

Lung Function Impairment and Metabolic Syndrome

The Critical Role of Abdominal Obesity

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Rationale: Increased risk for cardiovascular morbidity and mortality has been related to both lung function impairment and metabolic syndrome. Data on the relationship between lung function and metabolic syndrome are sparse.

Objectives: To investigate risk for lung function impairment according to metabolic syndrome traits.

Methods: This cross-sectional population-based study included 121,965 men and women examined at the Paris Investigations Préventives et Cliniques Center between 1999 and 2006. The lower limit of normal was used to define lung function impairment (FEV₁ or FVC < lower limit of normal). Metabolic syndrome was assessed according to the American Heart Association/National Heart, Lung, and Blood Institute statement.

Measurements and Main Results: We used a logistic regression model and principal component analysis to investigate the differential associations between lung function impairment and specific components of metabolic syndrome. Lung function impairment was associated with metabolic syndrome (prevalence = 15.0%) independently of age, sex, smoking status, alcohol consumption, educational level, body mass index, leisure-time physical activity, and cardiovascular disease history (odds ratio [OR] [95% confidence interval], 1.28 [1.20–1.37] and OR, 1.41 [1.31–1.51] for FEV₁ and FVC, respectively). Three factors were identified from factor analysis: “lipids” (low high-density lipoprotein cholesterol, high triglycerides), “glucose–blood pressure” (high fasting glycemia, high blood pressure), and “abdominal obesity” (large waist circumference). All factors were inversely related to lung function, but abdominal obesity was the strongest predictor of lung function impairment (OR, 1.94 [1.80–2.09] and OR, 2.11 [1.95–2.29], for FEV₁ and FVC, respectively). Similar results were obtained for women and men.

Conclusions: We found a positive independent relationship between lung function impairment and metabolic syndrome in both sexes, predominantly due to abdominal obesity. Further studies are required to clarify the underlying mechanisms.

Keywords: lung function tests; metabolic syndrome; abdominal fat; principal component analysis; epidemiologic studies

There is increasing evidence that impaired lung function is more than a simple reflection of airflow limitation; it may also be a marker of premature death (1). Several large prospective studies have shown that lung function impairment was predictive of increased cardiovascular morbidity and mortality, independent of smoking (2–4). Positive associations with lung function

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Lung function impairment and metabolic syndrome have been associated with an increased risk for cardiovascular disease. However, data on the relationship between lung function impairment and metabolic syndrome are sparse.

What This Study Adds to the Field

In a large-scale population-based study, we found a positive relationship between lung function impairment and metabolic syndrome, due mainly to abdominal obesity and independent of major cardiovascular risk factors, including body mass index.

impairment have been reported for major cardiovascular risk factors, such as hypertension (5, 6), type II diabetes mellitus (7–9), low-density lipoprotein cholesterol (10), and overall obesity (11, 12). Impaired lung function has also been shown to be predictive of atherosclerosis (13) and arterial stiffening (14), suggestive of parallel remodeling in the lung and the large arteries. Metabolic syndrome comprises a cluster of metabolically related cardiovascular risk factors (15): abdominal obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, and high arterial blood pressure. It has been associated with an increased risk of coronary heart disease in middle-aged subjects (16). The definition of metabolic syndrome remains a matter of debate (17), but a key conceptual advance in recent years has been the change in focus from insulin resistance (18) to abdominal adiposity as the core component of the metabolic abnormalities (19). The mechanisms underlying the relationship between impaired lung function and cardiovascular risk are unclear. Metabolic syndrome, or specific combinations of its components, may play a key role in this relationship, as metabolic syndrome is unlikely to be a homogeneous entity (20). Few data are available on the association between lung function impairment and metabolic syndrome (21–23). We therefore performed a large-scale French population-based study (1) to estimate the association between lung function impairment and metabolic syndrome, and (2) to determine the differential relationships between lung function impairment and specific components of the syndrome, including abdominal obesity in particular.

METHODS

Subjects

Between January 1999 and December 2006, 157,568 subjects living in the Paris area underwent a health examination at the Paris Investigations Préventives et Cliniques Center, as previously reported (24). After the exclusion of subjects lacking lung function measurements (n = 23,118), metabolic syndrome criteria (n = 4,945), and values for other covariates (n = 51), the study sample consisted of 129,454 subjects. Subjects with

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†Deceased.

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a history of lung cancer ($n = 181$), lung or pleural surgery ($n = 740$), pulmonary embolism ($n = 551$), lung tuberculosis ($n = 2,606$), or sarcoidosis ($n = 354$), and pregnant women ($n = 145$) were also excluded. We avoided bias related to illness-induced weight loss (25) by excluding underweight subjects ($n = 3,301$) with a body mass index (BMI) below 18.5 kg/m^2 . Finally, 121,965 subjects (mean age, 45.7 ± 12.3 yr; range, 16–96; men, 66.3%) were retained for analysis. Subjects lacking data for lung function were older, more likely to be women, less educated, never to have smoked, sedentary, and with a lower frequency of metabolic syndrome and respiratory diseases history than those for whom such measurements were available. No difference was observed for overall obesity (see Table E1 in the online supplement). All subjects gave their informed consent at the time of the examination and the Comité National d'Informatique et des Libertés (French Data Protection Agency) authorized these analyses.

