Do Different Dimensions of the Metabolic Syndrome Change Together Over Time?

Evidence supporting obesity as the central feature

PATRICK MAISON, MB[1,2]
CHRISTOPHER D. BYRNE, MB, PHD[3]
C. NICHOLAS HALES, MD, PHD[3]
NICHOLAS E. DAY, PHD[2]
NICHOLAS J. WAREHAM, MB, PHD[2]

OBJECTIVE — The metabolic syndrome is a loosely defined cluster of cardiovascular risk factors including low HDL cholesterol, hypertriglyceridemia, glucose intolerance, and hypertension. Evidence for inclusion of these features in the syndrome has mostly come from cross-sectional studies, and a few studies have examined how the various factors change together over time.

RESEARCH DESIGN AND METHODS — We conducted a prospective population-based cohort study of 937 individuals aged 40–65 years who underwent oral glucose tolerance testing on two occasions at 4.5-year intervals. Changes in the components of the metabolic syndrome were analyzed by principal component analysis in the entire population and in a subgroup of 471 individuals who did not receive pharmaceutical therapy for hypertension and dyslipidemia.

RESULTS — Principal component analysis identified three independent factors in men: a blood pressure factor (systolic and diastolic blood pressure and BMI), a glucose factor (fasting and 120-min postload glucose, BMI, waist-to-hip ratio [WHR], and fasting insulin level), and a lipid factor (triglycerides and HDL cholesterol, BMI, WHR, and fasting insulin level). In women, an additional factor was identified, which included BMI, WHR, fasting insulin, and triglycerides. Analysis of the contribution of these variables to the different subdimensions indicated that BMI was the central feature of the syndrome in both sexes.

CONCLUSIONS — This analysis of change in the features of the metabolic syndrome over time provides evidence of the fundamental importance of obesity in the origin of this disorder.

Diabetes Care 24:1758–1763, 2001

The metabolic syndrome, otherwise known as syndrome X or the insulin resistance syndrome, is a loosely defined clustering of cardiovascular risk factors, including low HDL cholesterol, hypertriglyceridemia, glucose intolerance, and hypertension. Because it predicts both diabetes and cardiovascular diseases (1,2), this syndrome is particularly important because it may provide a common pathway linking these two disorders. The variety of alternative names for the condition indicates the uncertainty about the definition of the syndrome and the importance that may be attributed to distinct features such as insulin resistance. Establishing definitions for the syndrome and its component features is an important step in the process of understanding its etiology and pathogenesis.

From the [1]Department of Clinical Pharmacology, Henri Mondor's Hospital, Créteil, France; and the Departments of [2]Public Health and Primary Care and [3]Clinical Biochemistry, University of Cambridge, Cambridge, U.K.

Address correspondence and reprint requests to Dr. N. J. Wareham, Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Robinson Way, Cambridge CB2 2SR, U.K. E-mail: njw1004@medschl.cam.ac.uk.

Received for publication 15 December 2000 and accepted in revised form 7 June 2001.

Abbreviations: PCA, principal component analysis; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Previous studies have indicated that the main features of the syndrome cluster together more frequently than would be expected by chance alone (2), suggesting the existence of a common underlying mechanism, such as insulin resistance (1–3). However, it is possible that the syndrome could center on other abnormalities such as overall or central obesity (4,5).

The lack of an accepted and experimentally justified definition makes epidemiological study of this disorder difficult. Attempts at defining it are often implicitly limited by assumptions about its etiology and run the risk of becoming tautological. An alternative approach may be to derive a definition directly from the data without prior hypotheses about how the various factors are linked or which of the factors is central or dominant. Factor analysis provides one possible means of allowing the clustering of variables within a population to be described without prior assumptions about their inter-relationship. This technique has been used previously in cross-sectional studies to identify underlying features of the metabolic syndrome (3,6,7). However, this method has not been used with longitudinal data to investigate how the features of the syndrome change together over time. This may provide stronger information about causal pathways than cross-sectional analysis. The aim of this study was to describe the inter-relationship of the features of the metabolic syndrome over time using longitudinal factor analysis.

