Metabolic Syndrome and the Progression of Carotid Intima-Media Thickness in Elderly Women

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Background: Although the metabolic syndrome can predict cardiovascular events in middle-aged individuals, data on its association with the progression of subclinical atherosclerosis, particularly in elderly women, are limited. We investigated the association of the metabolic syndrome with the progression of carotid intima-media thickness (IMT) in elderly women.

Methods: We performed a 12-year follow-up study in a population-based sample of 101 women (age range at baseline, 60-70 years). All study variables were measured at baseline and 12 years later. We used the National Cholesterol Education Program definition for metabolic syndrome (≥3 of 5 risk factors) and quantified carotid IMT noninvasively by ultrasonography.

Results: The prevalence of metabolic syndrome increased from 13% at baseline to 46% after 12 years of follow-up (P<.001). The mean±SD IMT increased by 21% (from 1.05±0.31 mm to 1.27±0.38 mm) during 12 years (P<.001). Among the individuals without metabolic syndrome at baseline, the increase in carotid IMT was greater in 34 women who developed metabolic syndrome during 12 years (0.31±0.37 mm) than in 54 women who did not (0.16±0.25 mm) after adjustment for age, prevalent cardiovascular diseases, physical activity, smoking, alcohol intake, serum low-density lipoprotein cholesterol level, use of cholesterol-lowering medication, carotid IMT, and National Cholesterol Education Program metabolic risk score at baseline (P=.04 for difference).

Conclusion: Incident metabolic syndrome is associated with accelerated progression of carotid IMT in elderly women.

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erosclerosis in elderly women at a high risk of CVD. We therefore investigated the association of incident metabolic syndrome with changes in carotid IMT during 12 years of follow-up in a population-based sample of elderly women.

**METHODS**

**STUDY POPULATION**

The subjects of the present study were derived from a population-based, randomly selected sample of 299 women 50 to 60 years of age who were examined as a part of the large risk factor survey in Finland in 1982. The women were invited for reexaminations in 1991, and altogether, 202 women 60 to 70 years of age completed the examinations between October 1991 and March 1992. Because 32 women had died or could not be contacted, 170 women 70 to 80 years of age were eligible for the follow-up study in 2003. Of 170 women who were invited to participate in the follow-up study, 57 did not participate. The reasons for not participating included musculoskeletal problems (n=11), dementia (n=2), stroke (n=1), cancer (n=1), death (n=4), other health problems (n=18), unwillingness (n=16), and unknown (n=4). The nonparticipants were older (65.4 years vs 63.9 years, P=.004) and less educated (7.2 years vs 8.5 years, P=.02) and had higher body mass index (BMI) (29.3 kg/m² vs 27.4 kg/m², P=.008), triglyceride level (1.28 mmol/L [143 mg/dL] vs 1.06 mmol/L [120 mg/dL], P=.04) and diastolic blood pressure reading (92.0 mm Hg vs 88.3 mm Hg, P=.02) and more metabolic risk factors (2.0 vs 1.6, P=.006) at baseline than the participants. Therefore, 113 women completed all study visits in 2003. The same methods were used to assess study variables in 1991-1992 (baseline of present study) and 2003. Because of missing data on carotid IMT in either examination, the final study sample consisted of 101 women with complete data on study variables. The study protocol was approved by the Research Ethics Committee of the University of Kuopio, Kuopio, Finland. All participants gave written informed consent.

**BIOCHEMICAL ANALYSES**

Venous blood samples were obtained after a 12-hour fast. Serum cholesterol and triglyceride levels were measured by enzymatic colorimetric methods. High-density lipoprotein (HDL) cholesterol levels were measured using an enzymatic colorimetric method in a supernatant after precipitation with dextran sulfate and magnesium chloride. Low-density lipoprotein (LDL) cholesterol level was calculated according to the Friedewald formula. The hexokinase method was used for blood glucose analyses.

