

## Heart Rate Variability from Short Electrocardiographic Recordings Predicts Mortality from All Causes in Middle-aged and Elderly Men

### The Zutphen Study

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Low heart rate variability is associated with high risk of sudden death in myocardial infarction patients. This has been attributed to unfavorable autonomic cardiac control. In the present study, the predictive value of heart rate variability for sudden death, mortality from coronary heart disease, and from all causes was investigated in the general population, using brief electrocardiographic recordings. From 1960 to 1985, 878 middle-aged Dutch men, aged 40–60 years, were followed and repeatedly examined as part of the Zutphen Study. In 1985 the remaining cohort was extended to 885 elderly men, aged 65–85 years, and followed until 1990. Heart rate variability (standard deviation of duration of normal RR intervals) was determined from the resting 12-lead electrocardiogram. The 5-year age-adjusted relative rate of total mortality of men with heart rate variability of <20 milliseconds (msec) compared with men with heart rate variability of 20–39 msec was 2.1 (95 percent confidence interval 1.4–3.0) in middle-aged men and 1.4 (95% confidence interval 0.9–2.2) in elderly men. Death from noncoronary causes, especially cancer, contributed significantly to this elevated risk. The association of low heart rate variability with sudden death or coronary heart disease mortality was less consistent. In conclusion, in middle-aged men and probably in elderly men, low heart rate variability is predictive of mortality from all causes. This suggests that low heart rate variability is an indicator of compromised health in the general population. *Am J Epidemiol* 1997;145:899–908.

aged; autonomic nervous system; electrocardiography; heart rate; men; middle age; mortality; population

The heart rate fluctuates regularly along with physiologic processes like breathing. This heart rate variability is mediated by the autonomic nervous system. Low heart rate variability is associated with high risk of mortality in myocardial infarction patients (1–3) and in subjects referred for Holter monitoring (4). Also, patients with heart failure (5), hypertensive hypertrophy (6), and atherosclerosis (7) have been reported to have less heart rate variability than healthy controls. This has been explained by a shift of autonomic cardiac control toward sympathetic predominance (1–8). In experimental conditions in short-term

recordings, an increase of sympathetic activity, usually with concomitant lowering of parasympathetic activity, leads to reduction of total heart rate variability, primarily in the breathing-related component (8). Because sympathetic predominance lowers the ventricular fibrillation threshold (9), it has been suggested to be an important factor underlying the observed high risk of sudden death in patients with low heart rate variability.

It is not clear whether, in the general population, low heart rate variability is associated with higher risk of mortality. In the Framingham Heart Study, low heart rate variability was associated with increased risk of mortality in a population of elderly subjects (10). The old age, and consequently high prevalence of subclinical cardiac diseases that are accompanied by low heart rate variability, precluded conclusions about the possible mechanisms underlying this association. Furthermore, in the elderly, heart rate variability is generally lower than in younger subjects (11). Because the importance of heart rate variability was not known until recently, no long-term follow-up studies in younger populations are available yet. In population

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Abbreviations: CI, confidence interval; msec, milliseconds.

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studies, electrocardiographic recordings are usually short. Because a standard electrocardiogram encompasses several breathing cycles, it may be used to characterize heart rate variability. In the Zutphen Study, the Dutch contribution to the Seven Countries Study (12), a cohort of middle-aged men has been followed for over 30 years and repeatedly examined. We used the electrocardiograms from this study and from an additional cohort of elderly men to investigate the predictive value of heart rate variability for mortality from several causes.

## MATERIALS AND METHODS

### Study population

The Zutphen Study is a prospective study of coronary heart disease carried out within the framework of the Seven Countries Study (12). This study started in 1960, when a random sample was drawn from the male residents in the town of Zutphen, Netherlands, who were born between 1900 and 1920 and had lived in Zutphen for at least 5 years. These 1,088 selected men (44 percent of the eligible population) were invited for a dietary interview and a general physical examination, including a standard 12-lead electrocardiogram. Thirty-two men declined to participate, while 179 of the remaining 1,056 men took part only in the dietary interview or had their physical examination later than 1960. The remaining 878 men hereafter will be referred to as the "middle-aged cohort." This cohort was invited for follow-up examinations in 1965 and 1970. None of these subjects was lost to follow-up, 683 were still alive in 1975, and 555 in 1985.

