Endocr (2009) 36:233–238
DOI 10.1007/s12020-009-9214-y

ORIGINAL PAPER

Impact of the metabolic syndrome and its individual components on risk and severity of coronary heart disease

Yifei Zhang · Jie Hong · Weiqiong Gu · Minghui Gui · Ying Chen · Yu Zhang · Zhenni Chi · Weiqing Wang · Xiaoying Li · Guang Ning

Received: 18 March 2009 / Accepted: 4 June 2009 / Published online: 18 July 2009

Abstract The clinical use of criteria for metabolic syndrome (MetS) and its individual components with respect to risk prediction of coronary heart disease (CHD) remains uncertain. In this study, we investigated whether and to what extent MetS and its individual components were related to risk for CHD. A total of 1,028 subjects, who had undergone coronary angiography or were diagnosed as acute myocardial infarction, were selected according to inclusion criteria. MetS was diagnosed with National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) criteria. CHD was diagnosed with clinical data and confirmed by coronary angiography. The severity of coronary atherosclerosis was estimated by CHD Gensini cumulative index. All the patients were aged 33–87 years. The results showed that the age- and sex-adjusted odds ratios (ORs) for CHD in different individual components of MetS were as follows: low-high density lipoprotein (low-HDL), 3.15 (1.94–5.12); high-fasting plasma glucose (high-FPG), 2.26 (1.63–3.69); high-blood pressure (high-BP), 2.13 (1.38–3.29); high-triglycerides (high-TG), 1.55 (1.13–2.11); all $P < 0.05$, whereas high-body mass index (high-BMI), 0.75 (0.55–1.03) and high-waist circumference, 0.75 (0.51–1.10), both $P > 0.05$. Among all the components, the triad of low-HDL, high-FPG, and high-BP had the highest OR for CHD: 4.28 (3.12–5.87) ($P < 0.001$). MetS subjects had significant increases in number of disease vessel and CHD Gensini index ($P < 0.001$). When individual components of MetS were considered separately, groups with low-HDL, or high-FPG, or high-BP had significant increases in number of disease vessel and Gensini index (all $P < 0.001$). In conclusion, our present results demonstrated that individual components of MetS and their various combinations may have different contributions to CHD and the severity of coronary artery stenosis. Clinical focus should remain on establishing optimum-risk algorithms for CHD.

Keywords Coronary heart disease · Metabolic syndrome · Risk factors · Coronary angiography

Yifei Zhang and Jie Hong contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s12020-009-9214-y) contains supplementary material, which is available to authorized users.

Y. Zhang · J. Hong · W. Gu · M. Gui · Y. Chen · Y. Zhang · Z. Chi · W. Wang · X. Li · G. Ning
Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai Institute of Endocrinology and Metabolism, Endocrine and Metabolic E-Institutes of Shanghai Universities (EISU) and Key Laboratory for Endocrinology and Metabolism of Chinese Health Ministry, Ruijin Hospital, Shanghai Jiao-Tong University School of Medicine, 197 Ruijin Er Road, Shanghai 200025, People's Republic of China

G. Ning
Laboratory of Endocrinology and Metabolism, Institute of Health Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences/Shanghai Jiao-Tong University School of Medicine, Shanghai, People's Republic of China

G. Ning (✉)
Shanghai Clinical Center for Endocrine and Metabolic Diseases, Ruijin Hospital, Shanghai Jiao-Tong University School of Medicine, 197 Ruijin 2nd Road, Shanghai 200025, People's Republic of China
e-mail: guangning@medmail.com.cn

Introduction

The metabolic syndrome (MetS), also termed the insulin resistance syndrome, is characterized by a clustering of cardiovascular risk factors including hyperglycemia,

obesity, dyslipidemia, and hypertension, and it was firstly defined by Reaven [1] in 1988 to improve the understanding of links between insulin resistance and vascular disease. Since its first definition, many studies have focused their attention on whether the MetS is associated with an increased risk of cardiovascular disease (CVD) [2–7]. Most of the studies have confirmed the contributive and predictive effects of MetS to CVD in population or community-based cross-sectional and prospective studies. However, in a recent investigation which addressed their analysis in two prospective studies in elderly populations, the results showed negligible clinical effects of MetS on incident vascular events [8]. In PROSPER study, over a mean of 3.2-year follow-up, MetS was not associated with increased risk of CVD in those with or without baseline disease. In BRHS study, over a mean of 7-year follow-up, MetS was only modestly associated with incident CVD despite strong association with diabetes. Furthermore, the results of some other studies also challenge the view that the criteria for MetS do offer more than the sum of its parts [9, 10]. Therefore, this clinical role of MetS remains contentious, and its definition is also under debate [11–13].

