Running title: Heart rate and incident diabetes

Higher heart rate increases risk of diabetes among men: The AusDiab Study

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Abstract

Aims: Elevated heart rate predicts cardiovascular disease risk and a very limited number of prospective studies have reported conflicting data on the relation between heart rate and diabetes risk. Our aim therefore was to determine in a large, national, population-based cohort if heart rate predicts the development of diabetes.

Methods: The Australian Diabetes Obesity and Lifestyle study followed up 6,537 people over 5 years. Baseline measurements included questionnaires, anthropometrics, blood and urine collection. Heart rate was recorded in beats per minute (bpm) (Dinamap). An oral glucose tolerance test was performed at baseline and follow-up, and diabetes was defined using World Health Organisation criteria.

Results: A total of 5817 participants were eligible for analysis, 221 of whom developed diabetes. Compared to participants with a heart rate <60 bpm, those with a heart rate ≥80 bpm were more likely to develop diabetes (OR: 1.89 [95% CI 1.07, 3.35]) over 5 years, independent of traditional risk factors. This relationship was highly significant particularly in non-obese men (OR: 5.61 [95% CI 1.75, 17.98]), but not in their obese counterparts or in women.

Conclusions: Resting heart rate is associated with an increased risk of diabetes over a 5 year period particularly among non-obese men. This suggests that sympathetic overactivity may be a contributing factor to the development of diabetes, and that resting heart rate may be useful in predicting risk of type 2 diabetes in non-obese men.

Introduction

It has been well established that heart rate is a predictor of cardiovascular disease and mortality (1) and that the lowering of heart rates is related to improved cardiovascular outcomes (2). Evidence is now emerging that suggests an increased heart rate may also be a predictor of diabetes (3-6). There have been few large prospective studies (5, 6) that have been able to confirm that a high heart rate can predict diabetes, independent of traditional risk factors. The 2003 ARIC study (6) was the first to report a prospective relationship between heart rate and diabetes. This has been confirmed by two Japanese studies (4, 5), but another US study failed to demonstrate such a relation (3). There is also some evidence that the relationship between heart rate and diabetes is stronger among non-obese persons (3, 5).

The association between an elevated heart rate and cardiovascular disease has in part been attributed to an over-active sympathetic nervous system, and it has been hypothesised that this is the mechanism underpinning the relationship between diabetes and heart rate (3-6). Aside from its role in cardiovascular control, it is widely accepted that increased sympathetic tone has adverse metabolic consequences and can cause insulin resistance as well as changes in other metabolic markers (7).

Alternatively, the presence of metabolic syndrome, abdominal obesity and insulin resistance per se may cause sympathetic nervous system activation with an increase in heart rate perhaps being a consequence rather than a cause of metabolic alterations (1).

Against this background, we sought to investigate the relationship between heart rate and diabetes, stratified by gender and obesity.

Methods

Study population.

The Australian Diabetes Obesity and Lifestyle (AusDiab) study methods and response rates are described elsewhere (8). In brief, a stratified cluster sample of 11,247 adults aged ≥25 years was drawn from 42 randomly selected census collector districts across Australia in 1999–2000. Over 85% of this population-based sample was from an Australian, New Zealand or British background. Information was collected using a household interview, followed by a biomedical examination (8). In 2004–2005, all living eligible participants were invited to attend follow-up. Among those eligible, 6,537 returned in 2004-05 for follow-up, at which the baseline assessment was repeated; the response rate was 60% (9). Differences between follow-up attendees and non-attendees have been described previously (9). Briefly, compared with those who did not attend (n= 4,710), attendees were significantly less likely to be hypertensive, to have a lower level of education attainment, to be smokers and had lower 2-hour plasma glucose (2hPG) and smaller waist circumferences at baseline (9). The study was approved by the International Diabetes Institute Ethics Committee (8).

