Resting Heart Rate in Middle Age and Diabetes Development in Older Age

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OBJECTIVE — Based on prior research showing inverse associations between heart rate and life expectancy, we tested the hypothesis that adults with higher resting heart rate in middle age were more likely to have diagnosed diabetes or to experience diabetes mortality in older age (>65 years).

RESEARCH DESIGN AND METHODS — Resting heart rate was measured at baseline (1967–1973) in the Chicago Heart Association Detection Project in Industry. We used Medicare billing records to identify diabetes-related hospital claims and non–hospital-based diabetes expenses from 1992 to 2002 in 14,992 participants aged 35–64 years who were free from diabetes at baseline. Diabetes-related mortality was determined from 1984 to 2002 using National Death Index codes 250.XX (ICD-8 and -9) and E10–E14 (ICD-10).

RESULTS — After age 65, 1,877 participants had diabetes-related hospital claims and 410 participants had any mention of diabetes on their death certificate. The adjusted (demographic characteristics, cigarette smoking, and years of Medicare eligibility) odds of having a diabetes-related claim was ~10% higher (odds ratio [OR] 1.10 [95% CI 1.05–1.16]) per 12 bpm higher baseline heart rate. Following adjustment for BMI and postload glucose at baseline, the association attenuated to nonsignificance. Higher heart rate was associated with diabetes mortality in adults aged 35–49 years at baseline following adjustment for postload glucose and BMI (1.21 [1.03–1.41]).

CONCLUSIONS — Higher resting heart rate is associated with diabetes claims and mortality in older age and is only due in part to BMI and concurrently measured glucose.

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Resting heart rate is inversely associated with life expectancy in mammals (1) and directly associated with cardiovascular and all-cause mortality in human populations (2–5). Heart rate is a straightforward clinical measurement that reflects a combination of inputs from the autonomic, cardiorespiratory, and adrenal systems. In general, the parasympathetic nervous system is responsible for vegetative functions and slows heart rate, while the sympathetic division predominates under conditions of increased energy requirements to raise heart rate. Cardiorespiratory fitness training is known to lower resting heart rate, and therefore lower resting heart rate is also a marker of more favorable fitness (6). Given that estimates of autonomic function and fitness are associated with the development of insulin resistance and hyperglycemia in population studies (7–10) and that heart rate is correlated with these physiologic measures, it is biologically plausible that higher heart rate is associated with the development of diabetes. In a sample of young and middle-aged adults, we tested the hypothesis that a faster resting heart rate was associated with a greater likelihood of experiencing diabetes morbidity or mortality in older age (after age 65 years).

RESEARCH DESIGN AND METHODS

— The Chicago Heart Association Detection Project in Industry is a prospective study of the association between cardiovascular disease risk factors and health outcomes. Approximately 75,000 employees aged 18 years and older at 84 Chicago-area companies were invited to undergo screening for cardiovascular disease risk factors from 1967 to 1973. The participation rate for the study was 53%; 39,523 black and white women and men were screened (11,12). The study received institutional review board approval at periodic reviews.

Sociodemographic characteristics (age, sex, race/ethnicity, years of education), health behaviors (cigarettes per day), and medical history including medication use to control diabetes and hypertension were ascertained via questionnaire. BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was obtained via a single casual supine measurement using a mercury sphygmomanometer. Standardized methods were used to determine total serum cholesterol (13). Participants without known diabetes were administered a 50-g oral glucose load in a nonfasting state. Plasma glucose levels were measured after 1 h (14,15). Diabetes at baseline was determined from a self-reported physician diagnosis of diabetes, use of diabetes medication, or postload glucose ≥11.1 mmol/l.

Heart rate was measured via electrocardiogram from participants in the supine position following a 5-min rest. During the early examination years, the inverse of the interval between R-waves for three consecutive QRS was used to determine heart rate during a segment of the electrocardiogram when the abstractor determined that the QRS complex was normal. Later in the examination cycle, heart rate was measured using a digital heart rate meter attached to skin electrodes. Participants' medical history of ar-

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Abbreviations: HRR, heart rate recovery.

rhythmias, premature beats, or atrial fibrillation was not collected; thus, no exclusions were made based on these conditions.