RESEARCH DESIGN AND METHODS

— The Ely study is a prospective population-based cohort established in 1990, which has previously been described in detail (8). Subjects for the study were recruited from a general practice register in Ely Cambridgeshire. A letter of invitation was sent to a random selection of 1,571 patients not previously known to have diabetes, between the ages of 40 and 65 years at recruitment, and 1,122 were screened. A total of 1,071 sub-

Table 1—*Characteristics of subjects grouped by sex at baseline and for change between follow-up and baseline*

	Men		Women	
	Baseline	Change	Baseline	Change
Ely study population:				
n	393		543	
Age (years)	54.4 (0.40)	4.45 (0.02)§	53.4 (0.32)	4.45 (0.02)§
BMI (kg/m^2)	26.0 (0.15)¶	0.83 (0.07)§	25.5 (0.20)	1.02 (0.08)§
WHR	0.91 (0.003)¶	0.06 (0.003)§	0.76 (0.002)	0.04 (0.02)§
Diastolic blood pressure (mmHg)	80.9 (0.55)¶	−1.06 (0.49)†	77.0 (0.45)	−1.86 (0.40)§
Systolic blood pressure (mmHg)	131.6 (0.83)¶	−0.74 (0.74)	127.5 (0.8)	−1.81 (0.65)‡
Fasting plasma glucose (mmol/l)	5.88 (0.03)¶	−0.72 (0.04)§	5.62 (0.02)	−0.73 (0.03)§
Plasma glucose 120 min (mmol/l)	6.30 (0.08)	−0.02 (0.11)†	6.31 (0.07)	−0.40 (0.07)§
Fasting insulin (pmol/l)*	40.3 (38.1–42.6)	5.56 (1.99)‡	39.1 (37.3–41.0)	2.56 (1.23)†
Triglycerides (mmol/l)*	1.36 (1.30–1.46)¶	−0.09 (0.02)§	1.11 (1.07–1.16)	−0.25 (0.04)§
HDL cholesterol (mmol/l)	1.29 (0.02)¶	0.03 (0.01)†	1.60 (0.02)	0.02 (0.01)
Individuals not being treated with antihypertensive or lipid-lowering drug:				
n	194		277	
Age (years)	53.7 (0.58)	4.54 (0.04)§	52.7 (0.46)	4.53 (0.02)§
BMI (kg/m^2)	25.7 (0.21)‖	0.66 (0.11)§	24.9 (0.25)	1.14 (0.11)§
WHR	0.90 (0.004)¶	0.05 (0.004)§	0.76 (0.003)	0.04 (0.003)§
Diastolic blood pressure (mmHg)	80.2 (0.69)¶	−0.04 (0.65)	75.3 (0.58)	−0.93 (0.48)
Systolic blood pressure (mmHg)	129.0 (1.0)¶	2.05 (0.94)†	123.1 (0.9)	1.38 (0.76)
Fasting plasma glucose (mmol/l)	5.80 (0.04)¶	−0.74 (0.07)§	5.51 (0.03)	−0.73 (0.03)§
Plasma glucose 120 min (mmol/l)	6.13 (0.09)	−0.37 (0.15)†	6.13 (0.07)	−0.47 (0.11)§
Fasting insulin (pmol/l)*	38.5 (36.0–41.0)	5.40 (2.30)†	35.9 (33.6–38.3)	3.60 (1.70)†
Triglycerides (mmol/l)*	1.31 (1.23–1.41)§	−0.21 (0.06)§	1.08 (1.02–1.14)	−0.11 (0.03)†
HDL cholesterol (mmol/l)	1.29 (0.03)¶	0.03 (0.02)	1.58 (0.02)	0.01 (0.02)

Data are arithmetic mean (SEM) and *geometric mean (95% CI). †$P < 0.05$, ‡$P < 0.01$, §$P < 0.001$ (difference vs. 0); ‖$P < 0.01$, ¶$P < 0.001$ (women versus men).

jects who participated in the first phase of the study (1990–1992) were found to have either normal or impaired glucose tolerance in a 75-g oral glucose tolerance test. Between 1994 and 1996, a 4.5-year follow-up study was undertaken and all previous participants were invited to reattend for a repeat oral glucose tolerance test. A total of 937 (87%) individuals were restudied (9). Those who were not restudied on follow-up included individuals who refused to participate, had moved outside the U.K., or had died. Ethical permission for the study was received from the Cambridge Local Research Ethics Committee, and all participants provided written informed consent.