Since the coronary heart disease (CHD) is the most important single event of CVD, in this study, we conducted a cross-sectional study in Chinese people in Shanghai to assess whether MetS and its individual components were related to the risk of CHD. Furthermore, since few studies have focused their attention on the effects of MetS on the severity of coronary vessel disease in Chinese population, we further investigated to what extent MetS and its components were related to coronary vessel disease by Gensini score and disease vessel counting using coronary angiography. Based on this qualitative and quantitative analysis, we may arrive at a more reliable conclusion on the relationship between MetS and CHD.

Results

Baseline characteristics

In this study, all the patients were aged 33–87 years (average 64 years), among whom, 65.9% were male. Descriptive statistics for the general characteristics of 1,028 participants according to MetS status (233 in non-MetS group and 795 in MetS group) are shown in Table 1. There were significant differences between non-MetS and MetS groups in most of the covariates, especially the individual components of MetS, whereas the age, sex composing, and smoking status in the two groups were not significantly different (all $P > 0.05$). The prevalence of CHD in those with MetS (83.6%) was significantly higher than those without MetS (57.2%) ($P < 0.001$).

Table 1 Demographic, anthropometric, and biochemical characteristics of the study subjects

Characteristics	MetS absent	MetS present	*P* value
Number of subjects	233	795	
Age (years)	63 ± 10	64 ± 10	0.433
Body mass index (kg/m^2)	23.1 ± 2.9	25.6 ± 3.1	<0.001
Waist circumference (cm)	85.7 ± 8.8	91.4 ± 9.4	<0.001
Systolic blood pressure (mmHg)	127.1 ± 19.2	134.8 ± 19.1	<0.001
Diastolic blood pressure (mmHg)	76.7 ± 10.6	80.1 ± 10.1	<0.001
Triglyceride (mmol/l)	1.4 ± 0.6	2.2 ± 1.4	<0.001
Total cholesterol (mmol/l)	4.4 ± 1.0	4.8 ± 1.7	0.006
HDL cholesterol (mmol/l)	1.3 ± 0.5	1.1 ± 0.3	<0.001
LDL cholesterol (mmol/l)	2.6 ± 1.0	2.8 ± 0.9	0.079
Fasting plasma glucose (mmol/l)	5.0 ± 1.1	6.8 ± 2.4	<0.001
Fasting serum insulin (μIU/ml)	8.1 ± 8.2	12.9 ± 14.3	<0.001
HOMA-IR (μIU mol/l^2)	2.0 ± 4.4	4.1 ± 6.2	<0.001
Smoking status			0.451
Never	141 (60.5)	443 (55.8)	
Former	11 (4.7)	79 (9.9)	
Current	81 (34.8)	273 (34.3)	
Current alcohol use	29 (19.1)	129 (24.6)	0.017
Hypertension	79 (52.0)	392 (74.7)	<0.001
Type 2 diabetes mellitus	6 (3.9)	333 (63.4)	<0.001
Coronary heart disease	87 (57.2)	439 (83.6)	<0.001
Acute myocardial infarction	39 (16.7)	251 (31.6)	<0.001
Family history of coronary heart disease	30 (12.9)	167 (21.0)	0.003

Data are mean ± SD, *n* (%), or as indicated

MetS metabolic syndrome, *HDL* high density lipoprotein, *LDL* low density lipoprotein

Odds ratios for CHD

In analyses inclusive of all the participants, the age- and sex-adjusted odds ratios (ORs) for CHD in those with MetS were 3.42 (95% CI 2.47–4.75, $P < 0.001$), compared with those without MetS.