Data collection

At both baseline and follow-up, all participants, except for those currently receiving treatment for diabetes or who were pregnant, underwent a standard 75-g oral glucose tolerance test (10). In the state of Victoria, after resting for five minutes, three blood pressure readings were taken in the supine position, at one minute intervals, using a standard mercury sphygmomanometer, recording the first and fifth Korotkoff sounds to

the nearest 2 mmHg, in a quiet area. Heart rate was recorded manually in beats per minute after the second blood pressure reading. In all other states a Dinamap® oscillometric blood pressure recorder was used to measure both blood pressure and heart rate. A comparison study of the sphygmomanometer and Dinamap® showed that an adjustment for diastolic blood pressure recorded in Victoria was required (Victorian adjusted diastolic blood pressure = 4.636 + (0.905 x Victorian manual diastolic blood pressure) (11).

Obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2 and hypertension was defined as systolic blood pressure greater than 140 mmHg, or diastolic blood pressure greater than 90 mmHg, or current use of anti- hypertensive medication. History of cardiovascular disease (CVD) was based on self report (myocardial infarction, stroke or angina), and anxiety was measured using the Hospital Anxiety and Depression Scale (12). HOMA-insulin sensitivity was calculated using the HOMA2 program (13) using human insulin specific radioimmunoassay kit (Linco Research Inc, St Charles, MO). Insulin assays were only conducted in participants aged older than 35 years. In 1999-2000 blood glucose was measured using a glucose oxidase method using an Olympus AU600 automated analyser (Olympus Optical, Tokyo, Japan), and in 2004–2005 a spectrophotometric-hexokinase method utilizing a Roche Modular (Roche Diagnostics, Indianapolis, IN) was used. To compare results from the two assays, 195 stored baseline fasting plasma glucose (FPG) samples and 171 2hPG samples were analyzed on the Roche assay used at follow-up. The median (10th-90th percentile) difference between the pairs of FPG and 2hPG values were 0.2 mmol/l (0.1-0.4) and 0.5 mmol/l

(0.0-0.4) respectively, with higher values from the baseline assay. Diabetes at both surveys was defined on the basis of fasting plasma glucose (FPG) ≥7.0 mmol/l or 2hPG ≥11.1 mmol/l or current treatment with insulin or oral hypoglycemic agents. An incident case of diabetes was defined as an individual who was free of diabetes at baseline but had developed diabetes at follow-up. Urinary albumin creatinine ratio (ACR) was used to define albuminuria, where ACR of 30 to 300 mg/g indicates microalbuminuria and ACR or 300 mg/g or greater indicates macroalbuminuria (9, 14, 15). The method used to measure ACR is described elsewhere (16).

Statistical analysis

Logistic regression was performed to calculate the odds ratio and 95% CIs for the association between resting heart rate and incident diabetes. Participants with diabetes at baseline (n= 453) were excluded from analysis. Baseline heart rate was stratified into four groups (<60 beats per minute (bpm), 60-69 bpm, 70-79 bpm and ≥80 bpm). The population was analysed as stratified into men and women, and then into non-obese (BMI < 30 kg/m^2) and obese groups (BMI ≥ 30 kg/m^2). Logistic regression models were adjusted for age and sex, and then further adjusted for family history of diabetes (yes/no), education level (secondary school qualification; trade or technician's certificate; associate, undergraduate diploma, nursing or teaching qualification; bachelor degree or post-graduate diploma), level of physical activity (sedentary, insufficient or sufficient) (17), smoking status (never, ex-smoker or current smoker) (18), waist circumference, hip circumference, cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), hypertension, treatment for hypertension (self reported), urinary ACR, HOMA-insulin sensitivity (13), history of cardiovascular disease, and anxiety (12).

Additional analyses included: a model which included confounding factors stated above except for treatment for hypertension and history of CVD and instead excluded all those who reported current use of antihypertensive treatment at baseline and those with history of CVD, a model which included menopause status (yes/no) in addition to the confounding factors stated above, and a model which included atrial fibrillation (yes/no) in addition to the confounding factors stated above. Statistical significance was defined as $p<0.05$. All analyses were conducted using Stata 10 (StataCorp, Texas USA).