Medicare data contain a complete record of claims for covered fee-for-service health care services for adults aged ≥65 years. Part A, the Hospital Insurance file, includes records for inpatient services, hospital-related outpatient services, skilled nursing facility stays after hospitalization, hospice care, and the first 100 days of home health agency. Each record includes provider encounter with charges, dates of service, admissions, and discharge for as many as six ICD-9 diagnosis codes and up to three surgical or procedure codes (both increased to 10 in 1991). Medicare Part B, the Supplemental Medical Insurance file, was publicly available beginning in 1992 and includes claims from physicians and other non–hospital-based providers, home health agencies not included in Part A, and durable medical equipment. Diabetes was defined using ICD-8 and -9 codes of 250.0 (diabetes without complications), 250.1–250.9 (diabetes with complications), 357.2 (polyneuropathy in diabetes), 362.01 (background diabetic neuropathy), 362.02 (proliferative diabetic neuropathy), and 366.41 (diabetic cataract).

We linked Medicare billing records from the Centers for Medicare and Medicaid Services for all cohort members aged 65 years and older between 1992 (the first year that records for both Parts A and B were available for public use) and 2002 using social security numbers, name, sex, and birth date information collected at baseline. However, we restricted our definition of diabetes to Part A (hospital claims) to evaluate what we considered was the most strict definition of diabetes. In a secondary analysis, we defined diabetes as both Part A (hospital claims) and Part B (durable medical equipment) between 1992 and 2002. To avoid misclassifying a diagnostic test for diabetes as a diabetes diagnosis, we required two or more mentions of diabetes to establish a diagnosis of diabetes (16).

Before 1984, diabetes was infrequently listed as the underlying cause of death among cohort participants who were free from diabetes at baseline. Thus, we restricted our analysis of diabetes mortality to older age to correspond with our analysis of diabetes diagnoses in participants aged 65 years and older. Between 1984 and 1994, vital status was determined from the National Death Index (NDI), with multiple causes of death coded from death certificates by trained research staff according to ICD-8. NDI*plus* was used to identify deaths from 1995 to 1998 (ICD-9) and 1999 to 2002 (ICD-10). Multiple causes of death were available, including an underlying cause of death. Because of the relatively small number of deaths attributed to diabetes as the underlying cause, we identified diabetes mortality as any mention on the death certificate according to ICD-8 and -9 code 250.0 and ICD-10 codes E10–E14.

Analysis sample. Our analysis included 23,401 participants aged 35–64 years at baseline, since participants were required to be at least 65 years of age by 1984 when Medicare data became publicly available. Further, we required that participants have at least 2 years of Medicare eligibility to increase the likelihood that they used Medicare services. We excluded participants who died before 1984 or age 65 years, had prevalent diabetes or myocardial infarction at baseline (determined based on self-reported history or from abnormal electrocardiogram changes), or were missing heart rate information. Our analysis of diabetes mortality and hospital-diagnosed diabetes (secondary analysis of Part A files) between 1984 and 2002 included 16,397 people, and our analysis of diabetes diagnosis between 1992 and 2002 was restricted to 14,992 people.

Statistical analyses. Baseline demographic and clinical characteristics are compared across heart rate quartiles. Tests for linear trend were conducting using linear and logistic regression models for continuous and categorical variables, respectively, with heart rate as a continuous variable and each covariate as the dependent variable. Next, we reported the number of diabetes outcomes (claims and mortality) and calculated the age-adjusted cumulative incidence by heart rate quartile. Multivariable logistic regression with statistical adjustment for length of time of Medicare eligibility was used to calculate odds ratios (ORs) and 95% CIs of each diabetes event per 12 (standard deviation) bpm higher heart rates and by quartiles of heart rate as compared with the lowest quartile by age category. We evaluated the presence of effect modification using interaction terms between heart rate and each covariate of interest in logistic regression models. Stratified analyses are presented when the *P* value for the multiplicative interaction term or set of terms (i.e., heart rate quartiles) was <0.10. Statistical significance was otherwise denoted at $P < 0.05$. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS — Participants were aged 47.5 ± 8.0 years (mean ± SD), 47% were female, 6% were black, and, on average, participants reported 12.5 ± 2.7 years of education at baseline. Over a third (36.6%) of participants were current smokers who reported smoking 21 ± 11 cigarettes/day. On average, heart rate was 76 ± 12 bpm, BMI was 26.1 ± 4.0 kg/m^2, and 1-h postload glucose levels were 140.1 ± 44.2 mg/dl. Resting heart rate quartile values were as follows (from lowest to highest): <68, 68–74, 75–83, and ≥84 bpm). Participants with higher heart rate were younger, were more likely to be female, had lower average years of education, smoked more cigarettes per day, and had higher postload glucose levels (all *P* trend <0.0001). A lower proportion of blacks were in the lowest heart rate quartile (5.3%), but there were no differences in the upper three quartiles (6.2, 6.3, and 6.2, for quartiles 2–4, respectively). There were no differences in BMI by quartiles of heart rate (BMI 26.1, 26.0, 26.1, and 26.2 kg/m^2 by ascending quartiles of heart rate, $P = 0.17$). Patterns were similar when stratified by baseline age category (data not shown).