**OTHER MEASUREMENTS**

Body height, weight, and waist circumference were measured according to the MONICA protocol. The BMI was computed by dividing weight in kilograms by height in meters squared. Blood pressure in the right arm was recorded as the mean of 2 measurements taken 5 minutes apart. The women completed a self-administered questionnaire on diseases diagnosed by a physician (previous year), medications (previous week), cigarette smoking (nonsmoker vs smoker), and alcohol intake (No. of drinks in previous week). Time spent in habitual physical activity was estimated using an interviewed questionnaire (minutes per week). Framingham risk score was calculated by summing up risk factors for age, LDL and HDL cholesterol levels, systolic and diastolic blood pressure readings, prevalent diabetes, and current smoking habits.

**DEFINITION OF THE METABOLIC SYNDROME**

The metabolic syndrome was defined by the National Cholesterol Education Program (NCEP) criteria, summing up the category scores (0, low risk; 1, increased risk) for blood pressure (≥130/85 mm Hg and/or drug treatment), blood glucose (≥110 mg/dL [≥6.1 mmol/L]), HDL cholesterol (<50 mg/dL [<1.29 mmol/L]), triglycerides (≥150 mg/dL [≥1.7 mmol/L]), and waist circumference (>88 cm). The sum of at least 3 risk factors was defined as metabolic syndrome.

**ASSESSMENT OF CAROTID ATHEROSCLEROSIS**

Carotid artery atherosclerosis was assessed noninvasively by ultrasonography as the mean IMT. The methods for carotid ultrasound imaging and reading have been described previously. The measurements were made by certified sonographers in both study years. An ultrasound device with a high-resolution 10-MHz transducer was used, following a standardized and pretested protocol, and the scanings were recorded on super-VHS videotape. Owing to missing data on the left carotid IMT in 1992 (available for 64 women), we used the mean IMT in the right carotid bifurcation for the statistical analyses to obtain more statistical power.

**STATISTICAL ANALYSIS**

Differences in demographic, metabolic, and clinical characteristics, as well as carotid IMT, among women with or without metabolic syndrome at baseline and between women who did or did not develop metabolic syndrome during the 12-year follow-up were analyzed using an independent samples t test or the Mann-Whitney test for continuous variables and the χ² test for categorical variables. To test changes in metabolic and clinical characteristics, as well as carotid IMT between study years, a paired samples t test or the Wilcoxon rank sum test for continuous variables and the McNemar test for categorical variables were used. Blood glucose levels were not normally distributed, and log-transformed values were used in statistical analyses. Because the distribution for alcohol intake was highly skewed, only nonparametric tests were used. Analysis of covariance was used to compare the change in mean carotid IMT in women with or without incident metabolic syndrome as well as in women with no increase or an increase of 1 or at least 2 metabolic risk factors during the follow-up. In multivariate analyses, data were adjusted for age, prevalent CVD (coronary heart disease or cardiac insufficiency), physical activity, smoking, alcohol intake, serum LDL cholesterol level, cholesterol-lowering medication, carotid IMT, and NCEP metabolic risk score at baseline. Linear regression analysis was used to assess the independent association of individual metabolic risk factors at baseline with the change in carotid IMT. A significance level of P=.05 was used for all statistical tests. Values are expressed as mean ± SD. Statistical analyses were performed using a commercially available software package (SPSS for Windows, Release 11.5; SPSS Inc, Chicago, Ill).

**RESULTS**

At baseline, the women had, on average, 1.5 metabolic risk factors, and 13% of them had metabolic syndrome (≥3 risk factors). Women with metabolic syndrome had higher body weight, BMI, waist circumference, and glucose and triglyceride levels as well as lower HDL cholesterol levels than those without metabolic syndrome (Table 1). None of the women had diabetes at base-
line. Women with metabolic syndrome had an 18% greater mean carotid IMT at baseline than those without metabolic syndrome (1.21 mm vs 1.03 mm, \(P = .06\)).