Results

Of 11,005 participants eligible for testing in 2004–2005, 6,400 attended the full examination, and a further 137 participants had blood and urine tests only. Thus, the response rate for the follow-up was 60% (6,537 of 11,005). Table 1 shows that compared to those who remained free of diabetes, those who developed diabetes over five years were significantly older, had a greater waist circumference, had lower level of physical activity, had a higher blood pressure and had a higher heart rate.

The distribution of the follow-up population among the four heart rate groups was as follows: <60 bpm (16%), 60-69 bpm (35%), 70-79 bpm (31%) and ≥80 bpm, (18%). When adjusted for age, men with a heart rate ≥60 bpm showed an increased risk of diabetes compared to those with a heart rate <60 bpm (Table 2). Among women there was a significantly increased age-adjusted risk among those with a heart rate greater than 80 bpm, compared to those with a heart rate less than 60 bpm [OR: 2.58 (95%CI 1.18, 5.63)]. After adjustment for potential confounding factors, the risk of developing diabetes remained elevated in heart rate quartiles 2-4, in both men and in women, but was significant only when men and women were analysed together. Additional adjustment for menopause status did not affect the results for women.

When participants who reported current use of antihypertensive medication at baseline were excluded (n = 731, including 61 cases of incident diabetes), the relationships remained similar in magnitude, but was significant only in the total population in those with a heart rate greater than 80 bpm compared to those with a heart rate less than 60

bpm [OR: 2.11 (95% CI 1.02, 4.35)]. Moreover, the relationship between heart rate and diabetes persisted after adjusting for atrial fibrillation, in those with a heart rate greater than 80 bpm compared to those with a heart rate less than 60 bpm [total population OR: 1.97 (95% CI 1.12, 3.48); men OR: 2.18 (95% CI 1.00, 4.72)].

Figure 1 shows the relationship between heart rate and diabetes among the non-obese and obese segments of the population, respectively. Among men, a much stronger relationship was apparent in the non-obese than in the obese participants ($p < 0.05$ for the interaction term), such that statistical significance was apparent only in the non-obese population. There was a significantly increased risk among those with a heart rate between 60-69 bpm [OR: 4.18 (95%CI 1.20, 14.49)] and those with a heart rate greater than 80 bpm [OR: 5.03 (95%CI 1.30, 19.37)], compared to those with a heart rate less than 60 bpm, adjusted for age, family history of diabetes, education level, level of physical activity, smoking status, waist circumference, hip circumference, total cholesterol, triglycerides, HDL-C, HOMA insulin sensitivity, hypertension, hypertension treatment, urinary albumin creatinine ratio and anxiety. This finding was unaffected by excluding those who reported using blood pressure treatment at baseline and those with history of CVD [OR: 5.53 (95% CI 1.26, 24.30) for heart rate 60-69 bpm; OR: 4.90 (95% CI 1.05, 22.74) for heart rate 70-79; and OR: 6.45 (95% CI 1.30, 32.02) for heart rate > 80 bpm]. Among women, an interaction between heart rate and obesity was not apparent.

Analyses were re-run after excluding participants whose heart rate was measured manually (n = 791), with no clinically significant changes in results or loss of statistical significance of any findings.

Discussion

Our findings suggest that a heart rate above 80 bpm is associated with a significantly increased risk of incident diabetes among non-obese men over a five year period. This relationship was independent of age, family history of diabetes, education level, level of physical activity, smoking status, waist circumference, hip circumference, total cholesterol, triglycerides, HDL-C, HOMA insulin sensitivity, hypertension, hypertension treatment, history of CVD, urinary albumin creatinine ratio and anxiety.

