Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2010;39:900–906
© The Author 2010; all rights reserved.
Advance Access publication 6 May 2010
doi:10.1093/ije/dyq068

Resting heart rate and risk of type 2 diabetes in women

Xianglan Zhang,[1]* Xiao-Ou Shu,[1] Yong-Bing Xiang,[2] Gong Yang,[1] Honglan Li,[2] Hui Cai,[1] Yu-Tang Gao[2] and Wei Zheng[1]

[1]Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Nashville, TN, USA and [2]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

*Corresponding author. Vanderbilt Epidemiology Center, Institute for Medicine & Public Health, Vanderbilt University Medical Center, Sixth Floor, Suite 600, 2525 West End Avenue, Nashville, TN 37203-1738, USA.
E-mail: xianglan.zhang@vanderbilt.edu

Accepted 22 March 2010

Background Resting heart rate has been shown to predict risk of cardiovascular disease; its association with diabetes remains unclear, particularly in non-Western populations.

Methods We evaluated the association between resting heart rate and risk of type 2 diabetes in the Shanghai Women's Health Study, a population-based prospective cohort study. The analysis included 47 571 Chinese women with no prior history of diabetes, cancer, cardiovascular disease or thyroid dysfunction at the time when resting heart rate was measured. Incident diabetes was ascertained through biennial in-person interviews.

Results During a mean follow-up of 4.9 years, 849 women developed type 2 diabetes. For heart rate categories of ⩽68, 69–72, 73–76, 77–80 and >80 beats/min, the incidence rates of diabetes per 1000 person-years were 2.91, 3.31, 3.71, 4.16 and 5.34, respectively. The multivariable-adjusted hazard ratios (HRs) [95% confidence intervals (CIs)] for diabetes across increasing heart rate categories were 1, 1.21 (0.99–1.47), 1.30 (1.05–1.62), 1.37 (1.12–1.69) and 1.60 (1.28–2.00), respectively. Further analyses of the joint effects of heart rate with body mass index (BMI), waist–hip ratio (WHR) and blood pressure (BP) showed increased risk of diabetes with increasing heart rate in all categories of BMI, WHR or BP. The combinations of the highest heart rate category with highest BMI, WHR or BP category were associated with the highest HRs, ranging from 4.81 to 6.34.

Conclusions A high resting heart rate is independently associated with an increased risk of type 2 diabetes in women. The combinations of high heart rate with high BMI, WHR or BP level are associated with a substantially increased risk.

Keywords Resting heart rate, type 2 diabetes, women

Introduction

Many epidemiological studies have shown that resting heart rate independently predicts cardiovascular events and mortality in the general population and in those with various cardiovascular diseases.[1–4] Relatively few studies, however, have evaluated the association between resting heart rate and risk of type 2 diabetes, particularly in non-Western populations. Furthermore, previous studies have focussed exclusively on resting heart rate measured in office settings.[5,6] Resting heart rate can be affected by a variety of environmental stimuli, including the 'white coat' effect.[7] Out-of-office measurement of resting heart rate may be preferable in epidemiologic studies, as it is more likely to reflect the true usual resting heart rate.

Some Asian populations, including Chinese, have been found to be particularly susceptible to insulin resistance and type 2 diabetes, despite having a low rate of obesity.[8,9] Identifying factors that may predict risk of type 2 diabetes is an important step toward improved understanding and prevention of this major disease in high-risk populations. We prospectively evaluated the association between resting heart rate measured at home and risk of type 2 diabetes in a large cohort of Chinese women enrolled in the Shanghai Women's Health Study (SWHS). We also examined joint effects of heart rate with body mass index (BMI), waist–hip ratio (WHR) and blood pressure (BP) on diabetes risk.

Methods

The SWHS is a population-based, prospective cohort study of adult Chinese women. Details of the study design and methods have been described previously.[10] Briefly, all eligible women 40–70 years of age and living in seven typical urban communities of Shanghai were invited to participate in the study. Between December 1996 and May 2000, a total of 74 942 women enrolled in the study and completed the baseline survey (participation rate: 92.7%). The baseline survey was conducted at participants' homes by trained interviewers who were retired medical professionals. Structured questionnaires were used during the survey to obtain information on demographics, lifestyle habits, medical history, medication use and other characteristics. Total physical activity was assessed using a validated physical activity questionnaire that captured information on regular exercise participation, walking and cycling for transportation and other reasons, and household activities.[11] Estimates of physical activity levels were calculated as metabolic equivalent (MET)-hours/day. Participants were also measured for weight, height and circumferences of the waist and hips following a standard protocol.[12] The study was approved by the Institutional Review Boards of all institutes involved, and written, informed consent was obtained from all participants.