In 1985, only half of the original cohort, who were by then 65–85 years old, was still alive. To create an elderly cohort of sufficient size to continue the Zutphen Study, an additional random sample was drawn from all men of the same age who lived in Zutphen. A total of 1,266 men (78 percent of the eligible population), including the survivors of the originally studied cohort, was invited to participate. Of these, 156 men refused to participate or could not be reached, 109 men could not be examined because of illness or death in the period between the invitation and the physical examination, 62 men had moved, and 54 men did not complete the physical examination, resulting in 885 men who will be referred to henceforth as "the elderly cohort." None of these subjects was lost to follow-up, and 656 were still alive in 1990.

### Data collection

A standard resting 12-lead electrocardiographic recording and assessment of cardiovascular risk factors were performed according to the protocol of the Seven

Countries Study (12) in 1960, 1965, 1970, and 1985. The duration of recording ranged from 15 to 30 seconds. Only clippings with a few intervals from each lead were kept from 25 percent of the 1,960 electrocardiograms.

At the end of all physical examinations, the supine systolic and diastolic blood pressures were measured twice on the right arm. Before 1985, only the last value was recorded. In 1985, the mean of duplicate readings was calculated. Serum total cholesterol was determined in a standardized laboratory by the Abell-Kendall method (13) in 1960 and 1965, by the method of Zlatkis et al. (14) in 1970, and by the enzymatic method of Siedel et al. (15) and Stähler et al. (16) in 1985. All methods produced Abell-Kendall equivalents. The body mass index was calculated from height and weight. Before 1985, smoking was assessed by the Seven Countries Study questionnaire on smoking habits. In 1985, a newly developed questionnaire (17) was used.

Mortality was recorded weekly by checking the municipal registry of the town of Zutphen. Causes of death were obtained from the death certificates, the hospital, and/or the general practitioner.

Coding of causes of death was performed according to the *International Classification of Diseases* (Eighth Revision for the middle-aged cohort (18), Ninth Revision for the elderly cohort (19)). Coronary heart disease mortality was defined as *International Classification of Diseases*, Eighth Revision, codes 410 and 411.9–413.9 and as *International Classification of Diseases*, Ninth Revision, codes 410–414. Sudden cardiac death was coded in retrospect. Because of the limitations of the available information, the "sudden cardiac death" code in this study was assigned in three situations: 1) when it was documented that death occurred within 2 hours after the onset of typical symptoms, and no other causes of death were known; 2) when "mors subita" was reported by the physician in subjects with known heart disease; or 3) when death occurred unwitnessed (within 12 hours after a man was seen alive and well) in subjects with known heart disease.

### Data analysis

The duration of all normal sinus intervals (RR intervals) was measured, using a digitizing tablet (Cal-Comp Digitizer Products Group, Anaheim, California) and a personal computer. The resolution of the tablet is 100 lines/mm. The reproducibility indicated by the manufacturer is 0.25 mm (corresponding to 10 milliseconds (msec)). When RR measurements were compared with machine (Marquette Electronics, Milwaukee, Wisconsin)-determined RR intervals in fifty

10-second recordings (correlation = 0.999), the actual accuracy appeared to be higher than indicated. Differences of more than 5 msec between the measured and the machine-determined RR intervals were rarely observed. All intervals were measured by observers who were blinded for other baseline information and survival. Electrocardiograms with more than one abnormal interval, second- or third-degree atrioventricular block, pacemaker spikes, or less than 10 normal intervals were excluded (also intervals differing more than 20 percent from the preceding interval were considered abnormal). The two intervals following abnormal beats were excluded. Heart rate variability was defined as the standard deviation of intervals between all normal beats. Subjects were categorized into three groups of heart rate variability: low (<20 msec), intermediate (20–39 msec), and high ( $\geq$ 40 msec). These cutoff points separate the lowest and the highest approximate 25 percent, based on the distribution of the combined observations of 1960, 1965, and 1970.

The interobserver variability between coders was studied in a subset of 30 electrocardiograms. The mean correlation between the standard deviation of RR intervals was 0.8 (range, 0.6–1.0).

The predictive value of heart rate variability for death from coronary heart disease, sudden death, death from causes other than coronary heart disease, and death from all causes during the period 1960–1975 for the middle-aged cohort, and the period 1985–1990 for the elderly cohort, was analyzed using Cox proportional hazards models. In order to take full advantage of the multiple measurements in the middle-aged cohort, the 15-year period was divided in three 5-year periods. Each examination and subsequent 5-year follow-up was regarded as one observation. These combined data were analyzed by a Cox proportional hazards model, stratified for the periods of measurement. The resulting coefficients can be interpreted as

short-term (5-year) rate ratios (20, 21). All risk analyses were performed twice: 1) adjusted for age only and 2) for age and other possible confounders (systolic blood pressure, serum total cholesterol, body mass index, current smoking status, and the product of the daily number of cigarettes and years smoked). Data analysis was performed with SAS software (22).