At both baseline and follow-up, individuals underwent a clinical examination, which included medical questionnaires and anthropometric measurements. BMI was calculated as weight in kilograms divided by height (in meters) squared. Waist circumference was measured at the midpoint between the inferior border of the coastal margin and the anterior superior iliac crest and hip circumference at the level of the greater trochanter. Diastolic and systolic blood pressure was recorded at rest, with the subject sitting, using an Accutorr automatic sphygmomanometer (Datascope, Cambridge, U.K.). The mean of three readings taken in the right arm (1 min apart) were analyzed in this study. In a health and lifestyle questionnaire, participants self-reported use of medicines.

The oral glucose tolerance test consisted of a 75-g oral glucose challenge with collection of venous blood samples at time 0 and 120 min. Plasma samples were immediately separated, kept on ice, and stored at −70°C within 4 h. Serum samples were separated after 30 min at room temperature and then stored at −70°C. Plasma glucose was measured by a hexokinase method (10), and triglyceride level was measured using the RA 1000 (Bayer Diagnostics, Basingstoke, U.K.), with a standard enzymatic method. Plasma insulin was determined by two-site immunometric assays with either ^{125}I or alkaline phosphatase labels (11,12). Fasting insulin was used in the analysis as a marker of insulin resistance (13).

Statistical methods

Arithmetic means and SEM are presented where the underlying variable was normally distributed. Triglycerides and insulin were normalized by logarithmic transformation and are presented as geometric mean and 95% CI. Unpaired Student's *t* tests were used to compare means between sexes, and paired Student's *t* tests were used to analyze the change between baseline and follow-up. The variables included in the principal component analysis (PCA) were the differences between baseline and follow-up results for the possible components of the syndrome. The relationship between individual pairs of variables was examined using Pearson correlation coefficients, separately for men and women. Bartlett's test of sphericity was used to test the hypothesis that the correlation matrix was an identity matrix in which all diagonal terms are 1 and all off-diagonal terms are 0. If a matrix is close to identity, this can indicate that the

Table 2—*Matrix of Pearson's correlation coefficients among changes in metabolic cardiovascular syndrome components stratified by sex*

Changes	BMI	WHR	Diastolic blood pressure	Systolic blood pressure	Fasting insulin	Fasting glucose	Glucose 120 min	HDL cholesterol	Triglycerides
Ely study population:									
BMI		**0.34†**	**0.17†**	**0.11†**	**0.28†**	**0.18†**	**0.24†**	**−0.28†**	**0.22†**
WHR	0.21†		**0.11†**	**0.07**	**0.10**	**0.04**	**0.08**	**−0.11***	**0.02**
Diastolic blood pressure	0.18†	0.11*		**0.79†**	**0.04**	**0.01**	**0.07**	**−0.07**	**0.12***
Systolic blood pressure	0.19†	0.08	0.78†		**0.04**	**−0.02**	**−0.04**	**−0.10**	**0.10**
Fasting insulin	0.23†	0.13†	0.08	0.07		**0.24†**	**0.13***	**−0.10***	**0.15†**
Fasting glucose	0.21†	0.01	0.07	0.05	0.12†		**0.56†**	**0.08**	**0.25†**
Glucose 120 min	0.21†	−0.02	0.01	−0.02	0.09†	0.33†		**−0.11***	**0.26†**
HDL cholesterol	−0.09†	−0.01	−0.03	−0.05	−0.06	0.01	−0.09*		**−0.26†**
Triglycerides	0.25†	0.05	0.05	0.06	0.16*	0.14†	0.19†	−0.09*	
Individuals not being treated with antihypertensive or lipid-lowering drugs:									
BMI		**0.37‡**	**0.32‡**	**0.22‡**	**0.27‡**	**0.21†**	**0.28‡**	**−0.32‡**	**0.30‡**
WHR	0.25†		**0.18‡**	**0.11**	**0.17***	**0.22‡**	**0.11**	**−0.15***	**0.14***
Diastolic blood pressure	0.15†	0.06		**0.79‡**	**0.15***	**0.07**	**0.09**	**−0.10**	**0.10**
Systolic blood pressure	0.16†	0.00	0.75†		**0.05**	**0.00**	**−0.06**	**−0.07**	**0.10**
Fasting insulin	0.19†	0.12*	0.05	0.06		**0.26‡**	**0.11**	**−0.07**	**0.18†**
Fasting glucose	0.21†	0.03	0.08	−0.03	0.10*		**0.42†**	**−0.00**	**0.02**
Glucose 120 min	0.22‡	0.11*	0.07	0.01	0.16†	0.27‡		**−0.13***	**0.11**
HDL cholesterol	−0.07	−0.03	−0.10*	−0.14*	−0.11*	0.04	−0.14*		**−0.19†**
Triglycerides	0.29‡	0.09	0.06	0.09	0.07	0.10*	0.16†	−0.11*	