The potential effects of various combinations of MetS traits on the risk for CHD were investigated according to presence of single trait and their occurrence in triplets, as shown in Table 2. Risk for CHD associated with single trait or specific triad was estimated with the group without that single trait or specific triad used as the comparator. Since the results obtained by grouping with body mass index (BMI) or waist circumference were similar in this study, we only used the BMI for grouping in the analysis in Table 2. The age- and sex-adjusted ORs and 95% CI for CHD in different individual components of MetS were as

Table 2 Age- and sex-adjusted odds ratios and 95% CI for CHD with individual components of MetS and with specific combinations of MetS components relative to those without that combination

Model	MetS components					CHD		
	High FPG	High BP	Low HDL	High TG	High BMI	Odds ratios	95% CI	*P* value
Individual components of MetS								
1.1	x					2.26	1.63–3.69	<0.001
1.2		x				2.13	1.38–3.29	0.001
1.3			x			3.15	1.94–5.12	<0.001
1.4				x		1.55	1.13–2.11	0.006
1.5					x	0.75	0.55–1.03	0.075
3 components of MetS								
3.1	x	x	x			4.28	3.12–5.87	<0.001
3.2	x		x	x		1.92	1.36–2.71	<0.001
3.3	x		x		x	2.78	1.94–4.00	<0.001
3.4	x	x			x	2.02	1.42–2.86	<0.001
3.5	x	x		x		2.77	1.92–4.00	<0.001
3.6	x			x	x	1.83	1.21–2.78	0.005
3.7		x	x	x		2.56	1.87–3.49	<0.001
3.8			x	x	x	1.83	1.30–2.59	0.001
3.9		x	x		x	1.79	1.33–2.42	<0.001
3.10		x		x	x	2.02	1.41–2.90	<0.001

CI confidence interval; *CHD* coronary heart disease; *MetS* metabolic syndrome; *FPG* fasting plasma glucose; *BP* blood pressure; *HDL* high density lipoprotein; *TG* triglycerides; *BMI* body mass index

follows: low high density lipoprotein (low HDL), 3.15 (95% CI 1.94–5.12); high fasting plasma glucose (high FPG), 2.26 (95% CI 1.63–3.69); high blood pressure (high BP) 2.13 (95% CI 1.38–3.29); high triglycerides (high TG), 1.55 (95% CI 1.13–2.11); all $P < 0.05$, whereas high body mass index (high BMI), 0.75 (95% CI 0.55–1.03); high waist circumference, 0.75 (95% CI 0.51–1.10); both $P > 0.05$. Among all the triplet components, low HDL plus high FPG and high BP had the highest OR for CHD: 4.28 (95% CI 3.12–5.87) ($P < 0.001$).

The extent of coronary atherosclerosis

Comparison of the number of disease vessel and severity of coronary atherosclerosis using Gensini score [14] between MetS and non-MetS groups is shown in Fig. 1. After adjustment for age, sex, and other factors, MetS subjects had significant increases in number of disease vessel (1.4 ± 1.2 vs. 1.0 ± 1.1, $P < 0.001$) and CHD Gensini cumulative index (26.8 ± 31.0 vs. 15.4 ± 23.2, $P < 0.001$).

The comparisons of the number of disease vessel and Gensini cumulative index between the group with individual MetS component and the group without that individual component are shown in Table 3. The number of disease vessel and Gensini cumulative index were both significantly increased in patients with low HDL compared with those without this trait (both $P < 0.001$). The similar

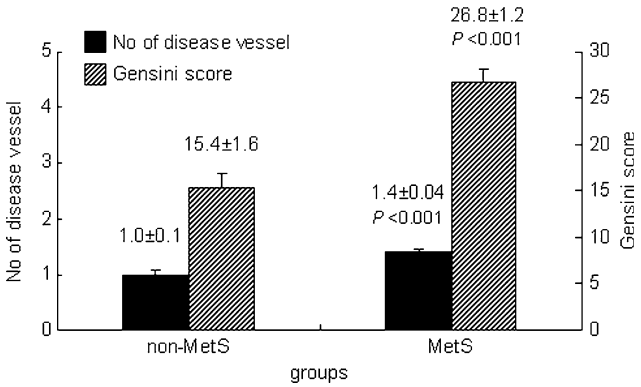

Fig. 1 Age- and sex- adjusted comparison for the number of disease vessel and severity of coronary atherosclerosis (Gensini score) between MetS and non-MetS groups

results were obtained in high FPG and high BP groups (all $P < 0.001$). However, no significant difference was found in group with high TG, high BMI, or high waist circumference group ($P > 0.05$).

