Reported use of beta blockers over 10 years was significantly associated with faster declines in SDNN and LF-HRV for women (P=0.029 and P=0.032) but not for men (data not shown).

HR and HRV Trajectories by SES, Ethnicity, and Habitual Physical Activity

At each phase, average levels of SDNN for men in the high employment grade were highest and average levels of HR were lower than for men in the middle and low grades. Average levels of HR were lower for women in the high

Table 2. Age-Adjusted Heart Rate and Heart Rate Variability Means (95% CI) at Baseline and 5- and 10-Year Follow-Up by Sex

	Men	Women
n	1198	460
HR, bpm		
Phase 5	68.3 (67.7–68.9)	70.4 (69.4–71.4)
Phase 7	66.6 (65.9–67.2)	67.3 (66.3–68.3)
Phase 9	66.7 (66.1–67.3)	68.9 (67.9–69.8)
Mean change per 10 years	−1.6 (−2.1 to −1.1)	−1.5 (−2.3 to −0.7)
SDNN, ms*		
Phase 5	34.8 (34.0–35.7)	33.1 (31.9–34.4)
Phase 7	33.6 (32.8–34.5)	34.7 (33.3–36.2)
Phase 9	30.2 (29.4–31.1)	29.3 (28.1–30.7)
Percentage change per 10 years	−13.6 (−16.4 to −10.8)	−11.7 (−16.2 to −7.2)
LF-HRV, ms^2*		
Phase 5	337.7 (320.8–355.4)	259.1 (238.5–281.4)
Phase 7	294.9 (278.7–311.9)	273.1 (249.4–299.1)
Phase 9	235.8 (221.6–250.9)	196.5 (177.7–217.2)
Percentage change per 10 years	−34.2 (−40.2 to −28.2)	−26.7 (−36.4 to −17.7)
HF-HRV, ms^2*		
Phase 5	121.4 (114.2–128.9)	145.3 (131.8–160.2)
Phase 7	112.5 (105.3–120.2)	150.3 (135.1–167.2)
Phase 9	87.9 (82.1–94.2)	103.7 (92.8–115.9)
Percentage change per 10 years	−30.6 (−37.4 to −23.7)	−32.8 (−43.8 to −21.8)
LFnu (%)		
Phase 5	71.9 (71.1–72.7)	62.7 (61.4–64.0)
Phase 7	70.7 (69.9–71.5)	63.3 (62.0–64.6)
Phase 9	71.1 (70.3–72.0)	63.9 (62.5–65.2)
Mean change per 10 years	−0.8 (−1.7 to 0.1)	1.2 (−0.3 to 2.6)

Whitehall II study participants with assessment of HR and HRV at each phase over the 10-year follow-up. bpm indicates beats per minute; HF-HRV, high-frequency heart rate variability; HR, heart rate; LF-HRV, low-frequency heart rate variability; LFnu, low-frequency heart rate variability in normalized units; SDNN, standard deviation of all intervals between R waves with normal-to-normal conduction.
*Geometric means calculated due to skewed distributions.

employment grade. Differences in the rate of change in HR and HRV across SES were not statistically significant (Table S2A and S2B). For both sexes, average values of LFnu were significantly higher, and for men, values of HF-HRV were significantly lower for participants of white ethnic origin. Differences in the rate of change across the white and nonwhite ethnic minority groups were not statistically significant (Table S3A and S3B). For men who consistently adhered to the WHO physical activity guidelines (at least 1 hour of vigorous activity 3 times or 2.5 hours of moderate activity 5 times per week) over the 10-year period, average levels of SDNN, LF-HRV, and HF-HRV were higher and average levels of HR were lower than for men who met the guidelines on ≤1 occasion. Differences in the rate of change across the physical activity groups were not significant for HRV in either sex and were not significant for HR for men. For women, levels of adherence to WHO guidelines were associated with differences in the rate of change in HR. Compared with women who met the guidelines on ≤1 occasion throughout 10-year follow-up, women who met the guidelines on each occasion showed a faster pace of decline in HR (Table S4A and S4B).

Discussion

The main finding in this large longitudinal UK population-based study is that HRV decreased with aging independent of pathological conditions or medication use, potentially suggesting that cardiac autonomic modulation diminishes due to normative aging. Men and women showed similar rates of HRV decline, with faster decline in younger age groups. Cross-sectionally, average levels of HRV were lower for men than for women, for participants with cardiometabolic condition, and for participants reporting the use of prescribed medications other than beta blockers. We further observed that women with a cardiometabolic condition experienced faster decline in SDNN, LF-HRV, and LFnu compared with women without a cardiometabolic condition. SES, ethnicity, and habitual physical activity did not show statistically significant associations with longitudinal HRV trajectories. Finally, women who met the WHO physical activity guidelines on each occasion over 10-year follow-up showed a faster pace of decline in HR than women who met the guidelines on ≤1 occasion.