At the end of the 12-year follow-up, the women had on average 2.3 metabolic risk factors (\(P < .001\) for difference for comparison with baseline), and 46% of them had metabolic syndrome (\(P < .001\) for difference for comparison with baseline). While waist circumference increased by 10% (from 82.4 ± 10.1 cm to 91.0 ± 11.5 cm, \(P < .001\)), BMI by 2% (from 27.1 ± 4.1 kg/m² to 27.7 ± 4.7 kg/m², \(P = .002\)), and glucose by 11% (from 85 ± 9 mg/dL [4.7 ± 0.5 mmol/L] to 95 ± 15 mg/dL [5.3 ± 0.8 mmol/L], \(P < .001\)) over the 12-year period, LDL cholesterol decreased by 16% (from 160 ± 43 mg/dL [4.1 ± 0.9 mmol/L] to 135 ± 32 mg/dL [3.5 ± 0.8 mmol/L], \(P < .001\)), HDL cholesterol by 21% (from 62 ± 12 mg/dL [1.6 ± 0.3 mmol/L] to 49 ± 11 mg/dL [1.3 ± 0.3 mmol/L], \(P < .001\)), systolic blood pressure by 8% (from 155.4 ± 21.4 mm Hg to 143.0 ± 20.2 mm Hg, \(P < .001\)), and diastolic blood pressure by 19% (from 88.7 ± 10.1 mm Hg to 72.1 ± 10.1 mm Hg, \(P < .001\)). Simultaneously, the use of drugs for hypercholesterolemia increased from 7% to 36% (\(P < .001\)), and the use of drugs for hypertension increased from 23% to 56% (\(P < .001\)). Although there were no women with diabetes at baseline, 11% (n = 11) of them had diabetes 12 years later. The mean carotid IMT increased by 21% during 12 years (from 1.05 ± 0.31 mm to 1.27 ± 0.38 mm, \(P < .001\)).

There was no difference in the change of carotid IMT during 12 years between the 88 women without the metabolic syndrome at baseline and the 13 women with it (\(+0.21 \text{ vs } +0.20\) mm, \(P = .92\)). After the women with metabolic syndrome at baseline were excluded, 34 women with incident metabolic syndrome had higher waist circumferences, BMIs, triglyceride levels, glucose levels, and blood pressure readings as well as lower HDL cholesterol levels at baseline than 54 women without the metabolic syndrome during 12 years (Table 2). After adjustment for age, prevalent CVD, physical activity, smoking, alcohol intake, LDL cholesterol level, use of drugs for hypercholesterolemia, carotid IMT, and NCEP metabolic risk score at baseline (Figure 1, model 1), the mean increase in the carotid IMT was 2.0 times greater in those who developed the metabolic syndrome than in those who did not. Adjustment for waist circumference reduced the difference in the carotid IMT increase by 23% (model 2) and adjustment for triglyceride levels reduced it by 19% (model 3). The difference did not change and remained statistically significant after adjustment for glucose, HDL cholesterol, and systolic blood pressure (models 4-6). Adjustment for Framingham risk score had no effect on the difference (IMT change 0.16 and 0.31 mm, \(P = .04\)).

In 88 women without metabolic syndrome at baseline, the more metabolic risk factors that occurred during the 12-year period, the greater the increase in the mean carotid IMT (Figure 2, model 1, \(P = .04\) for difference). The IMT increase was 2.4 times greater in women who developed at least 2 metabolic risk factors than in those with no increase in risk factors after adjustment for age, prevalent CVD, physical activity, smoking, alcohol intake, LDL cholesterol level, use of drugs for hypercholesterolemia, carotid IMT, and NCEP metabolic risk score at baseline (Figure 2, model 1). Adjustment for waist circumference reduced the difference in the carotid IMT increase by 21% (model 2) and triglyceride levels by 20% (model 3). Again, adjustment for serum levels of glucose and HDL cholesterol, systolic blood pressure (models 4-6), and the Framingham risk score (IMT change 0.15 and 0.37 mm, \(P = .03\) for difference) had no effect on the difference.