Our findings are consistent with that of previous studies (3-6). The first prospective study to examine heart rate in relation to diabetes incidence was conducted in 8185 participants over an average follow up period of 8.3 years (6). A near doubling of risk of diabetes development was reported in those with high (>73 bpm) compared to low (≤60 bpm) heart rate at baseline, which remained significant even after adjustment for physical activity and BMI, baseline glucose, as well as when those on antihypertensive medication were excluded. Shigetoh et al presented the findings of a 20 year prospective study consisting of 637 participants (5) and reported that those with a baseline heart rate of > 80 bpm had a greater than 5-fold increased risk of diabetes over a 20 year period compared to those with a baseline heart rate of less than 60 bpm (5). In another prospective Japanese study, Nagaya et al found that men in the second quartile of heart rate (54-58 bpm) had a 25% increase in risk of diabetes compared to those with a heart rate less than 54 bpm, and those in the 4^{th} quartile of heart rate (65-131 bpm) had an increased risk of 2.3 times those in the first quartile (4).

Interestingly, our findings indicated that the relationship was evident only amongst non-obese men. In the Chicago Heart Association Detection Project in Industry, Carnethon et al also found that the relationship was present only in non-obese subjects (3). However, Carnethon et al also found no relationship between heart rate and diabetes after adjustment for BMI (3). Shigetoh et al reported a significant relationship even after adjustment for BMI but suggested that the difference between their findings and those of Carnethon et al could be due to the low prevalence of obesity at baseline in their study. Of note, separate analyses for men and women were not performed in these studies.

Heart rate is predominantly determined by the sympathetic outflow to the heart and modulated by vagal inputs. It is therefore reasonable to speculate that sympathetic activation is the mechanistic link between an elevated heart rate and increased diabetes risk. Indeed, there is clear evidence for a critical role of sympathetic nervous system activation in the aetiology of the metabolic syndrome, the development of diabetes, and the increased cardiovascular risk associated with these conditions.

Insulin resistance is an important pathophysiological feature of the metabolic syndrome (MS). The resulting hyperinsulinemia may account for many of the features of MS including altered glucose and lipid metabolism, enhanced atherogenesis, increased blood pressure, and ultimately the development of type 2 diabetes (19). Sympathetic activation has been demonstrated to contribute to insulin resistance both via hemodynamic and cellular effects. In the human forearm, increased noradrenaline

release results in a substantial reduction in forearm blood flow and uptake of glucose, highlighting the adverse effect of sympathetic activation on the ability of the cell to transport glucose across its membrane, a hallmark of insulin resistance (20). Furthermore, a direct relationship has been established between sympathetic nerve firing rates to skeletal muscle tissue and insulin resistance (21) suggesting that sympathetic nervous system activation modulates insulin sensitivity through alterations in regional haemodynamics. In addition, sympathetic activation also affects glucose transport across the cell via non-hemodynamic effects, such as increased adipose tissue lipolysis, which releases free fatty acids into the circulation, thereby engaging a mechanism that directly inhibits glucose transport across the cell membrane.

Moreover, sympathetic activation is commonly present in subjects who are genetically predisposed to develop features of the metabolic syndrome (21-23). Interestingly, the number of sympathetic bursts to the skeletal muscle circulation is also greater in patients with diabetes and genetically predisposed individuals with normal blood glucose, but increased insulin resistance (24). In obese individuals, the increase in sympathetic activity is proportional to the increase in body weight, and further exaggerated if obesity is associated with hypertension (25). These findings may to some extent explain our finding of a more robust relationship between heart rate (as a marker of cardiac sympathetic drive) and the risk of diabetes in non-obese male subjects due to the lack of the confounding influence of obesity.