From 1992 to 2002, diabetes was identified in 1,877 participants (12.5%), and diabetes was identified by hospital diagnosis or ambulatory care in 3,471 participants (23.2%). A total of 400 (2.4%) participants who died after age 65 years had diabetes reported on their death certificate. Table 1 displays the positive association between heart rate quartile and any diagnosis of diabetes in younger and older participants at baseline. Heart rate is positively associated with diabetes mortality in younger participants only.

There was no evidence of interaction between age and heart rate in association with any diagnosis of diabetes ($\chi^2 = 0.52$, 1 d.f., $P = 0.47$); we therefore present all analyses pooled by age (Table 2). In multivariable logistic regression models, baseline heart rate was positively associated with diabetes diagnosis following adjustment for age, sex, education, cigarettes per day, and BMI. Comparisons across quartiles indicated that the highest odds of having diabetes were restricted to participants in the uppermost quartile of heart rate compared with those in the lowest. Further adjustment for postload

Table 1—*Diabetes diagnosis and mortality by heart rate quartile*

	Hospital diagnosis of diabetes 1992–2002			Diabetes mortality 1984–2002		
	Events (*n*)	%*	95% CI	Events (*n*)	%*	95% CI
Ages 35–49 years						
Heart rate quartile						
1: <68	226	11.1	9.7–12.5	18	0.9	0.4–1.4
2: 68–74	290	11.2	10.0–12.5	34	1.3	0.8–1.7
3: 75–83	292	11.8	10.5–13.0	35	1.4	0.9–1.8
4: ≥84	356	13.8†	12.6–15.1	60	2.2†	1.7–2.6
Ages 50–64 years						
Heart rate quartile						
1: <68	157	11.7	9.9–13.5	61	3.7	2.8–4.6
2: 68–74	210	13.5	11.8–15.2	73	3.7	2.9–4.5
3: 75–83	170	13.9	12.0–15.8	56	3.5	2.5–4.4
4: ≥84	176	14.6‡	12.7–16.6	63	3.9	3.0–4.8

*Age-adjusted proportion. †$P < 0.01$, ‡$P < 0.05$.

glucose attenuated the statistically significant association.

Obesity was a significant ($\chi^2 = 3.98$, 1 d.f., $P = 0.05$) modifier of the association between heart rate and diabetes diagnosis. Heart rate was only positively associated with diabetes in participants who were not obese (BMI <30 kg/m^2) at baseline (Table 3). The significant association attenuated following adjustment for continuously measured BMI and postload glucose. Findings were similar when we included all diagnoses of diabetes (hospital and ambulatory care).

Because we observed an age–heart rate interaction in relation to diabetes mortality ($\chi^2 = 10.3$, 1 d.f., $P < 0.01$), we stratified all mortality analyses by age (Table 2). Heart rate was strongly positively associated with diabetes mortality in participants aged 35–49 years at baseline. The association observed in younger adults retained statistical significance following adjustment for postload glucose.

CONCLUSIONS — Our findings describe a modest association between higher resting heart rate in middle age and the diagnosis of diabetes and diabetes mortality in older age. Not surprisingly, this association is attenuated largely by postload glucose levels at the time of the heart rate measurement. However, in some subpopulations, the magnitude of association varied. In adults who were not obese, the association between heart rate and diabetes diagnosis is relatively stronger, although still largely explained by concurrently measured postload glucose. By contrast, in younger middle-aged adults at baseline (ages 35–49 years), heart rate remains positively associated with mortality from diabetes in older age even following statistical adjustment.