Measurement of heart rate and BP

During the first follow-up home visit (2000–02), 68 412 living cohort members completed heart rate and BP measurements in addition to an in-person interview. Measurements were performed uniformly according to standard protocols. Participants were asked to sit and relax. After at least a 5-min rest, heart rate was measured by pulse palpation over a 30-s period, and BP was measured using the auscultatory method with a conventional mercury sphygmomanometer. Two BP measurements were taken at a 30-s interval.

Outcome ascertainment

Incident type 2 diabetes was identified through in-person follow-up interviews that were conducted approximately every 2 years. During the interviews, each participant was asked whether, since last interview, she had been diagnosed with diabetes by a physician. For each positive response, information was obtained on symptoms, diagnostic tests, the date of first diagnosis and the use of oral hypoglycaemic medications and insulin. The diagnosis of diabetes was considered to be confirmed if the participant reported having at least one of the following: (i) classic symptoms of hyperglycaemia plus elevated glucose levels [fasting blood glucose concentration $\geqslant$7.0 mmol/l or 2-h blood glucose value during an oral glucose tolerance test (OGTT) $\geqslant$11.1 mmol/l]; (ii) elevated glucose levels (fasting blood glucose $\geqslant$7.0 mmol/l or 2-h blood glucose during OGTT $\geqslant$11.1 mmol/l) on at least two separate occasions; or (iii) use of oral hypoglycaemic agents or insulin. The diagnostic criteria are in line with the American Diabetes Association guidelines.[13]

Statistical analysis

Since resting heart rate was measured during the first follow-up interview, we used the date of the first follow-up as the baseline for the present analysis. We excluded women with previously diagnosed diabetes, cancer, cardiovascular disease, cardiac arrhythmias, or thyroid dysfunction at the first follow-up interview. We also excluded women who reported use of antihypertensive medications, as some forms of antihypertensive medication can affect heart rate. After these exclusions, 47 571 women remained for the analysis. Participants were classified into five categories according to quintile cut-points of resting heart rate, with the lowest heart rate category serving as the reference category. Cox proportional hazards models were used, with age as the time scale, to estimate hazard ratios (HRs) of incident diabetes associated with resting heart rate and their 95% confidence intervals (CIs), and to adjust for potential confounders. Entry time was defined as age at the first follow-up interview, when resting heart rate was taken. Exit time was defined as age at the diagnosis of diabetes that occurred after the first follow-up interview, death or censoring. Covariates included age (continuous), education level (four categories), occupation (three categories), annual family income (four categories), cigarette smoking (yes or no), alcohol consumption (yes or no), BMI (quintiles), WHR (quintiles), overall physical activity level (quintiles) and systolic BP (continuous). Additional adjustment for dietary factors, including intakes of fat, vegetables, fruits, glycaemic load and sodium, did not appreciably alter the risk estimates, and these variables were not included in the final models. Tests for linear trend in risk across heart rate categories were performed by using the median value for each heart rate category and modelling them as continuous variables. We also conducted analyses stratified by age. Finally, we conducted analyses of the joint effects of heart rate with BMI, WHR and BP on diabetes risk. *P* values for multiplicative interaction were derived by using the likelihood ratio test for nested models with and without interaction terms. Statistical analyses were performed by using SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC, USA). All statistical tests were based on two-sided probability.

Results

The mean age [standard deviation (SD)] of the study population at baseline was 53.5 years (8.7). The mean resting heart rate was 73.6 (SD = 7.0). Very few women ever smoked cigarettes or drank alcohol. Table 1 presents selected characteristics of the study population according to five resting heart rate categories. Compared with women with lower resting heart rate, women with higher heart rate appeared to have lower levels of education, occupational status and family income. They tended to have higher levels of BMI, WHR and BP. In addition, they were more likely to have ever smoked cigarettes. Resting heart rate did not appear to be related to age, overall physical activity or alcohol consumption. The proportions of women with prevalent diabetes at baseline across five increasing heart rate categories were 3.91, 3.88, 3.83, 4.99 and 6.02%, respectively.