Discussion

The aim of this study was to investigate whether and to what extent MetS and its individual components were related to risk for CHD. This study found the following

Table 3 Comparison for the extent and severity of coronary atherosclerosis between individual components of MetS relative to those without that combination

Individual components of MetS	Number of disease vessels	*P* value	Gensini score	*P* value
High FPG				
No	1.0 ± 1.1	<0.001	18.2 ± 25.2	<0.001
Yes	1.6 ± 1.5		29.5 ± 32.5	
High BP				
No	0.8 ± 1.0	<0.001	11.0 ± 16.8	<0.001
Yes	1.4 ± 1.2		26.4 ± 30.9	
Low HDL				
No	0.7 ± 1.0	<0.001	8.9 ± 15.5	<0.001
Yes	1.4 ± 1.2		26.1 ± 30.6	
High TG				
No	1.3 ± 1.2	0.232	24.4 ± 30.8	0.52
Yes	1.3 ± 1.1		23.7 ± 28.7	
High BMI				
No	1.4 ± 1.2	0.153	25.9 ± 31.5	0.113
Yes	1.3 ± 1.2		22.2 ± 27.7	
Central obesity				
No	1.4 ± 1.2	0.064	26.1 ± 30.0	0.165
Yes	1.3 ± 1.1		21.9 ± 26.6	

FPG fasting plasma glucose; *BP* blood pressure; *HDL* high density lipoprotein; *TG* triglycerides; *BMI* body mass index

results. (1) In middle-aged-to-elderly Chinese patients, among all the MetS components, low HDL, high FPG, and high BP may have the relatively high association with CHD, whereas high TG, high BMI, or central obesity may have weak association. (2) When different combinations of three components were used for the definition of MetS, only triad of low HDL, high FPG, and high BP offers priority in the identify of subjects with increased risk of CHD, whereas no other combination offers more than its individual parts. (3) Results from coronary angiography showed that MetS subjects had significant increases in number of disease vessel and CHD Gensini score. When individual components of MetS were considered separately, group of low HDL, or high FPG or high BP had significantly increased Gensini index, whereas no significant difference was found in high TG, high BMI, or high waist circumference group. This study indicated that individual components of MetS and their various combinations may have different values in respect of risk prediction of CHD and the severity of coronary disease.

The value of a formal diagnosis of MetS in clinical practice for determination of vascular risk has been questioned since its first definition [11–13]. Many of the studies have confirmed the predictive effects of MetS to CVD in different populations. For example, in the Hoorn study (a Dutch population-based cohort study), the NCEP definition of MetS was associated with a twofold increase in age-adjusted risk of fatal CVD in men and nonfatal CVD in women [4]. Moreover, in a Swedish community-based sample of middle-aged men, the MetS significantly predicted total and cardiovascular mortality (Cox proportional hazard ratios 1.36 and 1.59, respectively) [6]. Both studies indicated a clinical value in diagnosing the MetS. The similar conclusion was also obtained in two Chinese population groups [2, 15]. However, despite such findings, the predictive value of MetS for CVD was poor in some other studies [5, 8, 16]. The results from the Casale Monferrato Study showed that MetS was not associated with 11-year all-cause or CVD mortality in a population-based cohort of 1,565 patients with T2DM [17]. The results from the PROSPER and BRHS studies suggested that although MetS was associated with T2DM, weak or no association was found between MetS and vascular risk in elderly populations [8]. Furthermore, a meta-analysis of 37 longitudinal studies which included 172,573 individuals also showed that after adjusting for traditional cardiovascular risk factors, only a modest relative risk was found in patients with MetS for CVD compared with those without [5]. In this study, since CHD is the most important single event of CVD, we investigated whether MetS was associated with CHD in Chinese patients who underwent coronary angiography or diagnosed as acute myocardial infarction. Our results showed that except for the combination of the triad of low HDL, high FPG, and high BP, the other triads did not offer more than the individual parts of the syndrome with respect to risk prediction of CHD. When combinations of four or all the five components of the MetS were considered, similar results were obtained (shown in supplementary Table 1). Moreover, when severity of coronary vessel disease was assessed using disease vessel counting and Gensini score, consistent results were obtained in these patients. Therefore, all these results indicated that different components of MetS may have different contributions with respect to CHD. Diagnosis of MetS may hold limited clinical value for CHD risk stratification.