Average levels of SDNN, LF-HRV, and HF-HRV in this large UK middle-aged cohort were similar to levels seen in population-based studies in the United States[19] and Germany[38] based on short-term HRV recordings measured using similar procedures. Given the dearth of longitudinal studies of patterns of HRV changes with aging, it is important that our current study replicated most of the cross-sectional evidence of HRV declines with aging.[10,12–14] Our study is unique in demonstrating age-related HRV changes based on short-term recordings. Most of the cross-sectional[10,11,14,15] and longitudinal[17,22] evidence on age-related changes in HRV has been

Table 3. Associations (Mixed-Models Analyses) Between Age at Baseline and Heart Rate and Heart Rate Variability Trajectories by Sex

	Men (n=3176)			Women (n=1238)		
	b	SE	*P* Value	b	SE	*P* Value
HR, beats/min						
Intercept	68.053	0.405	<0.001	69.175	0.594	<0.001
Time, per 10 years	−2.300	0.492	<0.001	−1.848	0.842	0.028
Age, y						
44–49*	0			0		
50–54	0.054	0.537	0.920	0.721	0.790	0.362
55–59	−0.737	0.589	0.211	−1.201	0.834	0.150
60–69	0.229	0.564	0.685	1.547	0.800	0.053
Time×age, y						
44–49*	0			0		
50–54	0.592	0.651	0.363	0.346	1.139	0.761
55–59	0.343	0.726	0.637	1.730	1.217	0.155
60–69	0.787	0.691	0.255	−1.412	1.150	0.220
P value†	0.689			0.063		
ln SDNN, ms						
Intercept	3.649	0.017	<0.001	3.673	0.026	<0.001
Time, per 10 years	−0.185	0.027	<0.001	−0.236	0.045	<0.001
Age, y						
44–49*	0			0		
50–54	−0.095	0.022	<0.001	−0.135	0.035	<0.001
55–59	−0.159	0.024	<0.001	−0.160	0.037	<0.001
60–69	−0.243	0.023	<0.001	−0.310	0.035	<0.001
Time×age, y						
44–49*	0			0		
50–54	0.045	0.036	0.210	0.068	0.060	0.261
55–59	−0.016	0.040	0.693	0.072	0.064	0.263
60–69	0.077	0.038	0.042	0.163	0.061	0.007
P value†	0.187			0.060		
ln LF-HRV, ms^2						
Intercept	6.071	0.037	<0.001	5.922	0.059	<0.001
Time, per 10 years	−0.469	0.059	<0.001	−0.479	0.098	<0.001
Age, y						
44–49*	0			0		
50–54	−0.229	0.049	<0.001	−0.264	0.079	0.001
55–59	−0.464	0.054	<0.001	−0.415	0.083	<0.001
60–69	−0.664	0.052	<0.001	−0.709	0.080	<0.001
Time×age, y						
44–49*	0			0		
50–54	0.072	0.077	0.353	0.014	0.132	0.916

Continued

Table 3. Continued

	Men (n=3176)			Women (n=1238)		
	b	SE	*P* Value	b	SE	*P* Value
55–59	0.063	0.086	0.469	0.166	0.141	0.239
60–69	0.189	0.082	0.022	0.317	0.133	0.017
P value†	0.139			0.049		
ln HF-HRV, ms^2						
Intercept	5.065	0.043	<0.001	5.364	0.067	<0.001
Time, per 10 years	−0.523	0.068	<0.001	−0.605	0.110	<0.001
Age, y						
44–49*	0			0		
50–54	−0.289	0.057	<0.001	−0.308	0.089	0.001
55–59	−0.466	0.062	<0.001	−0.355	0.094	<0.001
60–69	−0.634	0.059	<0.001	−0.761	0.090	<0.001
Time×age, y						
44–49*	0			0		
50–54	0.163	0.090	0.069	0.100	0.148	0.499
55–59	0.234	0.100	0.019	0.198	0.158	0.212
60–69	0.389	0.095	0.000	0.439	0.150	0.003
P value†	0.001			0.020		
LFnu (%)						
Intercept	71.564	0.421	<0.001	62.599	0.781	<0.001
Time, per 10 years	1.152	0.795	0.381	2.372	1.415	0.128
Age, y						
44–49*	0			0		
50–54	1.272	0.558	0.508	0.536	1.225	0.662
55–59	0.025	0.613	0.446	−1.577	1.293	0.223
60–69	−0.803	0.577	0.023	0.815	1.240	0.511
Time×age, y						
44–49*	0			0		
50–54	−2.056	1.103	0.062	−1.231	1.996	0.537
55–59	−3.800	1.231	0.002	0.278	2.132	0.896
60–69	−4.278	1.172	<0.001	−2.208	2.016	0.273
P value†	0.001			0.686		