During a mean of 4.9 years of follow-up, 849 incident cases of type 2 diabetes were documented. For five increasing heart rate categories, the incidence rates of type 2 diabetes per 1000 person-years were 2.91, 3.31, 3.71, 4.16 and 5.34, respectively. Table 2 summarizes the HRs and 95% CIs of type 2 diabetes according to five resting heart rate categories. In both analyses adjusted for age only and analyses adjusted for various potential confounders, including sociodemographic factors, BMI, WHR, physical activity, smoking, alcohol consumption and BP, resting heart rate was positively associated with risk of type 2 diabetes in a dose–response fashion (P for trend <0.0001). The multivariable-adjusted HRs for type 2 diabetes across five increasing categories of resting heart rate were 1 (reference), 1.21 (0.99–1.47), 1.30 (1.05–1.62), 1.37 (1.12–1.69) and 1.60 (1.28–2.00), respectively. When resting heart rate was analysed as a continuous variable, for each 1-SD increase (seven beats/min) in heart rate, the risk for type 2 diabetes increased by 17% (HR, 1.17; 95% CI, 1.10–1.24). This positive association persisted in sensitivity analyses that excluded early years of follow-up after heart rate was taken. For each 1-SD increase in heart rate, the adjusted HRs were 1.16 (95% CI, 1.08–1.24) and 1.11 (1.02–1.21) after excluding first 1 and 2 years of follow-up, respectively. The HRs (95% CIs) across five increasing heart rate categories were 1 (reference), 1.10 (0.88–1.37), 1.24 (0.98–1.57), 1.27 (1.01–1.59) and 1.53 (1.20–1.96), respectively, after excluding first year of follow-up. Further stratified analyses showed that the magnitude of the association appeared to be greater in women $\leqslant 55$ years than in women >55 years (Table 2). The *P*-value for multiplicative interaction was 0.56.

Table 3 presents the joint effects of resting heart rate with BMI, WHR and BP on diabetes risk. Within each category of BMI, WHR or BP, resting heart rate was positively associated with risk of diabetes; likewise, diabetes risk increased with increasing levels of BMI, WHR or BP across all heart rate categories. Women in both the highest category of heart rate and the highest category of BMI, WHR or BP had the highest HRs for type 2 diabetes. The *P*-values for multiplicative interaction between heart rate and BMI, WHR or BP were 0.21, 0.37 and 0.84, respectively.

We assessed the proportional hazards assumption by including interaction terms between exposure and log time and found no evidence of violation of the assumption.

Discussion

In this large, population-based cohort study of apparently healthy Chinese women, high resting heart rate was associated with a moderate increase in the risk of type 2 diabetes. This positive association persisted even after accounting for levels of BMI, WHR, BP and physical activity and other potential confounders. Analyses of the joint effects further revealed that the increased risk of type 2 diabetes associated with increasing heart rate existed across all categories of BMI, WHR or BP. The combinations of high heart rate and high BMI, WHR or BP level were associated with a substantially increased risk of developing type 2 diabetes.

Resting heart rate provides an overall index of autonomic tone.[14] An elevation in resting heart rate may reflect an imbalance in the autonomic nervous system favouring sympathetic activation.[14] Enhanced sympathetic activity has been linked to reduced insulin

Table 1 Characteristics of study participants according to five categories of resting heart rate[a]