Data are Pearson's correlation coefficients. Coefficients for men are in bold; those for women are not in bold. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

correlation between variables is too small to undertake factor analysis.

Factor extraction was performed using PCA to transform the correlated variables to a set of uncorrelated variables or factors by finding the linear combination to explain the maximum variance (14). PCA does not place an a priori restriction on the number of factors. Each factor was characterized by its loading or correlation with the original variables, which, in this case, was the change over time of the components of the syndrome. Only factors with a variance or eigenvalue >1 were retained, because a factor with a variance <1 is no better than the individual variable. Orthogonal rotation using the varimax method was used to identify a unique set of closely related original variables for each factor. Factor loadings ≥0.25 were retained and may be interpreted as the contribution of that variable to the specific factor. All analyses were conducted using SPSS for Windows software (SPSS, Chicago, IL).

RESULTS — A total of 89% of the nondiabetic women initially recruited (543 of 608) and 85% of the nondiabetic men (394 of 463) underwent follow-up testing (9). Of the individuals presenting both at baseline and at follow-up, 266 women and 200 men were either being treated with an antihypertensive and/or a lipid-lowering drug at some stage during the study, and the analyses were repeated with these subjects excluded. The baseline characteristics and change over the 4.5 years of follow-up are shown in Table 1. All of the change variables were normally distributed, even when single measures of the variable were non-normal. At baseline, BMI, WHR, blood pressure, and fasting plasma glucose, fasting insulin, triglyceride, and HDL cholesterol levels were higher in men (Table 1). In the whole population, the mean glucose, triglycerides, and blood pressure improved over the 4.5 years of follow-up, despite the cohort becoming older and, on average, more overweight. In the untreated subgroup, blood pressure increased on average.

Analysis of the correlation between changes in the metabolic parameters and change in BMI and WHR (Table 2) shows that increasing obesity was associated with increases in blood pressure, fasting insulin, glucose, and triglycerides and was negatively correlated with change in HDL cholesterol. Most of the changes in the components of the metabolic syndrome were correlated with each other, although minor differences existed between men and women. In general, the same pattern of associated change was observed in the whole cohort as in the untreated subgroup.

In the men and women, Bartlett's test of sphericity was significant ($\chi^2 = 387.8$, $P < 0.001$ and $\chi^2 = 541.6$, $P < 0.001$, respectively) in the whole population and in the untreated sub-group ($\chi^2 = 335.8$, $P < 0.001$ and $\chi^2 = 329.7$, $P < 0.001$, respectively). A large χ^2 value is a prerequisite for conducting PCA. Before rotation, the results of PCA indicated the presence of three independent factors in men and four in women. We performed rotation (Table 3), and in untreated men, three independent factors explained 58.3% of the total variance. In untreated women, four factors explained 63.4% of the variance. In the untreated men, the first factor was characterized by positive correlation coefficients (loadings) with both systolic and diastolic blood pressure, the second could be characterized as being related to glucose metabolism, and the third was related to lipid metabolism.