### Table 1. Baseline Characteristics of Women With or Without the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (n = 88)</th>
<th>Yes (n = 13)</th>
<th>(P) Value for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.7 (3.2)</td>
<td>64.3 (2.6)</td>
<td>.53</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65.9 (9.6)</td>
<td>76.5 (7.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>26.6 (3.9)</td>
<td>30.3 (4.4)</td>
<td>.002</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>80.9 (9.1)</td>
<td>92.9 (10.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical activity, min/wk</td>
<td>207.3 (107.3)</td>
<td>173.1 (125.0)</td>
<td>.30</td>
</tr>
<tr>
<td>Alcohol intake, drinks/wk</td>
<td>0.7 (1.3)</td>
<td>0.5 (1.0)</td>
<td>.68</td>
</tr>
<tr>
<td>Smoking, No. (%)</td>
<td>7 (8.0)</td>
<td>1 (7.7)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Cardiovascular disease‡ No. (%)</td>
<td>15 (17.0)</td>
<td>2 (15.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Drugs for hypercholesterolemia, No. (%)</td>
<td>7 (8.0)</td>
<td>0</td>
<td>.59</td>
</tr>
<tr>
<td>Drugs for hypertension, No. (%)</td>
<td>18 (20.5)</td>
<td>5 (38.5)</td>
<td>.17</td>
</tr>
<tr>
<td>Blood glucose level, mg/dL</td>
<td>84.3 (8.1)</td>
<td>91.6 (9.4)</td>
<td>.004</td>
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<tr>
<td>Serum low-density lipoprotein level, mg/dL</td>
<td>159.7 (34.0)</td>
<td>164.2 (38.3)</td>
<td>.66</td>
</tr>
<tr>
<td>Serum high-density lipoprotein cholesterol level, mg/dL</td>
<td>64.1 (11.5)</td>
<td>48.6 (5.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum triglyceride level, mg/dL</td>
<td>98.1 (29.8)</td>
<td>160.2 (44.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>154.2 (21.4)</td>
<td>163.4 (20.3)</td>
<td>.15</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>88.3 (9.7)</td>
<td>91.3 (12.6)</td>
<td>.31</td>
</tr>
</tbody>
</table>

*SI conversion factors: To convert blood glucose to millimoles per liter, multiply by 0.0555; to convert low-density lipoprotein, high-density lipoprotein, and total cholesterol to millimoles per liter, multiply by 0.0259; and to convert serum triglycerides to millimoles per liter, multiply by 0.0113. 
‡Coronary heart disease or cardiac insufficiency. 
§Calculated as weight in kilograms divided by the square of height in meters.
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The present study showed that incident metabolic syndrome and the increasing number of metabolic risk fac-

tered simultaneously into the model, only baseline IMT ($\beta=-0.302, P=.003$) and age ($\beta=0.193, P=.05$) were independently associated with the change in carotid IMT.

**COMMENT**

The present study showed that incident metabolic syndrome and the increasing number of metabolic risk fac-