In this study, however, we did not find any association of high BMI or central obesity with incident CHD (ORs: 0.75 [0.55–1.03], 0.75 [0.51–1.10], respectively, both $P > 0.05$). Moreover, none of high BMI, central obesity or high TG was associated with the severity of coronary vessel stenosis (both $P > 0.05$). These results can also be supported by another two studies, the PROSPER and BRHS studies, in which high BMI or waist circumference, or high TG was not associated with incident CVD despite strong association with incident diabetes [8]. For example, in the PROSPER study, after 3.2-year follow-up, the hazard ratio (HR) of high BMI for incident CVD and incident

diabetes was 0.99 (0.78–1.25) and 2.51 (1.89–3.34), respectively; HR of high TG for incident CVD and incident diabetes was 1.10 (0.90–1.35) and 2.10 (1.60–2.77), respectively. Similar results were obtained when they extended analysis to the BRHS study. Results of this study and the other two recent studies indicated that the classical pattern of risk factors for T2DM which includes obesity or central obesity differs in many respects to that which predicts vascular events in middle-aged or elderly people.

However, there are still some limitations to be found in this study. First, all the patients included were middle- or elderly aged and most of them were referred to the Department of Cardiology because of the occurrence of cardiac symptoms. These might have resulted in a higher CHD prevalence in this study population group than those in the common population. Second, among all the participants, 920 (about 89.5%) patients underwent coronary angiography for the diagnosis of CHD, whereas the other 108 subjects were diagnosed with an acute myocardial infarction according to the clinical manifestation and biochemical tests. Thus, the Gensini score and disease vessel analysis could include only 89.5% of all the study participants. This might to some extent weaken the power of correlation analysis.

In conclusion, in this study, in the middle-aged-to-elderly Chinese patients, individual components of MetS and their various combinations may have different values in respect of risk prediction of CHD and the severity of coronary artery stenosis. Except the triad of low HDL, high FPG, and high BP, the other combinations do not provide further prediction compared with the knowledge of its single components. Our findings may be helpful for other investigators to re-evaluate the predictive effects of MetS on CVD. Clinical focus should remain on establishing optimum-risk algorithms for CVD.

Materials and methods

Study participants

For inclusion, in this study, we considered consecutive patients who were referred to the Department of Cardiology in Ruijin Hospital (Shanghai). During the period from January 2005 to December 2007, we recruited 1,382 consecutive Chinese subjects who were diagnosed as acute myocardial infarction or undergoing coronary angiography for the evaluation of CHD at Department of Cardiology in Ruijin Hospital affiliated to Jiao-Tong University School of Medicine. Of these 1,382 study participants, 354 were excluded because oral glucose tolerance test (OGTT) was not measured ($n = 96$), or because of other missing clinical information ($n = 258$). Thus, this study analysis included only 1,028 subjects.

Among all the subjects, 920 patients were recommended to accept coronary angiography for the diagnosis of CHD, the other 108 subjects were diagnosed with an acute myocardial infarction without coronary angiography. All the subjects underwent an OGTT, and they were all Chinese living in the Shanghai region, and gave informed consent. The Institutional Review Board of the Ruijin Hospital approved the study protocol.

Oral glucose tolerance test

OGTT was performed in all subjects after an overnight fasting of 12 h. Blood samples were collected before and at 2 h after a standard oral glucose load of 75 g for the measurement of fasting plasma glucose (FPG), fasting serum insulin (FINS), hemoglobin A1c (HbA1c), triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein A (Apo A), apolipoprotein B (Apo B), lipoprotein(a) [Lp(a)], 2-h plasma glucose (2hPG), and 2-h serum insulin (2hINS). The blood samples were frozen at −80°C until assayed.