Table 3—*Results of factors analysis: factor loading for change in metabolic cardiovascular syndrome components after rotation of PCA*

	Men			Women			
Changes	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3	Factor 4
Ely study population:							
Systolic blood pressure	**0.93**	−0.06	−0.02	**0.94**	0.01	−0.04	0.05
Diastolic blood pressure	**0.93**	0.04	−0.07	**0.93**	0.04	0.08	−0.01
Fasting glucose	−0.06	**0.84**	−0.07	0.05	**0.72**	0.05	−0.21
Glucose 120 min	−0.03	**0.73**	0.07	−0.06	**0.72**	0.01	0.13
HDL cholesterol	−0.18	0.08	**0.69**	0.01	−0.02	0.04	**0.91**
Triglycerides	0.01	−0.04	**0.73**	0.08	**0.43**	0.15	**0.36**
Fasting insulin	0.03	**0.49**	**0.28**	0.01	0.15	**0.60**	0.14
BMI	0.20	**0.39**	**0.61**	0.20	**0.42**	**0.59**	0.14
WHR	0.17	**0.33**	**0.32**	0.03	−0.18	**0.81**	−0.13
Cumulative total variance (%)	20.6	40.2	57.6	20.0	36.2	51.6	63.5
Individuals not being treated with antihypertensive or lipid-lowering drugs:							
Systolic blood pressure	**0.94**	−0.05	0.05	**0.93**	0.05	−0.04	0.10
Diastolic blood pressure	**0.93**	0.11	0.10	**0.93**	0.06	0.06	0.01
Fasting glucose	0.01	**0.85**	−0.12	0.03	0.04	**0.85**	−0.17
Glucose 120 min	−0.08	**0.72**	0.08	−0.02	0.15	**0.66**	**0.32**
HDL cholesterol	−0.01	−0.02	**0.72**	0.09	−0.03	−0.07	**0.89**
Triglycerides	0.02	0.03	**0.68**	0.05	**0.41**	0.19	**0.30**
Fasting insulin	0.10	**0.46**	**0.25**	−0.01	**0.35**	0.16	**0.35**
BMI	**0.28**	**0.40**	**0.62**	0.17	**0.67**	**0.31**	0.06
WHR	0.17	**0.38**	**0.38**	−0.03	**0.81**	−0.16	−0.09
Cumulative total variance (%)	27.7	45.4	58.3	23.2	40.5	52.2	63.4

Loadings ≥0.25 are in bold type.

Changes in BMI, WHR, and fasting insulin were highly correlated with both the glucose and the lipid factors, and change in BMI alone was correlated with the blood pressure factor. In women, three factors related separately to blood pressure, lipid metabolism, and glucose metabolism, but changes in BMI, WHR, and fasting insulin were present as an additional independent factor. In the untreated women, change in BMI was correlated with change in the glucose factor and with the factor related to change in fasting insulin and triglyceride.

To examine the centrality of features to the various factors, we constructed three-dimensional loading plots separately for the untreated men and women (Fig. 1*A* and *B*). Each axis shows one of these factors, and the relationship to change in the features of the metabolic syndrome is represented by the factor loadings. The plots show that changes in BMI, WHR, and fasting insulin are central to the three independent factors in men, whereas change in BMI was central in women only. A similar observation was seen in the entire cohort (Fig. 1*C*).

CONCLUSIONS— To our knowledge, this is the first report of a PCA of change in the features of the metabolic syndrome over time. The examination of the pattern of change in these related variables provides stronger evidence of the nature of the underlying biological relationships than previous cross-sectional studies, because clustering of variables in a prospective study indicates that they change in a correlated way. Our results suggest that the pattern of change in the components of the syndrome can be reduced to three uncorrelated sets of features in men and four in women. In both sexes, change in overall obesity, as measured by the BMI, is central to all factors. This provides support for the hypothesis that the different dimensions of the syndrome are linked through obesity.

Our longitudinal results are consistent with previous cross-sectional studies, including that by Meigs et al. (15), which identified three identical factors among men. A separate study in older Japanese-American subjects identified four factors in men, but the analysis did not include measurements of postglucose load. The additional factor detected in this study was characterized by positive correlations with body weight, waist circumference, and fasting insulin. Meigs et al. (15) also showed the same three factors in women as in men. However, using the same method to retain factors in the analysis of our longitudinal data, we identified an additional factor among women. A previous factor analysis in a sample of 277 women also found four similar factors (6). An analysis conducted with our data only in women older than 50 years identified the same four factors, suggesting that menopausal status was not responsible for the difference between men and women.