## RESULTS

Table 1 shows the number of participants, usable electrocardiograms, and survival for the middle-aged cohort (measurements in 1960, 1965, and 1970; follow-up until 1975) and the elderly cohort (measurements in 1985, follow-up until 1990).

The mean heart rate variability was 33 msec in the middle-aged men in 1960, gradually decreasing to 24 msec in elderly men in 1985. With increasing age, the proportion of men with low heart rate variability increased from 17 to 47 percent, and the proportion of men with high heart rate variability decreased from 28 to 10 percent. In the elderly study in 1985, 357 men were newly recruited men, and 255 had been part of the middle-aged cohort. There were no differences in heart rate variability or other coronary heart disease risk factors between these two groups.

In tables 2 and 3, population characteristics are presented according to categories of heart rate variability. Age, systolic blood pressure, and heart rate were significantly higher in the group of middle-aged men with low heart rate variability; in the elderly men, only heart rate was higher in the low heart rate variability group. In both age groups, the proportion of men who died from causes other than coronary heart disease and from all causes was significantly higher in the low heart rate variability category. In figures 1 and 2, survival curves of total mortality according to heart

**TABLE 1. Overview of numbers of participants, electrocardiograms suitable for analysis, and survival at subsequent follow-up physical examinations, the Zutphen Study, 1960–1990**

Year	Cohort size (no.)*	ECG† recorded (no.)	Suitable‡ for HRV† (no.)	Alive§ 1965	Alive 1970	Alive 1975	Alive 1990
Middle-aged							
1960	878	877	557	528	492	453	
1965	820	717	659		610	551	
1970	760	625	557			498	
Elderly, 1985	885	836	612				504

\* Number of men alive in the original cohort.

† ECG, electrocardiogram; HRV, heart rate variability.

‡ Electrocardiograms with more than one abnormal interval, second or third degree atrioventricular block, pacemaker spikes, or less than 10 normal RR intervals were excluded.

§ Number of men still alive for whom HRV could be computed, during the medical examination in the year of the first column.

**TABLE 2. Population characteristics\* and mortality in categories of heart rate variability in middle-aged men, the Zutphen Study, 1960-1990**

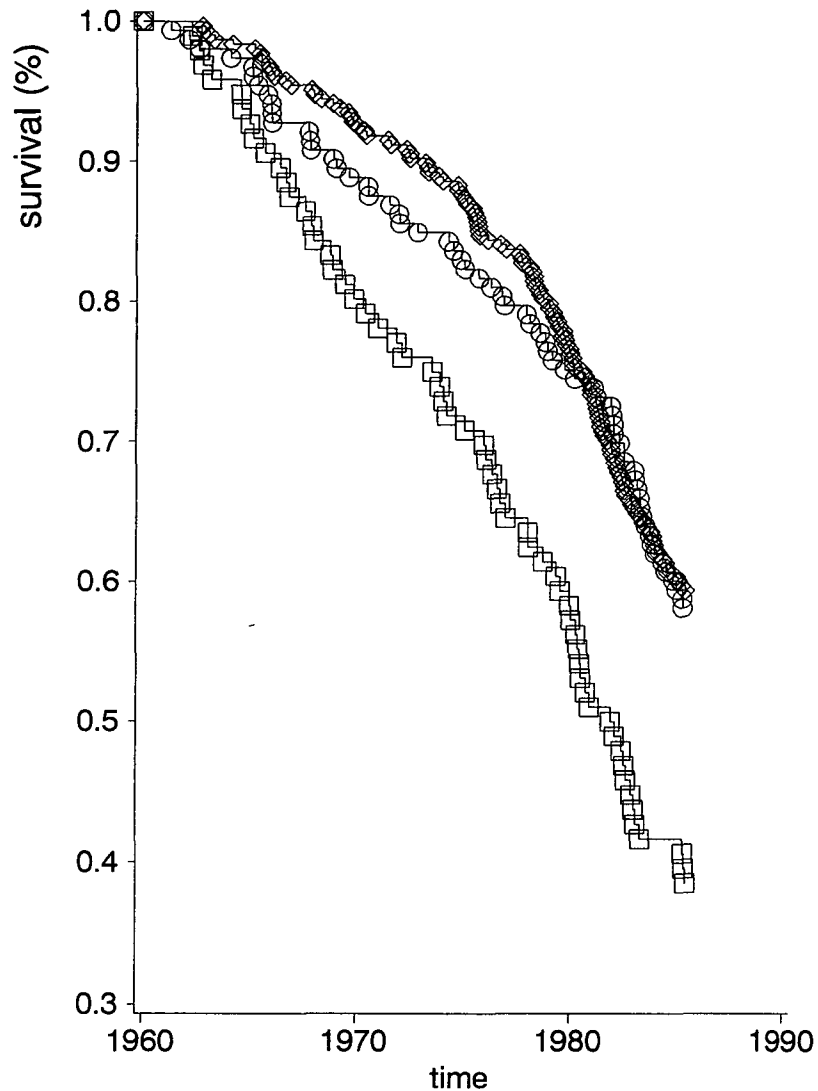
HRV† (milliseconds)	HRV (milliseconds)		Age (years)		Systolic blood pressure (mmHg)‡		Serum cholesterol (mmol/liter)		Body mass index (kg/m²)		Heart rate (beats/minute)‡		Product of cigarettes and years smoking	
	Mean	SD†	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<20¶	15.9	3.2	51.2	5.4	146.5	19.0‡	6.12	1.15	24.0	2.8	82.0	10.6‡	460	296
20-39#	29.0	5.5	49.7	5.4	139.9	17.6	5.97	1.09	23.9	2.7	74.0	10.6	399	246
≥40**	51.7	10.4	49.3	5.4‡	142.7	20.9‡	6.05	1.09	23.9	2.6	67.5	9.1‡	403	247
	Current smokers (%)	15-year sudden death (%)	15-year CHD† mortality (%)	15-year non-CHD mortality (%)	15-year total mortality (%)									
<20	82	6	10	20§	30§									
20-39	75	2	5	10	15									
≥40	75	3	5	14	18									