Characteristic	Resting heart rate categories, beats/min ⩽68 (n = 12 613)	69–72 (n = 13 060)	73–76 (n = 8110)	77–80 (n = 8620)	>80 (n = 5168)	*P* for trend
Age (years), mean	54.0	53.1	53.3	53.4	54.1	0.41
Education level						<0.0001
Elementary school or less	18.7	16.1	16.8	17.8	20.5	
Middle school	39.0	41.4	41.6	41.5	39.1	
High school	29.1	29.6	28.9	28.9	28.7	
College or more	13.2	12.9	12.7	11.7	11.7	
Occupation						0.0004
Manufacturing and agricultural workers	50.6	50.9	51.1	52.3	52.4	
Clerical and service workers	20.8	21.5	21.0	21.0	21.2	
Professionals, technicians, administrators	28.7	27.6	27.8	26.7	26.4	
Annual family income (yuan)						<0.0001
<10 000	15.7	15.1	14.9	15.8	17.4	
10 000–19 999	37.8	37.9	39.6	40.1	39.3	
20 000–29 999	28.3	29.6	28.6	27.9	26.7	
⩾30 000	18.2	17.3	16.9	16.1	16.6	
Ever smoked cigarettes	2.2	2.4	2.7	2.6	3.3	0.0001
Ever drank alcohol	2.3	2.4	2.4	2.5	2.4	0.44
BMI (kg/m^2), mean	23.5	23.5	23.6	23.7	23.9	<0.0001
WHR, mean	0.80	0.80	0.81	0.81	0.81	<0.0001
Physical activity (MET-h/day), mean	15.4	15.5	15.5	15.4	15.3	0.26
Systolic BP (mmHg), mean	118.7	118.4	118.8	119.7	121.9	<0.0001
Diastolic BP (mmHg), mean	75.8	76.0	76.5	77.0	78.1	<0.0001

[a]Unless otherwise indicated, data are given as percentage of subjects.

Table 2 HRs of type 2 diabetes according to five categories of resting heart rate

	Resting heart rate categories, beats/min ⩽68	69–72	73–76	77–80	>80	*P* for trend
All subjects						
Number of subjects	12 613	13 060	8110	8620	5168	
Number of cases	180	212	147	176	134	
Age-adjusted HR	1.00	1.19 (0.98–1.46)	1.32 (1.06–1.65)	1.48 (1.21–1.83)	1.83 (1.47–2.29)	<0.0001
Multivariate HR[a]	1.00	1.21 (0.99–1.47)	1.30 (1.05–1.62)	1.37 (1.12–1.69)	1.60 (1.28–2.00)	<0.0001
Age ⩽55 years						
Number of subjects	7815	8656	5271	5592	3196	
Number of cases	64	97	74	77	57	
Multivariate HR[a]	1.00	1.37 (1.00–1.88)	1.63 (1.16–2.27)	1.51 (1.08–2.10)	1.82 (1.27–2.61)	0.0007
Age >55 years						
Number of subjects	4798	4404	2839	3028	1972	
Number of cases	116	115	73	99	77	
Multivariate HR[a]	1.00	1.12 (0.87–1.45)	1.09 (0.81–1.46)	1.29 (0.99–1.69)	1.47 (1.10–1.96)	0.007

[a]Adjusted for age, education, occupation, family income, cigarette smoking, alcohol consumption, BMI, WHR, physical activity and systolic BP.

Table 3 Joint effects of resting heart rate with BMI, WHR and BP on the risk of type 2 diabetes

	Resting heart rate, beats per minute		
	⩽70	71–80	>80
BMI (kg/m²)			
Tertile 1 (⩽22.0)			
Number of subjects	5347	8960	1619
Number of cases	22	57	16
Multivariate HR[a]	1.00 (reference)	1.54 (0.94–2.52)	2.09 (1.10–3.99)
Tertile 2 (22.1–24.7)			
Number of subjects	5162	8927	1633
Number of cases	45	133	22
Multivariate HR[a]	1.40 (0.84–2.34)	2.44 (1.55–3.84)	2.03 (1.12–3.67)
Tertile 3 (>24.7)			
Number of subjects	5103	8904	1916
Number of cases	149	309	96
Multivariate HR[a]	3.14 (1.99–4.96)	3.86 (2.48–6.00)	5.10 (3.18–8.19)
WHR			
Tertile 1 (⩽0.78)			
Number of subjects	5285	9022	1596
Number of cases	16	57	8
Multivariate HR*	1.00 (reference)	2.05 (1.18–3.57)	1.52 (0.65–3.54)
Tertile 2 (0.79–0.82)			
Number of subjects	5318	8944	1676
Number of cases	62	135	38
Multivariate HR*	2.56 (1.47–4.45)	3.38 (2.01–5.69)	4.85 (2.70–8.71)
Tertile 3 (>0.82)			
Number of subjects	5009	8825	1896
Number of cases	138	307	88
Multivariate HR*	4.02 (2.38–6.80)	5.31 (3.19–8.84)	6.34 (3.69–10.89)
BP (mmHg)			
Normal (SBP < 120 and DBP < 80)			
Number of subjects	6732	10870	1777
Number of cases	33	75	12
Multivariate HR[a]	1.00 (reference)	1.37 (0.91–2.06)	1.26 (0.65–2.44)
Prehypertension (SBP: 120–139 or DBP: 80–89)			
Number of subjects	5838	11 023	2167
Number of cases	89	231	63
Multivariate HR[a]	2.03 (1.36–3.03)	2.82 (1.95–4.07)	3.69 (2.41–5.63)
Hypertension (SBP ⩾ 140 or DBP ⩾ 90)			
Number of subjects	3042	4898	1224
Number of cases	94	193	59
Multivariate HR[a]	3.03 (2.03–4.54)	3.93 (2.70–5.72)	4.81 (3.12–7.40)