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**Table 2. Baseline Characteristics of Women With or Without Incident Metabolic Syndrome During 12 Years of Follow-up**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (n = 54)</th>
<th>Yes (n = 34)</th>
<th>P Value for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.3 (2.9)</td>
<td>64.5 (3.4)</td>
<td>.06</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.0 (8.6)</td>
<td>72.0 (7.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>25.0 (3.3)</td>
<td>29.1 (3.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>76.3 (6.4)</td>
<td>88.2 (7.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical activity, min/wk</td>
<td>213.9 (99.3)</td>
<td>196.8 (119.7)</td>
<td>.47</td>
</tr>
<tr>
<td>Alcohol intake, drinks/wk</td>
<td>0.8 (1.1)</td>
<td>0.8 (1.6)</td>
<td>.57</td>
</tr>
<tr>
<td>Smoking, No. (%)</td>
<td>4 (7.4)</td>
<td>3 (8.6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Cardiovascular disease,‡ No. (%)</td>
<td>9 (16.7)</td>
<td>6 (17.6)</td>
<td>.91</td>
</tr>
<tr>
<td>Drugs for hypercholesterolemia, No. (%)</td>
<td>4 (7.4)</td>
<td>3 (8.6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Drugs for hypertension, No. (%)</td>
<td>9 (16.7)</td>
<td>9 (26.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>83.4 (8.0)</td>
<td>85.7 (8.2)</td>
<td>.002</td>
</tr>
<tr>
<td>Serum low-density lipoprotein cholesterol, mg/dL</td>
<td>161.0 (33.8)</td>
<td>157.7 (34.6)</td>
<td>.78</td>
</tr>
<tr>
<td>Serum high-density lipoprotein cholesterol, mg/dL</td>
<td>66.7 (12.7)</td>
<td>60.1 (8.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum triglycerides, mg/dL</td>
<td>90.6 (27.5)</td>
<td>109.9 (29.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>150.0 (20.8)</td>
<td>161.0 (20.9)</td>
<td>.002</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>87.2 (9.3)</td>
<td>90.0 (10.2)</td>
<td>.03</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert blood glucose to millimoles per liter, multiply by 0.0555; to convert low-density lipoprotein, high-density lipoprotein, and total cholesterol to millimoles per liter, multiply by 0.0259; and to convert serum triglycerides to millimoles per liter, multiply by 0.0113.

*The statistical tests used in the study were the independent samples t test, Mann-Whitney test, and χ² test. The values are expressed as mean (SD) unless indicated otherwise.

†Calculated as weight in kilograms divided by the square of height in meters.

‡Coronary heart disease or cardiac insufficiency.
tors was able to predict the progression of carotid IMT in elderly women over a 12-year period. The progression rate of carotid IMT in these women was comparable to that which we recently reported in men from Eastern Finland who were 10 years younger. The present findings are potentially important from the public health, clinical, and economic points of view. Given the rapidly increasing elderly population in Western societies and the high risk of clinical cardiovascular events in this population, carefully planned health promotion programs and treatments for the metabolic syndrome are urgently needed.

The present results support the findings of studies in middle-aged individuals that have reported a direct relationship of metabolic risk factors with carotid IMT and the risk of CVD. In a previous 5-year study, patients with the metabolic syndrome had an increased risk of developing carotid atherosclerosis. Also, individuals with multiple risk factors at baseline had a higher carotid IMT 15 years later. Consistent with previous cross-sectional findings, incident metabolic syndrome was a stronger predictor for the progression of carotid IMT than the individual components of the syndrome in the present follow-up study. Of the components, increased waist circumference and triglyceride levels contributed most to the association between the metabolic syndrome and the change in carotid IMT. These data suggest that emphasis should be focused on multiple metabolic risk factors in elderly women rather than on each risk factor separately. With this approach, it would be possible to identify a large number of individuals who are at an increased risk for clinical CVD.

An important finding of our study is that incident metabolic syndrome was associated with the progression of carotid IMT even after the Framingham risk score was controlled for. This observation suggests that incident metabolic syndrome provides additional information regarding the progression of preclinical atherosclerosis beyond conventional risk factors and can therefore improve the prediction of clinical CVD.

The progression of atherosclerosis clearly increases after menopause, and CVD is the primary cause of death in women. The prevalence of stroke increases with age in both sexes, but the lifetime risk of dying of stroke has been reported to be 2 times higher in women than in men. Also, women with metabolic syndrome, even without diabetes, were found to have at least a 2-fold risk of ischemic stroke or transient ischemic attack. The present 12-year population-based follow-up study emphasizes the importance of early detection of metabolic syndrome to prevent CVD in elderly women.