\* Individual parameters have missing data.  
 † HRV, heart rate variability (standard deviation of duration of normal RR intervals); CHD, coronary heart disease; SD, standard deviation.  
 ‡ Significant F test ( $p < 0.05$ ) over the HRV categories; indicated value significantly different from 20- to 40-millisecond HRV category (Scheffé's test,  $p < 0.05$ ).  
 § Significantly different from 20- to 40-millisecond HRV category (chi-square test for different proportions,  $p < 0.05$ ).  
 ¶  $n = 96$  (17%).  
 #  $n = 308$  (55%).  
 \*\*  $n = 153$  (28%).

**TABLE 3. Population characteristics\* and mortality in categories of heart rate variability in elderly men, the Zutphen Study, 1960-1990**

HRV† (milliseconds)	HRV (milliseconds)		Age (years)		Systolic blood pressure (mmHg)		Serum cholesterol (mmol/liter)		Body mass index (kg/m²)		Heart rate (beats/minute)‡		Product of cigarettes and years smoking	
	Mean	SD†	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<20¶	15.1	2.9	72.0	5.2	150.8	21.9	6.09	1.02	25.7	3.1	77.3	11.8‡	546	529
20-39#	27.2	5.3	71.0	4.9	149.8	21.3	6.11	1.28	25.5	3.0	70.7	10.0	494	504
≥40**	53.4	13.9	72.5	5.8	150.7	22.4	6.15	1.20	25.5	2.8	67.4	7.9	533	403
	Current smokers (%)	5-year sudden death (%)	5-year CHD† mortality (%)	5-year non-CHD mortality (%)	5-year total mortality (%)									
<20	36	3	5	15§	20§									
20-39	29	4	4	10	14									
≥40	27	6	7	16	23									

\* Individual parameters have missing data.  
 † HRV, heart rate variability (standard deviation of duration of normal RR intervals); CHD, coronary heart disease; SD, standard deviation.  
 ‡ Significant F test ( $p < 0.05$ ) over the HRV categories; indicated value significantly different from 20- to 40-millisecond HRV category (Scheffé's test,  $p < 0.05$ ).  
 § Significantly different from 20- to 40-millisecond HRV category (chi-square test for different proportions,  $p < 0.05$ ).  
 ¶  $n = 290$  (47%).  
 #  $n = 260$  (43%).  
 \*\*  $n = 62$  (10%).



**FIGURE 1.** Kaplan-Meier survival curves of total mortality in categories of heart rate variability in middle-aged men: <20 milliseconds (msec) (low, □), 20–39 msec (intermediate, ◇), and ≥40 msec (high, ○), the Zutphen Study, 1960–1990.