To our knowledge, this is the longest follow-up study to investigate the association between heart rate and diabetes. We have previously demonstrated that markers of autonomic function derived from heart rate, such as heart rate variability and heart rate recovery (HRR), are inversely associated with the development of diabetes (8–10) in longitudinal studies. In the Atherosclerosis Risk in Communities Study (ARIC), higher heart rate and lower heart rate variability was associated with an increased likelihood of developing diabetes over 9 years of follow up, even when concurrent BMI and physical activity levels were taken into account (8). Cardiorespiratory fitness was an important modifier of the association between slower 2-min HRR (<42 bpm) and incident diabetes in the Coronary Artery Risk Development in Young Adults Study (CARDIA). Participants who were less fit and had slow HRR had a threefold higher likelihood of developing diabetes than those with faster HRR (9). Finally, in a post hoc analysis of the Diabetes Prevention Program (DPP) trial (17), we demonstrated that participants in the lifestyle modification arm had the greatest declines in heart rate over time and that a lower heart rate was associated with a lower risk of developing diabetes independent of weight change (10). Our findings of a modest association between higher heart rate and diabetes diagnosis or mortality are consistent with prior research.

The association is plausible because heart rate is a marker of both autonomic nervous system function and cardiorespiratory fitness, both of which are associated with the development of diabetes in

Table 2—*Adjusted ORs (95% CIs) of the association among resting heart rate, diagnosis of diabetes, and diabetes mortality in older age*

	Hospital diagnosis of diabetes 1992–2002	Diabetes Mortality 1984–2002	
		35–49 years	50–64 years
Model 1			
Per 12 bpm	1.10 (1.05–1.16)	1.30 (1.11–1.51)	1.03 (0.91–1.17)
Quartile 1	1	1	1
2	1.08 (0.94– 1.24)	1.39 (0.77–2.47)	1.00 (0.71–1.41)
3	1.13 (0.97–1.31)	1.42 (0.80–2.53)	0.92 (0.64–1.34)
4	1.30 (1.13–1.50)	2.12 (1.23–3.64)	1.03 (0.71–1.48)
Model 2			
Per 12 bpm	1.07 (1.02–1.12)	1.27 (1.09–1.49)	0.99 (0.87–1.13)
Quartile 1	1	1	1
2	1.07 (0.92–1.23)	1.36 (0.76–2.43)	0.97 (0.68–1.37)
3	1.07 (0.92–1.24)	1.31 (0.73–2.35)	0.86 (0.59–1.25)
4	1.19 (1.03–1.38)	1.96 (1.14–3.39)	0.92 (0.64–1.33)
Model 3			
Per 12 bpm	1.00 (0.95–1.06)	1.21 (1.03–1.41)	0.88 (0.77–1.01)
Quartile 1	1	1	1
2	1.04 (0.90–1.21)	1.28 (0.71–2.29)	0.94 (0.66–1.34)
3	1.02 (0.88–1.19)	1.22 (0.68–2.19)	0.80 (0.55–1.17)
4	1.02 (0.88–1.19)	1.71 (0.99–2.97)	0.72 (0.49–1.05)

Model 1: adjusted for age, sex, cigarette smoking, education, years of Medicare eligibility; model 2: Adjusted for model 1 + BMI; model 3: adjusted for model 2 + baseline postload glucose. Quartile 1, <68 bpm; quartile 2, 68–74 bpm; quartile 3, 75–83 bpm; quartile 4, ≥84 bpm.

Table 3—*Adjusted ORs for the development of hospital diagnosis of diabetes by baseline heart rate, stratified by obesity status in adults aged 35–49 years at baseline*