SBP, Systolic BP; DBP, Diastolic BP.
Variables were not included in the model when used for joint analysis.
[a]Adjusted for age, education, occupation, family income, cigarette smoking, alcohol consumption, BMI, WHR, physical activity and systolic BP.

sensitivity, high BP, obesity, sub-clinical inflammation and the metabolic syndrome, conditions that are all associated with the development of type 2 diabetes.[15–19] These observations support the biological plausibility of a positive association between resting heart rate and diabetes risk.

The findings of our study based on resting heart rate measured at home are generally in agreement with the results of previous studies, in which heart rate was measured in office settings.[5,6,20] In a recent analysis from the Chicago Heart Association Detection Project in Industry Study, resting heart rate in middle age was positively associated with diabetes diagnosis and diabetes mortality in older age.[5] Likewise, a positive association between resting heart rate and incident diabetes was also observed in the Atherosclerosis Risk in the Communities (ARIC) Study and a post hoc analysis of the Diabetes Prevention Program.[6,20] However, unlike our study, the positive association between heart rate and diabetes was not consistently observed across various age or BMI subgroups in previous studies.[5] In addition to resting heart rate, other measures of autonomic function, including heart rate variability and heart rate recovery after exercise, were also linked to the risk of diabetes in the ARIC study and the Coronary Artery Risk Development in Young Adults (CARDIA) Study.[6,21] In the CARDIA study, the association between heart rate recovery and diabetes risk was observed in individuals with low physical fitness but not those with high fitness. Overall, these findings are consistent with the notion that autonomic nervous system dysfunction may not only be the consequence of diabetes but also a potential contributor to the disease.

BMI, WHR and BP are strong predictors of type 2 diabetes and significant correlates of resting heart rate.[22,23] Our study has shown, for the first time, that women in both the highest category of BMI, WHR or BP level and highest category of resting heart rate are at the greatest risk for type 2 diabetes. This finding suggests that a simple measure of heart rate, along with measures of BMI, WHR or BP, may provide enhanced assessment of diabetes risk. Women with elevated levels of BMI, WHR or BP, as well as elevated resting heart rate may need more frequent surveillance of blood glucose levels and more aggressive intervention.

Several limitations of our study need to be considered when interpreting the results. Because of the observational nature of the study, we cannot conclude that the observed association between resting heart rate and diabetes risk is a causal one. The average follow-up time of 4.9 years in our study is relatively short, raising concern about the effect of sub-clinical or undiagnosed diabetes. We have conducted sensitivity analyses excluding early follow-up and found no material change in the risk estimates. However, because of the lack of baseline glucose measurements, we were unable to evaluate whether the association between heart rate and diabetes risk could be explained by baseline glucose levels. Although we have adjusted for a range of potential confounding variables, including socio-economic status, BMI, WHR, BP, physical activity and other lifestyle factors, we cannot rule out the possibility of residual confounding due to unmeasured or inaccurately measured covariates. One such concern is related to the lack of a direct measure of physical fitness, which is known to be associated with resting heart rate and diabetes risk.[5] We have assessed the potential confounding effect of total physical activity and found that adjustment for physical activity did not alter the risk estimates considerably, suggesting that the observed association between resting heart rate and diabetes is unlikely to be fully explained by the potential confounding effect of physical fitness. Another limitation of the study is that diabetes was assessed through in-person interviews and this could lead to some misclassification in outcome ascertainment. Because of the prospective design and because that study interviewers were unaware of study hypothesis, the outcome misclassification would likely be non-differential and thus would tend to result in an underestimate of the associations.