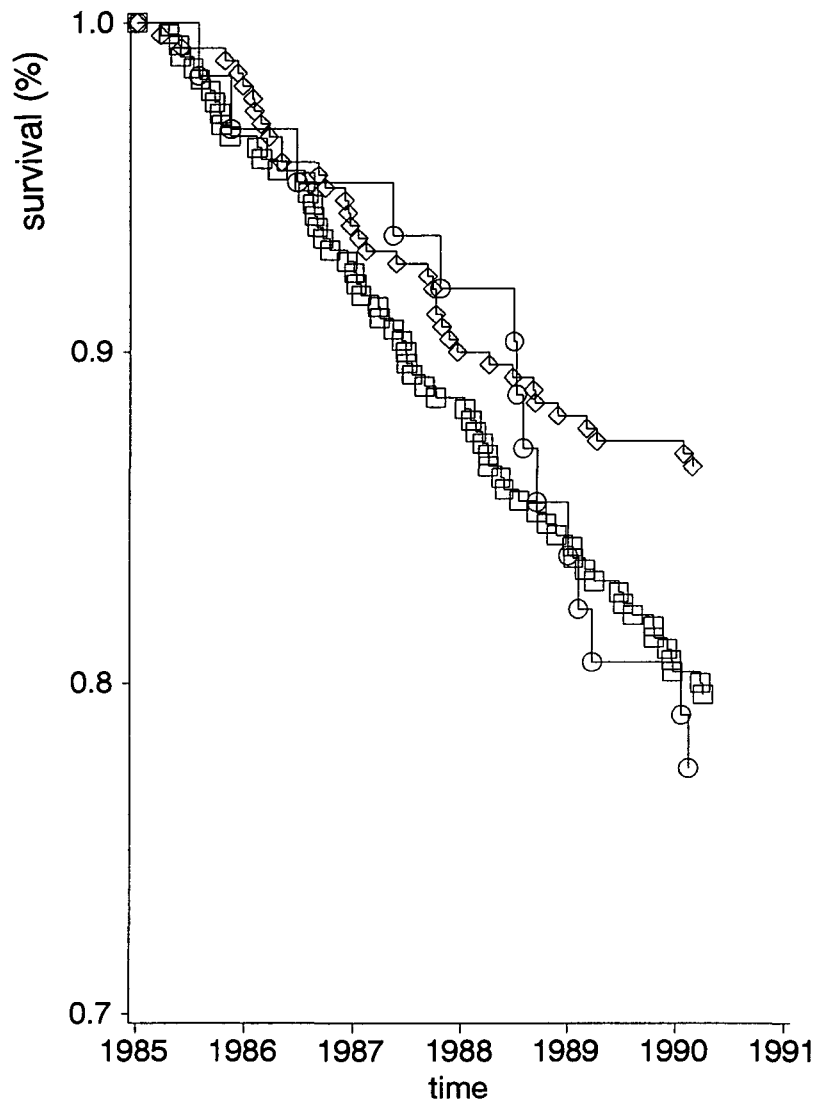
rate variability are shown. When the time to the event and possible confounding factors were taken into account in multivariate hazards analyses (table 4), the 15-year total mortality rate ratio in middle-aged men in the low heart rate variability category was 1.9 (95 percent confidence interval (CI) 1.2–3.2) compared with the intermediate heart rate variability category. Besides coronary heart disease mortality, mortality from other causes was also higher in the low heart rate variability category. Because 50 percent of noncoronary deaths were due to cancer of all sites, we studied the association between cancer mortality and heart rate variability. The age-adjusted 15-year relative risk of cancer death in the 1960 low heart rate variability category was 1.8 (95 percent CI 0.9–3.8).

In order to assess the stability of the observed associations, analyses were repeated using the heart rate variability measurement of 1965 or 1970 as baseline. The relative mortality rates in the 1965 low heart rate variability category during 1965–1980 were lower and nonsignificant, whereas 15-year mortality ratios of all endpoints (including cancer) following measurements in 1970 were higher and highly significant (data not shown).

The short-term predictive value of heart rate variability for total and noncoronary mortality among the middle-aged men was similar to the long-term predictive value.

Also in the elderly men, 5-year total and noncoronary heart disease mortality was increased in the low





**FIGURE 2.** Kaplan-Meier survival curves of total mortality in categories of heart rate variability in elderly men: <20 milliseconds (msec) (low, □), 20–39 msec (intermediate, ◇), and ≥40 msec (high, ○), the Zutphen Study, 1985–1991.

heart rate variability category. There was no significant association of heart rate variability with sudden death, coronary heart disease mortality, or cancer mortality.