Whitehall II study participants with ≥2 assessments of HR and HRV over the 10-year follow-up. The 10-year rate of change is presented in Table 4. HF-HRV indicates high-frequency heart rate variability; HR, heart rate; LF-HRV, low-frequency heart rate variability; LFnu, low-frequency heart rate variability in normalized units; SDNN, standard deviation of all intervals between R waves with normal-to-normal conduction.

*Reference category.

†*P* value from adjusted Wald test.

based on 24-hour HRV recordings that provide different physiological information than short-term recordings during which conditions are controlled and stable.[5] Consequently, we can compare our findings with only 1 other longitudinal population-based study. In the Atherosclerosis Risk in Communities (ARIC) study, the mean annual decrease in SDNN for >6000 middle-aged men and women (aged 45–64 years) was similar to our results.[8,18,19] No studies of ARIC data have reported on longitudinal changes of frequency-domain HRV or on differences in HRV trajectories according to sex and/or across age groups. An earlier study using Whitehall II data based on 2 short-term HRV recordings[20] showed that HRV declined for men but increased for women over the 5-year follow-up period. Using additional follow-up of HRV measure-

Table 4. Estimated Age-Specific 10-Year Rates of Change (95% CIs) in Heart Rate and Heart Rate Variability Trajectories by Sex

HR and HRV, by Age at Baseline	Men	Women
HR, bpm		
44–49 y	−2.3 (−3.3 to −1.3)	−1.8 (−3.5 to −0.2)
50–54 y	−1.7 (−2.5 to −0.9)	−1.5 (−3.0 to 0.0)
55–59 y	−2.0 (−3.0 to −0.9)	−0.1 (−1.8 to 1.6)
≥60 y	−1.5 (−2.5 to −0.6)	−3.3 (−4.8 to −1.7)
SDNN, ms		
44–49 y	−18.5% (−23.8 to −13.2)	−23.6% (−32.3 to −14.9)
50–54 y	−14.0% (−18.6 to −9.4)	−16.8% (−24.8 to −8.9)
55–59 y	−16.9% (−22.7 to −11.2)	−16.4% (−25.5 to −7.3)
≥60 y	−10.7% (−16.0 to −5.5)	−7.3% (−15.4 to 0.8)
LF-HRV, ms^2		
44–49 y	−46.9% (−58.3 to −35.4)	−47.9% (−67.0 to −28.7)
50–54 y	−39.7% (−49.6 to −29.7)	−46.5% (−63.9 to −29.1)
55–59 y	−40.6% (−53.1 to −28.1)	−31.3% (−51.2 to −11.3)
≥60 y	−28.0% (−39.3 to −16.6)	−16.2% (−34.0 to 1.6)
HF-HRV, ms^2		
44–49 y	−52.3% (−65.5 to −39.0)	−60.5% (−82.0 to −39.0)
50–54 y	−36.0% (−47.4 to −24.5)	−50.5% (−70.0 to 31.0)
55–59 y	−28.9% (−43.3 to −14.5)	−40.7% (−63.1 to −18.4)
≥60 y	−13.3% (−26.4 to −0.2)	−16.6% (−36.6 to 3.4)
LFnu (%)		
44–49 y	1.2% (−0.5 to 2.8)	2.4% (−0.5 to 5.3)
50–54 y	−0.9% (−2.3 to 0.5)	1.1% (−1.5 to 3.8)
55–59 y	−2.6% (−4.4 to −0.9)	2.1% (−0.9 to 5.1)
≥60 y	−3.1% (−4.7 to −1.5)	0.2% (−2.5 to 2.9)

HF-HRV indicates high-frequency heart rate variability; HR, heart rate; LF-HRV, low-frequency heart rate variability; LFnu, low-frequency heart rate variability in normalized units; SDNN, standard deviation of all intervals between R waves with normal-to-normal conduction.

ments for the same cohort, we no longer observed increases in mean HRV for women over the 10-year period. Moreover, our analyses revealed similarities in the temporal course and rate of decline in HRV measures for both sexes. We examined the influence of a number of factors that could have accounted for the unexpected increase in HRV levels for women from phase 5 to 7, including use of hormone replacement therapy and oral contraceptives or menopausal status. These factors did not explain the 5-year increase in HRV or the longer term decline in HRV over the 10-year period (data not shown).