The results in our study are similar, whether we considered the entire cohort or the subgroup of individuals who were not treated with antihypertensive medication or drugs for dyslipidemia. Because of the possibility that such drugs could alter the inter-relationships between change in the various features of the syndrome, we would tend to put more weight on the findings in the untreated subgroup. It is interesting to note that even in this group, there was an apparent overall improve-

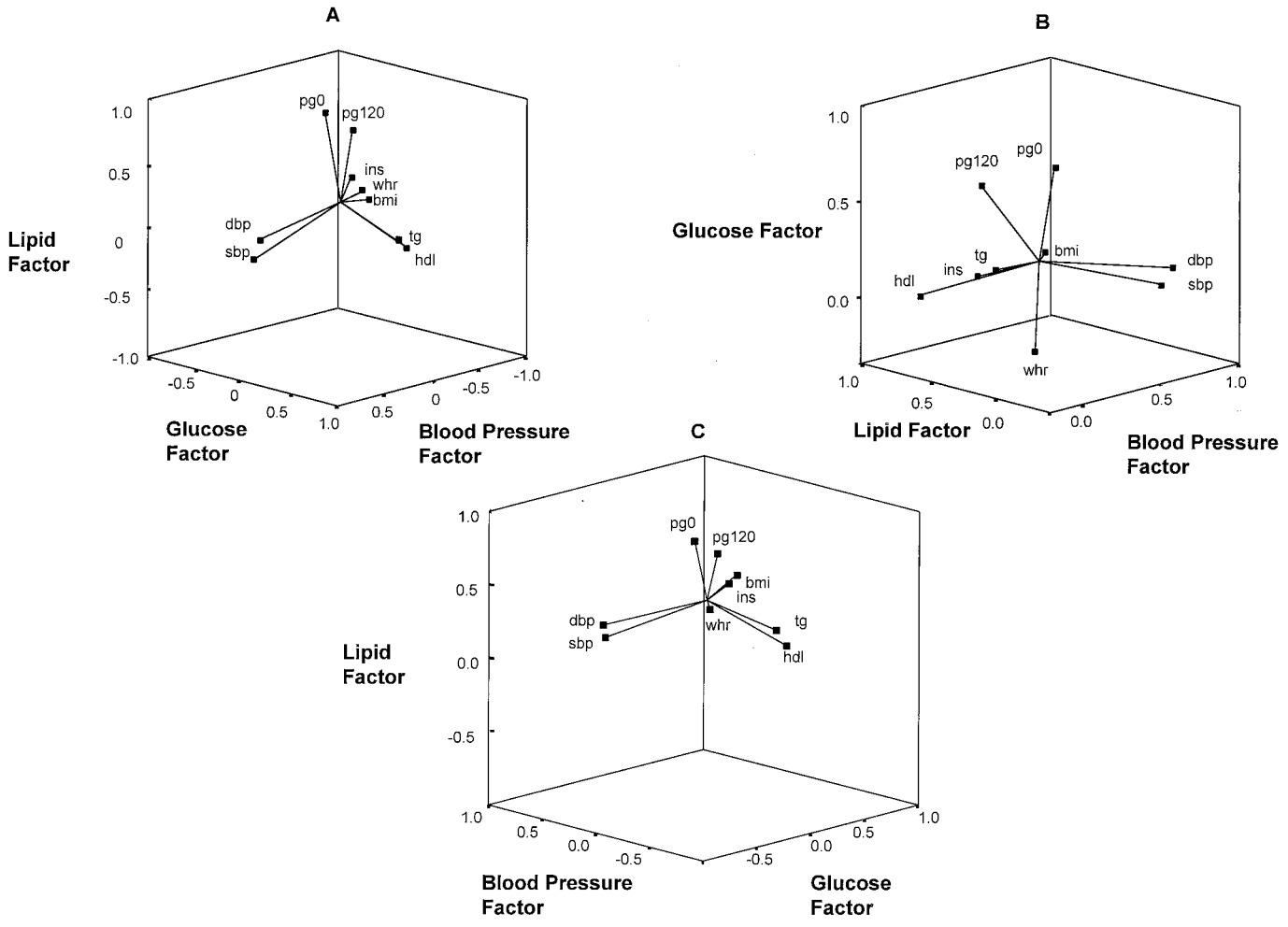

Figure 1—*Factor-loading plots in three-dimensional factor space in men without antihypertensive or lipid-lowering drugs* (A)*, in women without antihypertensive or lipid-lowering drugs* (B)*, and in both sexes in the whole population* (C)*. sbp, systolic blood pressure; dbp, diastolic blood pressure; pg, plasma glucose, tg, triglycerides; hdl, HDL cholesterol; whr, waist-to-hip ratio; ins, fasting insulin. The sign of the HDL variable was changed in the factor analysis from positive to negative.*

ment in fasting and 2-h glucose and triglyceride over the 4.5 years of follow-up despite an increase in mean BMI. Because the same laboratory measured these biochemical parameters throughout the study and had consistent quality control results, it is more likely that such changes represent either an alteration in health behavior as a consequence of observation (a Hawthorne effect) or a secular change in the determinants of glucose and lipid levels at the population level. However, the important observation from the perspective of this particular analysis is not the absolute change, but rather the pattern of the correlated change in the different dimensions of the syndrome, which clearly indicates the importance of obesity.

Previous cross-sectional factor analysis studies have also suggested the centrality of obesity, as measured by the BMI, within the syndrome (3,6,7). Our longitudinal data show that change in BMI is central to the correlated change in the other features of the metabolic syndrome. Although our data also show that change in insulin levels and WHR are common to change in the other parameters, the strength of association is weaker than for BMI. Previously, Reaven (1) postulated that insulin resistance was the underlying defect of the syndrome, and in prospective studies, it has been shown that an increase in fasting insulin concentrations predicts the clustering of metabolic disorders (2). However, Liese et al. (5) showed in a cohort study that overall and central obesity and hyperinsulinemia were independently predictive of the metabolic syndrome and that there was evidence of a synergistic effect between them. Our data confirm the importance of obesity as the central component of the syndrome, an hypothesis supported by the effect of weight loss on insulin sensitivity (16).