Despite the limitations, our study suggests that resting heart rate, a simple, easily accessible measure of autonomic tone, independently predicts the risk of type 2 diabetes in middle-aged and elderly Chinese women. The combinations of high heart rate with high BMI, WHR or BP level are associated with a substantially increased risk.

Funding

National Institutes of Health (R01CA70867 and R01HL079123); National Institutes of Health-sponsored Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Program at Vanderbilt University (2K12HD043483-06) to X.Z. The funding bodies had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest: None declared.

KEY MESSAGES

- Resting heart rate, a simple, easily accessible measure of autonomic tone, independently predicts the risk of type 2 diabetes in middle-aged and elderly Chinese women.
- The combinations of high resting heart rate with high BMI, WHR or BP level are associated with a substantially increased risk of type 2 diabetes.

References

1 Hsia J, Larson JC, Ockene JK *et al*. Resting heart rate as a low tech predictor of coronary events in women: prospective cohort study. *BMJ* 2009;**338:**b219.

2 Fox K, Borer JS, Camm AJ *et al*. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007;**50:**823–30.

3 Greenland P, Daviglus ML, Dyer AR *et al*. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol* 1999;**149:**853–62.

4 Palatini P, Thijs L, Staessen JA *et al*. Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. *Arch Intern Med* 2002; **162:**2313–21.

5 Carnethon MR, Yan L, Greenland P *et al*. Resting heart rate in middle age and diabetes development in older age. *Diabetes Care* 2008;**31:**335–39.

6 Carnethon MR, Golden SH, Folsom AR, Haskell W, Liao D. Prospective investigation of autonomic nervous system function and the development of type 2 diabetes: the Atherosclerosis Risk In Communities study, 1987-1998. *Circulation* 2003;**107:**2190–95.

7 Palatini P, Parati G, Julius S. Office and out of office heart rate measurements: which clinical value? *J Hypertens* 2008;**26:**1540–45.

8 Shai I, Jiang R, Manson JE *et al*. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. *Diabetes Care* 2006;**29:**1585–90.

9 Torrens JI, Skurnick J, Davidow AL *et al*. Ethnic differences in insulin sensitivity and beta-cell function in premenopausal or early perimenopausal women without diabetes: the Study of Women's Health Across the Nation (SWAN). *Diabetes Care* 2004;**27:**354–61.

10 Zheng W, Chow WH, Yang G *et al*. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol* 2005;**162:**1123–31.

11 Matthews CE, Shu XO, Yang G *et al*. Reproducibility and validity of the Shanghai Women's Health Study physical activity questionnaire. *Am J Epidemiol* 2003;**158:**1114–22.

12 Zhang X, Shu XO, Yang G *et al*. Abdominal adiposity and mortality in Chinese women. *Arch Intern Med* 2007;**167:** 886–92.

13 Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;**20:** 1183–97.

14 Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol* 2008;**51:**1725–33.

15 Mancia G, Bousquet P, Elghozi JL *et al*. The sympathetic nervous system and the metabolic syndrome. *J Hypertens* 2007;**25:**909–20.

16 Flanagan DE, Vaile JC, Petley GW *et al*. The autonomic control of heart rate and insulin resistance in young adults. *J Clin Endocrinol Metab* 1999;**84:**1263–67.

17 Shibao C, Gamboa A, Diedrich A *et al*. Autonomic contribution to blood pressure and metabolism in obesity. *Hypertension* 2007;**49:**27–33.

18 Shigetoh Y, Adachi H, Yamagishi S *et al*. Higher heart rate may predispose to obesity and diabetes mellitus: 20-year prospective study in a general population. *Am J Hypertens* 2009;**22:**151–55.

19 Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Abedini S, Hansen JF. Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. *Eur Heart J* 2004;**25:**363–70.

20 Carnethon MR, Prineas RJ, Temprosa M, Zhang ZM, Uwaifo G, Molitch ME. The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. *Diabetes Care* 2006;**29:**914–19.

21 Carnethon MR, Jacobs DR Jr, Sidney S, Liu K. Influence of autonomic nervous system dysfunction on the development of type 2 diabetes: the CARDIA study. *Diabetes Care* 2003;**26:**3035–41.

22 Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev* 2007;**29:**115–28.

23 Conen D, Ridker PM, Mora S, Buring JE, Glynn RJ. Blood pressure and risk of developing type 2 diabetes mellitus: the Women's Health Study. *Eur Heart J* 2007; **28:**2937–43.