The cross-sectional associations found in our study between cardiometabolic conditions (history of coronary heart disease, heart failure, stroke, diabetes, hypertension, and obesity) and/or cardiovascular-related medications (other than beta blockers) and HRV levels were also in line with previous studies.[9,18–21,34,35] Participants reporting use of beta blockers had similar or slightly more favorable HR and HRV levels compared with untreated participants. HR and HRV levels were much more favorable for participants using beta blockers compared with those on other medications; however, the beneficial effects of beta blockers on sympathetic nervous system activity[36] declined for women over the 10-year follow-up, as reflected by their faster rate of decline in SDNN compared with those not taking medication. This finding should be treated with caution because small sample sizes meant that our study lacked sufficient power to detect small differences in the rate of change in HR and HRV according to beta blocker use.

Although HRV decreases were influenced by cardiometabolic condition for women, none of the 5 key covariates fully explained the declining trend in HRV as both

Table 5. Associations (Mixed-Models Analyses) Between Cardiometabolic Condition and Medication Use and Heart Rate and Heart Rate Variability Trajectories by Sex

	Cardiometabolic Condition			Prescribed Medication (Other Than Beta Blockers)		
	b	SE	*P* Value	b	SE	*P* Value
	Men (n=3176)			Men (n=2735)		
HR, beats/min	−0.177	0.504	0.726	0.905	0.564	0.108
SDNN, ms	0.026	0.027	0.343	−0.005	0.032	0.884
LF-HRV, ms^2	0.086	0.059	0.147	0.012	0.070	0.863
HF-HRV, ms^2	0.116	0.069	0.092	0.037	0.080	0.649
LFnu (%)	−0.004	0.008	0.602	−0.003	0.010	0.770
	Women (n=1238)			Women (n=1072)		
HR, beats/min	1.099	0.848	0.195	1.281	0.980	0.191
SDNN, ms	−0.096	0.044	0.031	−0.096	0.055	0.082
LF-HRV, ms^2	−0.227	0.098	0.020	−0.208	0.121	0.086
HF-HRV, ms^2	−0.066	0.110	0.548	−0.187	0.137	0.174
LFnu (%)	−0.036	0.015	0.015	−0.011	0.018	0.566

Estimates were obtained from mixed models including time, age at baseline, time×age, cardiometabolic condition or medication use, and time×cardiometabolic condition or medication use. The table shows the coefficients for the time×cardiometabolic condition or medication use interaction term. The interaction term for models including cardiometabolic condition shows the estimated difference in the 10-year rate of change between the no cardiometabolic condition and cardiometabolic condition groups. Likewise, the interaction term for models including medication use shows the estimated difference in the 10-year rate of change between participants reporting and not reporting use of prescribed medication. HF-HRV indicates high-frequency heart rate variability; HR, heart rate; LF-HRV, low-frequency heart rate variability; LFnu, low-frequency heart rate variability in normalized units; SDNN, standard deviation of all intervals between R waves with normal-to-normal conduction.