In our study, the prevalence of metabolic syndrome increased from 13% to 46% in 12 years. Although the body weight of the women remained the same during follow-up, their waist circumference increased by 10%. This finding may reflect an aging-associated progressive decrease in muscle mass and an increase in body adiposity, particularly in the abdominal area. Abdominal obesity has been found to predict the development of metabolic syndrome, and clinical cardiovascular events. In the present study, the women with metabolic syndrome had a higher waist circumference and BMI at baseline than those without metabolic syndrome. These findings suggest that abdominal obesity is a major component of metabolic syndrome and also partly explain the association between incident metabolic syndrome and the progression of carotid IMT. Lifestyle modification, including regular physical activity and dietary changes, helps to prevent metabolic syndrome and CVD by maintaining healthy body weight and avoiding aging-related loss of muscle mass in later life.

The strengths of the present study include the population-based cohort of elderly women and the long follow-up period. Change in carotid IMT, as assessed by ultrasonography, has been validated as a vascular marker of atherosclerosis progression. We used carotid bifurcation IMT to assess atherosclerosis and its progression because carotid bifurcations are prone to local plaque formation. The same ultrasound device and standard protocols and methods were used by trained and experienced staff in 1992 and 2003. Three certified sonographers performed ultrasonography scans, and one of them read all the recordings.

One limitation of our study was the potential selection of healthier women into the study. The participants in the follow-up were younger and better educated and had less metabolic risk factors than the nonparticipants. The study sample was relatively small, which limits statistical power and could have resulted in an underestimation of the true associations because of smaller differences in variables of interest in population extremes. A considerable increase in the use of antihypertensive and cholesterol-lowering medications in the present study apparently decreased blood cholesterol and blood pressure levels during the 12 years. Because cholesterol-lowering medication was not considered in the NCEP definition, it was included in the multivariate model. Moreover, only a few elderly women in the present study population were smokers. These factors may also have resulted in an underestimation of the true associations of the metabolic syndrome, smoking, and increased LDL cholesterol levels with the progression of carotid IMT.

Our findings demonstrate that incident metabolic syndrome can predict the progression of carotid IMT, an indicator of development of preclinical atherosclerosis, in elderly women. They emphasize the importance of ongoing efforts to identify and control metabolic syndrome as early as possible to prevent CVD, even in the aging population.

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Additional Information: Dr Lakka was a Research Fellow at the Academy of Finland.

REFERENCES

Call for Papers

Sleep Theme Issue

A special issue of the *Archives of Internal Medicine* will be devoted to further our understanding of the relationship of sleep and metabolic, cardiovascular, or immunological disorders and the effects of chronic medical disease on sleep disorders.

The importance of sleep quality for health has been reported yet remains underappreciated by both health care professionals and the general public. Several lines of evidence indicate that sleep quality may be a marker of overall health. Epidemiologic surveys show an association between shortened sleep duration and obesity, cardiovascular, and diabetes. Physiological studies indicate that short-term sleep loss results in alterations in metabolic and immune function. Survey data show that medical disorders are often associated with self-reported poor sleep. Patients with chronic pain (arthritis, fibromyalgia) and gastrointestinal (gastroesophageal reflux disease), cardiovascular (coronary heart disease, congestive heart failure, hypertension), pulmonary (chronic obstructive pulmonary disease, asthma), and metabolic disorders (obesity, diabetes) are at increased risk for disturbed sleep. Increasing evidence points to a bidirectional relationship between sleep and health, so that sleep disturbances contribute to the development of or increase in the severity of various medical disorders; these same disorders result in poor sleep quality. Still, little is known about the mechanisms for these relationships and whether improving sleep can modify the course of comorbid medical disorders.

Papers on medical topics, whether descriptive or mechanistic, will be considered. The deadline for submission is March 15, 2006. Peer-reviewed and accepted sleep theme manuscripts will appear in the September 11, 2006, issue.