Of note, the association between sympathetic activation and insulin sensitivity appears to be bidirectional. Whilst increased sympathetic activity reduces insulin sensitivity, systemic infusion of insulin in during glucose clamp is accompanied by a marked increase in sympathetic neural outflow to the skeletal muscle circulation (26). Insulin resistance and hyperinsulinemia may therefore be either cause or consequence of sympathetic activation. In this setting, it is possible that increased heart rate was simply a consequence of insulin resistance and was not in the causal pathway to diabetes. However, our findings were independent of HOMA (a surrogate of insulin sensitivity). Interestingly, a study in Japanese individuals demonstrated that while both noradrenaline and insulin levels were increased in those who had developed hypertension at follow up, only noradrenaline levels were elevated at baseline testing some 10 years earlier (27), suggesting that sympathetic activation indeed precedes insulin resistance, which would be in line with our findings of an increased diabetes risk in those subjects with higher heart rates.

Also of interest is a recent study which revealed a strong association between body mass index and sympathetic nerve activity only in men but not in women (28), which may to some extent explain our finding of a less pronounced, albeit still significant association between heart rate and diabetes risk when anthropometric indices were taken into account in men, whereas these factors virtually played no role in the relation in women.

There are several other potential explanations for the absence of a relation between heart rate and diabetes risk in women, such as women have a lower central sympathetic output than men, possibly explained by a greater baroreceptor reflex inhibitory effect of blood pressure (29), and the existence of gender specific differences in the cardiovascular and autonomic response to stressors with women displaying a smaller increase of heart rate with isometric hand grip testing than men (29).

Perhaps most relevant in this context is the finding that male subjects with faster heart rates have higher levels of muscle sympathetic nerve activity and increased systolic blood pressure, whereas no such relation was found in women (30). Given the previous demonstration of a direct relationship between sympathetic nerve firing rates to skeletal muscle tissue and insulin resistance (21), the absence of a link between heart rate and muscle sympathetic nerve activity in women may also account for the absence of a relationship between heart rate and diabetes risk in women. Hormonal status is also likely to be of relevance in this context. While sympathetic regulation of heart rate was enhanced in post-menopausal women compared to premenopausal women, estrogen replacement therapy appeared to facilitate vagal control and attenuate sympathetic regulation, indicating that estrogens may have a modulating role on autonomic control of heart rate (31).

Limitations

The response rate was modest, and therefore, our results may not be representative of the whole Australian population. However, the findings that the incidence of self-

reported diabetes was very similar in those who attended the bio-medical follow-up testing and the 2200 participants who completed the self-report questionnaires for follow-up only, and that the predictors of self-reported diabetes did not change if these non-attendees were grouped with attendees (data not shown), suggest that the impact of the response rate on our findings is likely to be small (9). Although information on blood pressure treatment was collected at baseline, specific use of beta blockers was not. Beta blockers reduce heart rate and have been associated with increased risk of developing diabetes. However, analyses excluding those on any antihypertensive medication showed similar results to the full population, rendering a significant effect of concomitant medication on our results unlikely. Moreover, it may be that some effects were missed due to the modest number of participants with incident diabetes (n=221). Notably, our study had a relatively short follow up period compared to other studies and to better unravel the association between heart rate and diabetes may require a longer follow up.

In conclusion, in our prospective cohort, resting heart rate was associated with an increased risk of diabetes over a 5 year period among non-obese men. This lends support to the concept that sympathetic over-activity plays a role in the development of type 2 diabetes, and suggests the possibility that heart rate may be a useful addition to identifying risk of type 2 diabetes in non-obese men.

NMG analysed the data and wrote manuscript. SKT assisted with analysing the data, and edited the manuscript. DJM, SS, MPS and JES. reviewed and edited manuscript.