Because men with low heart rate variability were more often smokers, analyses were performed in categories of smoking status. In table 5, the 15-year predictive value of heart rate variability, as determined in 1970, is shown. Since only 43 men in the Zutphen Study never smoked, never smokers were grouped together with men who successfully gave up smoking before 1960 and thus were nonsmoking for at least 10 years. The association between heart rate variability and mortality was present in all smoking categories, though not always statistically significant.

## DISCUSSION

In this follow-up study of middle-aged and elderly men, low heart rate variability in the resting 12-lead electrocardiogram was associated with elevated risk of death. This association was not specifically due to cardiac causes of death.

### Methodological issues

Because the electrocardiograms originally were made for diagnostic purposes, only 15–30 seconds were recorded, with interruptions for lead switching. Therefore, spectral analysis of heart rate variability was not possible, and the standard deviation was used as a measure of heart rate variability. In short-term

**TABLE 4. Age- and multivariate-adjusted hazard ratios of mortality from several causes in categories of heart rate variability, the Zutphen Study, 1960–1990**

	% of subjects	Sudden death*	CHD† mortality‡	Non-CHD mortality§	All-cause mortality¶
<i>Middle-aged men</i>					
15-year mortality					
HRV† < 20 msec†	17	3.0# (1.0–8.8)**	2.0 (0.9–4.5)	2.0 (1.2–3.6)	2.0 (1.3–3.2)
		2.8†† (0.9–8.6)	1.5 (0.6–3.7)	1.8 (1.0–3.4)	1.7 (1.0–2.9)
HRV ≥ 40 msec	28	1.3 (0.4–4.3)	1.0 (0.4–2.4)	1.5 (0.9–2.0)	1.3 (0.8–2.1)
		1.1 (0.3–4.0)	0.9 (0.3–2.2)	1.6 (0.9–2.0)	1.4 (0.9–2.3)
5-year mortality‡‡					
HRV < 20 msec	28	1.8 (0.7–4.5)	2.1 (1.1–4.1)	2.1 (1.3–3.3)	2.1 (1.4–3.0)
		1.6 (0.6–4.2)	1.9 (0.9–3.8)	2.3 (1.4–3.8)	2.1 (1.4–3.1)
HRV ≥ 40 msec	23	0.9 (0.2–3.3)	1.1 (0.5–2.8)	1.3 (0.7–2.2)	1.2 (0.8–2.0)
		1.0 (0.3–3.7)	1.3 (0.5–3.2)	1.6 (0.9–2.9)	1.5 (0.9–2.4)
<i>Elderly men</i>					
5-year mortality					
HRV < 20 msec	47	0.8 (0.3–1.8)	1.3 (0.6–2.9)	1.5 (0.9–2.4)	1.4 (0.9–2.2)
		0.8 (0.3–1.9)	1.3 (0.6–2.9)	1.6 (0.9–2.6)	1.5 (1.0–2.3)
HRV ≥ 40 msec	10	1.3 (0.4–4.2)	1.5 (0.5–4.9)	1.5 (0.7–3.2)	1.5 (0.8–2.3)
		1.2 (0.4–3.9)	1.4 (0.4–4.7)	1.6 (0.7–3.3)	1.5 (0.8–2.9)

\* For middle-aged men, the number of cases of sudden death at 15 years was 17 and at 5 years, 21. For elderly men at 5 years, it was 25.

† CHD, coronary heart disease; msec, milliseconds.

‡ For middle-aged men, the number of cases of CHD mortality at 15 years was 33 and at 5 years, 43. For elderly men at 5 years, it was 29.

§ For middle-aged men, the number of cases at non-CHD mortality at 15 years was 71 and at 5 years, 94. For elderly men at 5 years, it was 79.

¶ For middle-aged men, the number of cases of all-cause mortality at 15 years was 104 and at 5 years, 137. For elderly men at 5 years, it was 108.

# Age-adjusted hazard ratio (reference category, HRV 20–39 msec).

\*\* Numbers in parentheses, 95% confidence interval.

†† Hazard ratio adjusted for age, body mass index, systolic blood pressure, serum total cholesterol, and smoking (reference category, HRV 20–39 msec).

‡‡ Taking measurements in 1960, 1965, and 1970 and subsequent 5 years of follow-up as separate observations, stratified for period.

recordings, the standard deviation is highly correlated with the high frequency spectral component, which is parasympathetically mediated (23). Another consequence of the short recording is lower precision of the heart rate variability measure, which may lead to misclassification. Nondifferential misclassification between adjacent categories of heart rate variability would be expected to bias estimates of relative risk toward one, and therefore the true association may be higher (24).