		Heart rate quartiles			
	Per 12 bpm	1: <68 bpm	2: 68–74 bpm	3: 75–83 bpm	4: ≥84 bpm
BMI <30 kg/m^2					
n	12,847	2,926	3,581	3,151	3,189
Events	1,305 (10.2)	257 (8.8)	352 (9.8)	331 (10.5)	365 (11.5)
Model 1	1.12 (1.06–1.19)	1 (ref.)	1.13 (0.95–1.34)	1.22 (1.02–1.45)	1.32 (1.11–1.57)
Model 2	1.05 (0.99–1.11)	1 (ref.)	1.11 (0.93–1.32)	1.14 (0.96–1.37)	1.13 (0.95–1.35)
BMI ≥30 kg/m^2					
n	2145	454	561	550	580
Events	572 (26.7)	126 (27.8)	148 (26.4)	131 (23.8)	167 (28.8)
Model 1	1.00 (0.91–1.11)	1 (ref.)	0.94 (0.71–1.24)	0.83 (0.62–1.11)	1.08 (0.82–1.43)
Model 2	0.91 (0.82–1.01)	1 (ref.)	0.90 (0.68–1.21)	0.77 (0.57–1.04)	0.84 (0.63–1.13)

Data are *n* (%) and HR (95% CI). Model 1: adjusted for age, sex, cigarette smoking, education (years), years of Medicare eligibility; model 2: adjusted for model 1 + postload glucose and BMI.

prior longitudinal studies. The pancreas is heavily innervated by parasympathetic nerve fibers that stimulate the β-cells to release insulin in response to circulating glucose levels, and sympathetic activation can inhibit insulin secretion. If, as hypothesized, autonomic function is already impaired in the presence of obesity, glucose levels may gradually rise unabated by insulin release if peripheral nerve fibers are already damaged. This negative feedback cycle may lead to the development of frank diabetes (18–20).

The present findings must be interpreted in light of some important considerations. First, our measure of diabetes at baseline was based on glucose measurements 1-h after a 50-g load, which was standard at that time (21). However, our measured glucose levels may be lower than those ascertained using current standard measurement techniques. Consequently, we may have underestimated the number of participants with fasting glucose >11.1 mmol/l who had undiagnosed diabetes. Our diagnosis of diabetes over follow-up was based on Medicare claims data, which restricted us to studying individuals who reached at least 65 years of age. Participants with higher heart rate may have died before reaching age 65 years, thus prohibiting us from studying the association between heart rate and diabetes in that high-risk subset. Therefore, our findings are only generalizable to adults who live to older age. Diabetes is often a comorbid condition in people who have premature coronary heart disease; thus, our estimates based on survivors may have been biased toward the null. Competing mortality may be one explanation for the weaker association among those who were obese at baseline. Individuals who were obese in early middle age may have been at higher risk for mortality from coronary heart disease, cancer, or other causes. Similarly, adults who were older at baseline may have died from other causes before age 65 years, when we began to evaluate diabetes-related mortality, thus providing one explanation for our findings being restricted to younger adults. Relying on hospital visit diagnosis codes to identify diabetes introduces another source of misclassification, since diabetes develops, on average, 4–7 years before diagnosis (22). We do not, however, expect that misclassification based on underdiagnosis would be differential based on heart rate levels.

The reason we did not use proportional hazards modeling to investigate our association is because it is possible that diabetes was diagnosed earlier than the actual claims data we used to estimate incidence. Study participants may have developed diabetes and begun treatment during the time interval before they became eligible for Medicare (i.e., before age 65 years). If we were to rely on the Medicare claims date as the diabetes diagnosis date, we could misrepresent the "failure date" when participants developed diabetes. Consequently, our analyses using logistic regression to estimate the cumulative incidence of diabetes by heart rate is the most precise analysis we can conduct with the data available. We adjusted all models for years of Medicare eligibility in an attempt to reduce disparities in the length of time that a study participant would have been able to have a diagnosis.

Covariate ascertainment took place during a single baseline examination. Thus, we were unable to evaluate the role of changes in covariates over time on the association between heart rate and diabetes. Even though a single baseline measure of BMI had little influence on the measures of association, weight change over time may have been an important unmeasured factor leading to diabetes development. We had no measurement of physical activity available for statistical adjustment. Given that physical activity is a primary behavioral determinant that can raise cardiorespiratory fitness, which is reflected by lower resting heart rate, it is likely that accounting for a measure of activity would have resulted in an attenuation of the observed ORs.

In conclusion, in our study of a large sample of middle-aged adults, baseline heart rate (measured up to 35 years before) was associated with diabetes diagnoses and mortality in older age. Our findings provide further evidence that higher heart rate is associated with adverse morbidity and mortality from a number of causes including diabetes.

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