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Table 1 Baseline characteristics according to diabetes status at follow-up: the AusDiab study

	Diabetes status at follow-up		
	With diabetes (n=221)	Without diabetes (n=5596)	P value
Men (%)	51.1	44.9	0.07
Age (yrs)	55.9 (11.9)	50.7 (12.6)	<0.01
Waist circumference (cm)			
Men	104.2 (11.6)	96.4 (10.5)	<0.01
Women	92.5 (14.7)	83.8 (12.4)	
Obesity (BMI ≥30 kg/m^2, %)	39.8	19.4	<0.01
Smoking status (%)			
Current smoker	11.9	9.1	0.025
Ex-smoker	38.6	31.9	
Never smoked	49.5	59.0	
Education level (%)			
Secondary school qualification	47.3	36.2	0.003
Trade, technician's certificate	28.4	29.6	
Associate, undergraduate diploma, nursing or teaching qualification	11.9	14.0	
Bachelor degree, post-graduate diploma	12.4	20.3	
Level of physical activity (%)			
Inactive (0 min/week)	21.7	12.7	<0.01
Insufficient (1-149 min/ week)	37.8	29.1	
Sufficient (≥150 min/week)	40.6	58.2	
Family history of diabetes (%)	29.4	17.7	<0.01
Total cholesterol (mmol/l)	5.9 (1.0)	5.6 (1.0)	<0.01
Hypertension* (%)	54.8	27.6	<0.01
History of cardiovascular disease (%)	14.2	5.6	<0.01
Heart rate (bpm)	72.8 (11.3)	69.4 (10.4)	<0.01
Systolic BP (mmHg)	136.5 (17.5)	127.5 (17.2)	<0.01
Diastolic BP (mmHg)	74.7 (11.9)	69.8 (11.5)	<0.01
Blood pressure treatment (%)	29.2	12.2	<0.01

Data are percentages and means (SD). *Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic ≥90 mmHg or reporting antihypertensive medication use.

Table 2. The association between heart rate and the incidence of diabetes over 5 years: the AusDiab study.

	Men		Women		Total	
	n/N	OR (95%CI)	n/N	OR (95%CI)	n/N	OR (95%CI)
Model 1 *						
<60 bpm	*12/608*	1.00	*8/343*	1.00	*20/951*	1.00
60-69 bpm	*41/962*	2.39 (1.24, 4.59)	*28/1095*	1.13 (0.51, 2.50)	*69/2057*	1.81 (1.09, 3.01)
70-79 bpm	*30/698*	2.44 (1.23, 4.82)	*36/1109*	1.48 (0.68, 3.21)	*66/1807*	2.08 (1.25, 3.47)
≥80 bpm	*30/360*	4.88 (2.46, 9.71)	*36/642*	2.58 (1.18, 5.63)	*66/1002*	3.86 (2.30, 6.47)
Model 2 †						
<60 bpm	*12/608*	1.00	*8/343*	1.00	*20/951*	1.00
60-69 bpm	*41/962*	2.01 (0.99, 4.09)	*28/1095*	1.03 (0.42, 2.50)	*69/2057*	1.55 (0.89, 2.67)
70-79 bpm	*30/698*	1.54 (0.73, 3.25)	*36/1109*	1.25 (0.53, 2.94)	*66/1807*	1.44 (0.83, 2.51)
≥80 bpm	*30/360*	2.02 (0.93, 4.39)	*36/642*	1.72 (0.72, 4.12)	*66/1002*	1.89 (1.07, 3.35)

n = number of participants with incident diabetes, N = total number of participants

* Model 1: Adjusted for age, and total population additionally adjusted for sex

† Model 2: Adjusted for age, family history of diabetes, waist circumference, hip circumference, smoking status, education level, level of physical activity, cholesterol, HDL-cholesterol, triglycerides, hypertension, hypertension treatment, history of CVD, HOMA- insulin sensitivity, urinary albumin creatinine ratio and anxiety, and total population additionally adjusted for sex.

Figure legend

Figure 1. The association between heart rate and 5-year incidence of diabetes in a) non-obese and b) obese men and women, adjusted for age, family history of diabetes, waist circumference, hip circumference, smoking status, education level, level of physical activity, cholesterol, HDL-cholesterol, triglycerides, hypertension, hypertension treatment, history of CVD, HOMA- insulin sensitivity, urinary albumin creatinine ratio and anxiety.