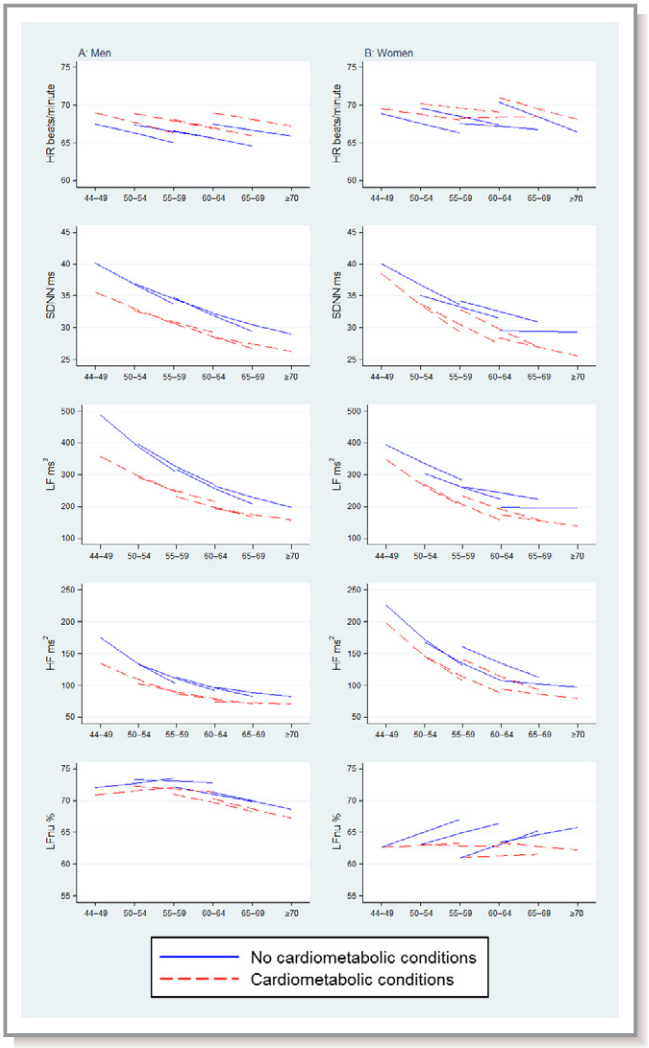

Figure 1. Model-predicted trajectories of age-related change in HR and HRV measures in men (A) and women (B) aged 44 to 69 years (1997–1999) with and without reported cardiometabolic condition over a 10-year follow-up period. The trajectories for each age group at phases 5, 7, and 9 were predictions from a linear mixed model including time, age at baseline, time×age, cardiometabolic condition, and time×cardiometabolic condition. Predicted values for HRV measures were based on geometric means. HR indicates heart rate; HRV, heart rate variability; HF, high-frequency heart rate variability; LF, low-frequency heart rate variability; LFnu, low-frequency heart rate variability in normalized units; SDNN, standard deviation of all intervals between R waves with normal-to-normal conduction.

men and women aged over the 10-year period. Our sensitivity analysis focusing specifically on a subset of healthy participants—those without cardiometabolic condition and with no reported medication use at any of the 3 data collection phases—produced largely similar results of declining HRV trajectories. Although the biological interpretation of HRV indices is complex, the decreasing SDNN and HF-HRV trajectories may suggest that both normative and potentially pathological aging is accompanied by gradual reduction of overall fluctuation in cardiac autonomic input and by gradual reduction in parasympathetic modulation. Mechanisms underlying changes in parasympathetic modulation with aging may be related to changes in cholinergic and muscarinic pathways through which vagal signal is carried. This may include disturbed cardiac acetylcholine release response to stimulation,[39] decreases in muscarinic receptor activity,[40] and reductions in M2 muscarinic receptor density with aging,[41] all of which have been shown to decrease with aging in clinical trials. Loss of protective vagal reflexes seems to hinder physical and psychological functioning and capacity to respond flexibly to efferent stimuli, resulting in increased vulnerability to the diseases[2,42] that are often prevalent at older ages.[43]