In 1960, 25 percent of the electrocardiograms could not be used (table 1) because only clippings with a few intervals from each lead were available, resulting in less than the 10 RR intervals required for heart rate variability computation. These 25 percent turned out to be a group with a higher risk of coronary heart disease: 75 percent of them had an electrocardiographic abnormality according to the Minnesota Code. Also, mean age, blood pressure, and serum cholesterol were higher. Therefore, the 1960 cohort represents a relatively healthy selection of the middle-aged popu-

lation. For an etiologic study this is not a problem, because this does not affect the association between baseline characteristics and later disease outcome. Furthermore, the results from the 1965 and 1970 data were similar.

Misclassification of heart rate variability because of the use of cardioactive medication is a concern in this study. In the middle-aged men, these drugs were not frequently prescribed, but in the elderly population, a substantial part used medication. In 1985, 76 of the elderly subjects were using cardioactive medication ( $\beta$ -blockers, antiarrhythmics), and 400 were using any medication. Exclusion of men using antiarrhythmic or  $\beta$ -blocking agents did not markedly change the results. Certain other drugs, like psychoactive or respiratory drugs or antihypertensives, may affect heart rate variability as well. However, in the 212 men who did not use any medication, only 29 deaths occurred, resulting in insufficient numbers for analysis. Thus, confounding by medication cannot be excluded for the elderly population.

**TABLE 5. Age- and multivariate-adjusted hazard ratios of mortality from several causes in the period 1970–1985 in categories of heart rate variability in 1970, according to smoking status, the Zutphen Study, 1960–1990**

	%	Cancer*	Sudden death†	CHD‡ mortality§	Non-CHD mortality¶	All-cause mortality#
<i>Never smoked or stopped smoking before 1960 (n = 120)</i>						
HRV‡ < 20 msec‡	28	2.0** (0.7–5.5)††	2.4 (0.7–7.8)	3.4 (1.0–11.8)	1.2 (0.6–2.6)	1.6 (0.9–3.0)
		1.9‡‡ (0.7–5.6)	2.2 (0.7–7.7)	2.9 (0.8–10.5)	1.0 (0.4–1.3)	1.3 (0.7–2.5)
HRV ≥ 40 msec	25	0.4 (0.0–2.1)	0.4 (0.0–3.4)	1.5 (0.3–6.6)	0.4 (0.1–1.3)	0.6 (0.3–1.5)
		0.5 (0.1–2.2)	0.4 (0.0–3.6)	1.5 (0.3–6.8)	0.5 (0.2–1.3)	0.6 (0.3–1.5)
<i>Exsmokers who stopped between 1960 and 1970 (n = 135)</i>						
HRV < 20 msec	36	1.6 (0.5–4.7)	0.8 (0.2–3.8)	1.9 (0.6–6.8)	1.6 (0.8–3.5)	1.7 (0.9–3.3)
		2.1 (0.7–6.6)	0.6 (0.1–3.2)	1.7 (0.5–6.1)	1.7 (0.8–3.8)	1.7 (0.9–3.4)
HRV ≥ 40 msec	22	0.7 (0.1–3.8)	1.2 (0.2–6.8)	2.3 (0.6–9.5)	0.6 (0.2–2.1)	1.0 (0.4–2.5)
		1.0 (0.2–5.7)	1.0 (0.2–5.6)	2.0 (0.5–8.2)	0.6 (0.2–2.2)	0.9 (0.4–2.3)
<i>Smoking in 1970 (n = 301)</i>						
HRV < 20 msec	42	1.8 (0.9–3.4)	2.2 (0.9–5.0)	2.1 (1.1–3.9)	1.5 (0.9–2.4)	1.7 (1.2–2.5)
		1.7 (0.8–3.3)	1.5 (0.7–3.6)	1.9 (1.0–3.6)	1.3 (0.8–2.1)	1.5 (1.0–2.2)
HRV ≥ 40 msec	14	0.9 (0.3–2.8)	0.9 (0.2–4.0)	1.0 (0.3–2.9)	1.0 (0.5–2.2)	1.0 (0.5–1.9)
		0.9 (0.3–2.8)	0.7 (0.2–3.5)	0.9 (0.3–2.8)	1.0 (0.5–2.2)	1.0 (0.9–1.8)

\* For those who never smoked or stopped smoking before 1960, the number of cases of cancer was 19; for exsmokers, 16; for those smoking in 1970, 40.

† For those who never smoked or stopped smoking before 1960, the number of cases of sudden death was 13; for exsmokers, 9; for those smoking in 1970, 26.