Because the metabolic syndrome is a combination of several features, which are themselves continuous variables, a dichotomous definition is probably not appropriate. Analysis of the syndrome using continuous variables, which is a feature of PCA, is probably more appropriate, because this method avoids choosing cutoff points for each component, which are still debated, especially for fasting insulin (17). Choosing arbitrary cutoffs and reducing the syndrome to a binary state can also ignore some of the more subtle metabolic abnormalities (18). In most previous studies, the syndrome has been

defined with a minimum number (two or three) of features, with each weighted equally based on a dichotomous definition (2,5). However, the inclusion in some definitions (19) of a mixture of possible underlying factors (insulin resistance and obesity), along with those that may be secondarily related (hypertension or dyslipidemia), may prove to be a barrier to understanding pathophysiology.

Our analysis suggests that the metabolic syndrome could be characterized by three primary components: obesity (BMI), central obesity (WHR), and hyperinsulinemia (fasting insulin), which may be essential for the development of the syndrome; and three secondary components: hypertension, dyslipidemia (high triglycerides and low HDL cholesterol), and glucose intolerance (PG0 and PG120), which may be related to the central features. Such a proposal would need verification in other populations.

Acknowledgments— This study was supported by grants from the British Diabetic Association, the Medical Research Council, and the Anglia and Oxford National Health Service Research and Development Directorate. P.M. is a visiting Research Fellow supported by the Association Française pour la Recherche Thérapeutique. N.J.W. is a Medical Research Council Clinician Scientist.

We thank R. Beck, B. Mission, M. Sheldon, and A.F.M. Tullock for technical assistance; D. Brown, P. Clark, B. Cox, S. Curran, S. Hennings, J.M. Lipscombe, J. Mitchell, M. Quinn, S. Farmer, L. Koncewicz, H. Shanassy, and T. Wang for assistance with the field work and data entry; the volunteers who participated in the study; and Dr. J. Shackleton and his colleagues at St Mary's Surgery, Ely.