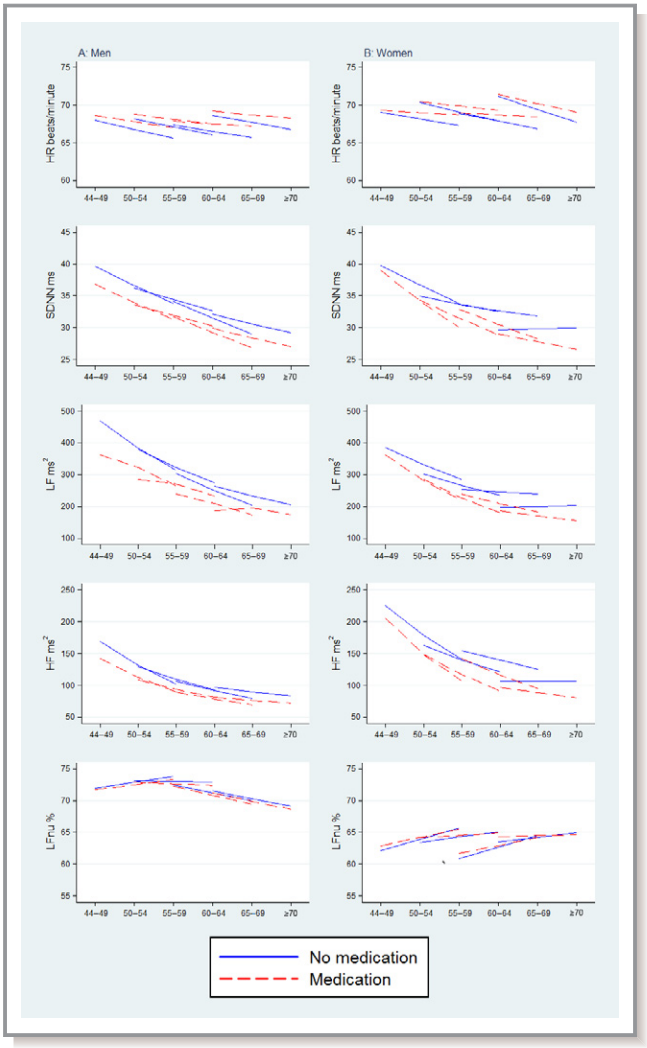

Figure 2. Model-predicted trajectories of age-related change in HR and HRV measures in men (A) and women (B) aged 44 to 69 years (1997–1999) with and without reported medication use (other than beta blockers) over a 10-year follow-up period. The trajectories for each age group at phases 5, 7, and 9 were predictions from a linear mixed model including time, age at baseline, time×age, use of prescribed medication, and time×medication use. Predicted values for HRV measures were based on geometric means. HR indicates heart rate; HRV, heart rate variability; HF, high-frequency heart rate variability; LF, low-frequency heart rate variability; LFnu, low-frequency heart rate variability in normalized units; SDNN, standard deviation of all intervals between R waves with normal-to-normal conduction.

Trajectories in LF-HRV, measured in the supine position in our study, changed in the same direction and in a similar pattern to HF-HRV, suggesting that LF-HRV not only is a measure of sympathetic activity, as reported in some studies, but also represents the variation in RR interval caused by more graduated interplay between sympathetic and parasympathetic activities.[5]

Our results may also provide possible insight into plausible biological pathways of sex differences in cardiac autonomic functioning. Cardiometabolic conditions affected HRV trajectories for women but not for men. In addition, we observed differences in LFnu trajectories by sex that may reflect sex-specific differences in balance between the 2 branches of autonomic nervous system with aging. A number of authorities[22,44] have suggested that the parasympathetic and sympathetic branches of the autonomic nervous system operate differently for men and for women to achieve homeostasis. The observed sex differences in our study may thus be related to different biological ways of responding to stress[44] and/or health conditions.[45] The exact mechanisms underlying sex differences in cardiac autonomic functioning, however, are poorly understood.[22]

Strengths and Limitations

A key strength of our investigation is the use of participant-level longitudinal data with 3 repeated measures of HRV over a decade in a nonclinical setting. Multiple measures of short-term HRV in both the time and frequency domains allowed us to attribute HRV changes to parasympathetic or/and sympathetic modulation changes and generally to changes in cardiac autonomic function. We used repeated measures of covariates, not just baseline measures, allowing the presence of cardiometabolic condition and reported medication use to vary over the 10-year period. The analytical sample for our study was reduced in size due to death and nonresponse or withdrawal from the study prior to the start of HR and HRV data collection in phase 5 and through staff not being available for 2 months at phase 5. In addition, we restricted the analytical sample to the subset of participants with at least 2 HRV measurements to estimate within-person change in HR and HRV levels. Although the sizeable amount of missing data at phase 5 has been shown to be random,[24] the observed declines in HRV are most likely underestimated to some extent in our study because of a healthy survival bias (selective attrition in the cohort); those with the presence of risk factors or low HRV levels may be more likely to drop out.[46]

Sample sizes were too small to examine the age- and sex-specific trajectories for nonwhite minority ethnic groups such as people of South Asian and African Caribbean origin. We cannot rule out the contribution of device effects because different recording equipment was used in each phase; however, the HRV protocols were consistent across all data collection phases. Although 5-minute HRV recordings are highly repeatable[47] and considered representative of 24-hour ambulatory HRV recordings,[48] long-term recordings may offer more comprehensive and accurate evaluation of HRV changes over time.

Finally, the Whitehall II study is an occupation-based cohort and thus is healthier on average than the general population.

Nevertheless, etiological findings from the Whitehall II cohort have been shown to be comparable to other population-based studies.[49]

Conclusion

Our study shows that normative HRV-declining trajectories exist largely independently of cardiometabolic conditions or reported use of medication. We have further described the age-related progression of HRV according to sex, ethnicity, SES, and habitual physical activity, and that information could help improve understanding of cardiac autonomic functioning in aging populations.

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Disclosures

None.

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