‡ CHD, coronary heart disease; HRV, heart rate variability; msec, milliseconds.

§ For those who never smoked or stopped smoking before 1960, the number of cases of CHD mortality was 15; for exsmokers, 15; for those smoking in 1970, 47.

¶ For those who never smoked or stopped smoking before 1960, the number of cases of non-CHD mortality was 34; for exsmokers, 32; for those smoking in 1970, 73.

# For those who never smoked or stopped smoking before 1960, the number of cases of all-cause mortality was 49; for exsmokers, 47; for those smoking in 1970, 120.

\*\* Age-adjusted hazard ratio (reference category, HRV 20–39 msec).

†† Numbers in parentheses, 95% confidence interval.

‡‡ Hazard ratio adjusted for age, body mass index, systolic blood pressure, serum total cholesterol (reference category, HRV 20–39 msec).

Age, systolic blood pressure, body mass index, past and current smoking, and serum cholesterol were considered as possible confounding factors. Adjusting for current smoking especially somewhat lowered the estimates. Because smoking is known to lower heart rate variability (25), and smoking is a strong risk factor for mortality, the analyses were repeated for smokers and exsmokers separately. Although the numbers were very small, leading to loss of statistical power, the relative risks were roughly comparable across smoking categories. In addition, the heart rate may be considered as a confounding factor. In a number of large studies (26, 27), a high heart rate was associated with increased mortality from coronary heart disease. Including heart rate as a possible confounder did not change the results. Furthermore, when we adjusted heart rate variability for heart rate by dividing heart rate variability by the mean interval (28), the lowest quartile still had the highest risk of all endpoints. This indicates that the heart rate was not responsible for the observed associations with heart rate variability.

## Elderly

In the present study, almost 50 percent of men in the 65- to 85-year age group had low heart rate variability. In previous studies, reduced heart rate variability in elderly men has also been reported (11, 29). In the Framingham Heart Study, an association between low heart rate variability, based on 2-hour recordings, and all cause mortality was observed during a 4-year follow-up of 736 elderly subjects (10). Our study is in agreement with their results. In addition, we observed that high heart rate variability was associated with a higher risk of mortality, though not significantly. In contrast to the middle-aged men, elderly men with high heart rate variability and in sinus rhythm often had electrocardiographic abnormalities. In these men, visual inspection by an experienced cardiologist indicated that the heart rate fluctuations did not appear to be respiration related. The data are insufficient to determine sick sinus syndrome as a possible cause. In the Framingham Heart Study, heart rate variability



was analyzed as a continuous variable, so a possible U-shaped relation may have been missed.

### Mechanism

Heart rate variability represents adaptive responses of the autonomic nervous system to challenges to the circulation, like respiration. The sum of sympathetic and vagal effects determines the total amount of variability. Therefore, heart rate variability to a certain extent reflects the sympathovagal balance (8, 30). A lower ventricular fibrillation threshold because of sympathetic predominance in individuals with low heart rate variability (9) would only explain the association with coronary heart disease mortality and sudden death and not with noncardiovascular mortality. The results do not seem to be explained by prevalent heart disease either, since exclusion of men with a history of angina pectoris, previous myocardial infarction, or electrocardiographic signs (36 men in 1960, 86 in 1965, 95 in 1970, and 247 in 1985) did not change the results nor did the level of significance.

A number of other characteristics are also related to heart rate variability, including baroreflex sensitivity (31, 32), participation in sports activities (33), the frequency and depth of breathing (34, 35), and depression (36). These determinants may partially account for the predictive value of heart rate variability for mortality. On the other hand, it may be hypothesized that low heart rate variability is an indicator of unfavorable general health, including immune function. The unexpected association with cancer could not be explained by subclinical cancer, which may have increased sympathetic activity, because after exclusion of the first 5 years of follow-up the relation persisted. When the periods of follow-up were prolonged from 15 to 20 or 25 years, we found even higher relative risks, and the elevated risk was not confined to a specific site of cancer, which may suggest an association with general immune function. Direct effects of sympathetic activity on the function, number, and subset distribution of circulating lymphocytes (37, 38) have indeed been reported. Moreover, in a large British cohort study, a high heart rate and a low level of physical activity (both associated with unfavorable autonomic nervous system functioning and general health) were independent predictors of long-term cancer mortality (39).

In conclusion, low heart rate variability is associated with risk of death from all causes in both middle-aged and elderly men. The association does not exclusively result from coronary heart disease mortality. This suggests that low heart rate variability may be an indicator of poor general health.

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