The homeostasis model assessment index HOMA-IR and HOMA-IS was used to access insulin resistance and insulin sensitivity, respectively. They were calculated using the following formula: HOMA-IR = [FINS (μIU/mL) × FPG (mmol/L)]/22.5; HOMA-IS = [20 × FINS (μIU/mL)]/[FPG (mmol/L) − 3.5] [18].

Coronary angiography and diagnostic criteria for CHD

Selective coronary angiography was performed using multiple projections with the Judkins technique. The severity of coronary atherosclerosis was estimated by the Gensini score which is based on the number of stenotic coronary artery segments, the degree of their lumen stenosis. The extent and severity of CHD were assessed by assigning points to each lesion as follows: (1) <50% stenosis of the luminal diameter, (2) 50–74% stenosis; (3) 75–99%, and (4) total obstruction. In addition, the severity of CHD was also classified as one-, two-, or three-vessel disease according to the number of stenotic coronary artery in the three major vessels. Significant CHD by coronary angiography was defined as more than 50% stenosis in at least one coronary artery segment. Acute myocardial infarction was diagnosed by a representative set of electrocardiogram, cardiac enzyme values, and typical symptoms.

Definitions of metabolic syndrome

In this analysis, we used the updated 2005 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria to define MetS [19]. In detail, the

definition of MetS requires the presence of any three or more of the following five criteria: (1) high blood pressure: blood pressure ≥ 130/85 mmHg or known treatment for hypertension; (2) hypertriglyceridemia; fasting plasma triglycerides ≥ 1.7 mmol/l; (3) low HDL: fasting HDL cholesterol <1.0 mmol/l in men, <1.3 mmol/l in women; (4) hyperglycemia: fasting glucose level of ≥6.1 mmol/l or known treatment for diabetes; (5) central obesity: waist circumference >90 cm in men, >80 cm in women. Furthermore, in this study, we also used body mass index (BMI) ≥ 25 kg/m^2 as the cut-off point of obesity according to the criteria of Asia-Oceania [20].

Clinical and biochemical measurements

Patients' visits were studied between 0700 and 0800 in the morning, after an overnight fasting of 10–12 h. Date of birth, smoking, alcohol consumption, and past medical history were assessed. Height and weight (light clothes and without shoes), waist and hip circumference, and seated blood pressure (measured on the patient's nondominant arm supported at heart level) were determined by a senior physician. Biochemical measurements of serum lipids and insulin were performed in a central laboratory (Shanghai Institute of Endocrinology and Metabolism, Shanghai, China). All patients were required to refrain from alcohol, cigarettes, and heavy physical exercise for at least 1 week before obtaining blood samples for biochemical measurement and performing the 75-g OGTT. Glucose was measured immediately using an enzymatic method (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA). Serum insulin was measured using a double antibody radioimmunoassay (DSL, Webster, TX, USA). Serum total cholesterol and triglycerides were measured by enzymatic methods (Beckman coulter Inc., Fullerton, CA, USA). HDL-c and LDL-c were determined by immunoinhibition methods (HDL-c, LDL-c Direct, Wake Pure Chemical Industries Ltd. GmbH, Neuss, Germany).

Statistical analysis

Statistical analysis was performed using the SPSS 11.0 system for windows (SPSS Inc., Chicago, IL, USA), and data are presented as mean ± SD (in Fig. 1 as mean ± SEM) if not denoted otherwise. Logistic regression was used to calculate ORs and their 95% confidence interval (CI). Logarithmic transformation was used for HOMA-IR, number of disease vessel, and Gensini score because of the high degree of skewing. Differences in studied variables were tested for statistical significance with the χ^2-test for categorical variables, with the analysis of variance (ANOVA) for normally distributed continuous variables, and with the Mann–Whitney *U*-tests for non-normally distributed continuous variables. P values < 0.05 were considered statistically significant.