References

1. Reaven GM: The role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
2. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP: Prospective analysis of insulin-resistance syndrome (syndrome X). *Diabetes* 41:715–722, 1992
3. Ferrannini E, Haffner SM, Mitchell BD, Stern MP: Hyperinsulinemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 34:416–422, 1991
4. Bjorntorp P: Abdominal obesity and the metabolic syndrome. *Ann Med* 24:465–468, 1992
5. Liese AD, Mayer-Davis EJ, Tyroler HA, Davis CE, Keil U, Duncan BB, Heiss G: Development of the multiple metabolic syndrome in the ARIC Cohort: joint contribution of insulin, BMI, and WHR. *Ann Epidemiol* 7:407–416, 1997
6. Edwards KL, Austin MA, Newman B, Mayer E, Krauss RM, Selby JV: Multivariate analysis of the insulin resistance syndrome in women. *Arterioscler Thromb* 14: 1940–1945, 1994
7. Edwards KL, Burchfiel CM, Sharp DS, Curb JD, Rodriguez, Fujimoto WY, Lacroix AZ, Vitiello MV, Austin MA: Factors of the insulin resistance syndrome in non-diabetic and diabetic elderly Japanese-American men. *Am J Epidemiol* 147:441–447, 1998
8. Williams DRR, Wareham NJ, Brown DC, Byrne CD, Clarck PMS, Cox BD, Cox LJ, Day NE, Palmer CR, Shackleton JR, Wang TWM: Undiagnosed glucose intolerance in the community: the Isle of Ely Diabetes Project. *Diabet Med* 12:30–35, 1995
9. Wareham NJ, Byrne CD, Williams DRR, Day NE, Hales CN: Fasting proinsulin concentrations predict the development of type 2 diabetes. *Diabetes Care* 22:262–270, 1999
10. Kunst A, Draeger B, Ziegenhorn J: UV-methods with hexokinase and glucose-6-phosphate dehydrogenase. In *Methods of Enzymatic Analysis*. Vol. VI. Bergmeyer HU, Ed. Deerfield, Weinheim Verlag Chemie 1983, p. 163–172
11. Sobey WJ, Beer SF, Carrington CA, Clark PM, Frank BH, Gray IP, Luzio SD, Owens DR, Schnieder AE, Siddle K: Sensitive and specific two site immunoradiometric assays for human insulin, proinsulin, 65–66 split and 32–33 split proinsulins. *Biochem J* 260:535–541, 1989
12. Alpha B, Cox L, Crowther N, Clark PMS, Hales CN: Sensitive amplified immunoenzymometric assays (IEMA) for human insulin and intact proinsulin. *Eur J Clin Chem Biochem* 30:27–32, 1992
13. Laasko M: How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 137:959–965, 1993
14. Cattell RB: Factor analysis: an introduction to essentials. *Biometrics* 21:190–215, 1965
15. Meigs JB, D'Agostino RB, Wilson PWF, Adrienne Cupples L, Nathan DM, Singer DE: Risk variable clustering in the insulin resistance syndrome: the Framingham offspring study. *Diabetes* 46:1594–1600, 1997
16. Muscelli E, Camastra S, Catalano C, Galvan AQ, Ciociaro D, Baldi S, Ferrannini E: Metabolic and cardiovascular assessment in moderate obesity: effect of weight loss. *J Clin Endocrinol Metab* 82:2937–2943, 1997
17. Taskinen MR: Strategies for the diagnosis of metabolic syndrome. *Curr Opin Lipidol* 4:434–443, 1993
18. Balkau B, Charles MA, European Group for the Study of Insulin Resistance (EGIR): Comment on provisional report from the WHO consultation. *Diabet Med* 16:442–443, 1999
19. Alberti KGMM, Zimmet PZ, for the WHO Consultation: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: definition, diagnosis and classification of diabetes mellitus: provisional report of the WHO consultation. *Diabet Med* 15:539–553, 1998