Acknowledgments This study is supported by the Grant from 973 Project (No. 2006 CB 503904), National Natural Science Foundation of China (Nos. 30570880 and 30725037), and 863 Project (No. 2006AA02A409).

References

1. G.M. Reaven, Diabetes **37**, 1595–1607 (1988)
2. Y. He, B. Jiang, J. Wang, K. Feng, Q. Chang, L. Fan, X. Li, F.B. Hu, J. Am. Coll. Cardiol. **47**, 1588–1594 (2006)
3. C.A. Cull, C.C. Jensen, R. Retnakaran, R.R. Holman, Circulation **116**, 2119–2126 (2006)
4. J.M. Dekker, C. Girman, T. Rhodes, G. Nijpels, C.D. Stehouwer, L.M. Bouter, R.J. Heine, Circulation **112**, 666–673 (2005)
5. A.S. Gami, B.J. Witt, D.E. Howard, P.J. Erwin, L.A. Gami, V.K. Somers, V.M. Montori, J. Am. Coll. Cardiol. **49**, 403–414 (2007)
6. J. Sundström, U. Risérus, L. Byberg, B. Zethelius, H. Lithell, L. Lind, BMJ **332**, 878–882 (2006)
7. J.B. Meigs, M.K. Rutter, L.M. Sullivan, C.S. Fox, R.B. D'Agostino, P.W.F. Wilson, Diabetes Care **30**, 1219–1225 (2007)
8. N. Sattar, A. McConnachie, A.G. Shaper, G.J. Blauw, B.M. Buckley, A.J. de Craen, I. Ford, N.G. Forouhi, D.J. Freeman, J.W. Jukema, L. Lennon, P.W. Macfarlane, M.B. Murphy, C.J. Packard, D.J. Stott, R.G. Westendorp, P.H. Whincup, J. Shepherd, S.G. Wannamethee, Lancet **371**, 1927–1935 (2008)
9. D.A. Lawlor, G.D. Smith, S. Ebrahim, Diabetologia **49**, 41–48 (2006)
10. J. Wang, S. Ruotsalainen, L. Moilanen, P. Lepisto, M. Laakso, J. Kuusisto, Eur. Heart J. **28**, 857–864 (2007)
11. R. Kahn, J. Buse, E. Ferrannini, M. Stern, Diabetes Care **28**, 2289–2304 (2005)
12. E. Ferrannini, J. Clin. Endocrinol. Metab. **92**, 396–398 (2007)
13. E.A. Gale, Diabetologia **48**, 1679–1683 (2005)
14. I. Ringqvist, L.D. Fisher, M. Mock, K.B. Davis, H. Wedel, B.R. Chaitman, E. Passamani Jr., R.O. Russell, E.L. Alderman, N.T. Kouchoukas, G.C. Kaiser, T.J. Ryan, T. Killip, D. Fray, J. Clin. Invest. **71**, 1854–1866 (1983)
15. D. Zhao, S.M. Grundy, W. Wang, J. Liu, Z. Zeng, W. Wang, Z. Wu, Am. J. Cardiol. **100**, 835–839 (2007)
16. M.P. Stern, K. Williams, C. Gonzalez-Villalpando, K.J. Hunt, S.M. Haffner, Diabetes Care **27**, 2676–2681 (2004)
17. G. Bruno, F. Merletti, A. Biggeri, G. Bargero, S. Ferrero, C. Runzo, S. Prina, Cerai, G. Pagano, P. Cavallo-Perin, Diabetes Care **27**, 2689–2694 (2004)
18. S.M. Haffner, E. Kennedy, C. Gonzalez, M.P. Stern, H. Miettinen, Diabetes Care **19**, 1138–1141 (1996)
19. S.M. Grundy, J.I. Cleeman, S.R. Daniels, K.A. Donato, R.H. Eckel, B.A. Franklin, D.J. Gordon, R.M. Krauss, P.J. Savage, S.C. Smith Jr., J.A. Spertus, F. Costa, Circulation **112**, 2735–2752 (2005)
20. M. Kanazawa, N. Yoshiike, T. Osaka, Y. Numba, P. Zimmet, S. Inoue, Asia Pac. J. Clin. Nutr. **8**, S732–S737 (2002)