Covariates

Demographic background, medical history, drug use, and lifestyle factors, such as cigarette and alcohol consumption, were noted on a standardized questionnaire. Personal history of cough or phlegm from the chest over a period of up to 3 months in a 2-year period was included in the analysis as “chronic bronchitis-like” symptoms. Asthma was defined as a positive answer to the question: “Have you ever had asthma?” Cardiovascular disease was defined as a history of angina pectoris, myocardial infarction, cardiac surgery, stroke, or peripheral vascular disease. Diabetes mellitus was defined as a fasting glucose level $\geq 126 \text{ mg/dL}$ or greater and/or diabetes treatment. Waist circumference (WC, cm) was measured by a trained nurse using a nonelastic tape midway between the last rib and the top of the iliac crest, on the midaxillary line. BMI was calculated from measured height and weight and classified into three groups (normal, $< 25 \text{ kg/m}^2$; overweight, $25\text{--}29.9 \text{ kg/m}^2$; and obese, $\geq 30 \text{ kg/m}^2$). Metabolic syndrome was defined according to the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) (26) and the International Diabetes Federation (IDF) (15) statements. The results presented are based on the AHA/NHLBI (26) statement, unless otherwise stated. This definition is satisfied if at least three of the five following criteria are met: large WC ($\geq 102 \text{ cm}$ in men and $\geq 88 \text{ cm}$ in women), high triglycerides ($\geq 150 \text{ mg/dL}$) or lipid-specific treatment, low high-density lipoprotein (HDL) cholesterol (men < 40 and women $< 50 \text{ mg/dL}$) or lipid-specific treatment, high fasting glucose ($\geq 100 \text{ mg/dL}$) or diabetes treatment, and high systolic blood pressure ($\geq 130 \text{ mm Hg}$) or diastolic blood pressure ($\geq 85 \text{ mm Hg}$) or use of antihypertensive therapy. The IDF (15) statement defines metabolic syndrome as the presence of abdominal obesity (WC $\geq 94 \text{ cm}$ in men and $\geq 80 \text{ cm}$ in women, Europids) plus at least two of the other AHA/NHLBI (26) criteria.

Lung Function Testing

We performed lung function tests, including FEV₁ and FVC, and best maximal effort selected to satisfy as much as possible the American Thoracic Society/European Respiratory Society statement (27). Spirometry tests were performed with a Spyro Analyzer spirometer (Model ST-200; Fukuda Sangyo Co., Tokyo, Japan) as previously reported (14), with subjects in a sitting position and noseclips in place. Each subject performed at least three tests (with at least two reproducible and acceptable maneuvers). Results were considered reproducible if the second highest FEV₁ and FVC values were within 5% of the highest values. The highest measured FEV₁ and the corresponding measured value of FVC were coded for computer analysis. The correlation coefficient between observed FEV₁ and FVC was $r = 0.93$ ($P < 0.001$). The ratio of FEV₁ to FVC (FEV₁/FVC) was also calculated. Internal reference values for spirometry were derived from a “healthy” subgroup: lifelong nonsmokers with no respiratory symptoms or respiratory or cardiovascular disease history ($n = 39,896$; men, 61.6%). Multiple linear regression analysis was performed against age and height to estimate predicted mean value and lower limit of normal (LLN) (28) for FEV₁, FVC, and FEV₁/FVC separately for women and men. The method used for these measurements is described in more detail in the online supplement. Lung function impairment was defined as FEV₁ or FVC less than LLN (reference categories: FEV₁ or FVC \geq LLN). With reference to the American Thoracic Society/European Respiratory Society guidelines (28), ventilatory patterns were also defined taking

into account an obstructive pattern (FEV₁/FVC $<$ LLN; $n = 7,923$; 6.5%) and a restrictive pattern (FVC $<$ LLN with FEV₁/FVC \geq LLN; $n = 5,654$; 4.6%). According to a modified version of the Global Initiative for Chronic Obstructive Lung Disease criteria (29), classification of the severity of the obstructive ventilatory pattern was based on FEV₁% predicted and mild and moderate-to-severe categories were defined as $60\% \leq$ FEV₁ $<$ 80% predicted ($n = 2,707$; 2.2%) and FEV₁ $<$ 60% predicted ($n = 734$; 0.6%), respectively.

Statistical Analysis

Logistic regression models were used to assess the association between the metabolic syndrome and lung function impairment (FEV₁ or FVC $<$ LLN and ventilatory patterns, as defined above), after adjustment for potential confounders (age, sex, educational level, smoking status, alcohol consumption, BMI, leisure-time physical activity, and cardiovascular disease history). Further analyses were also performed in subjects without chronic bronchitis-like symptoms and/or asthma, cardiovascular disease history, or diabetes mellitus. We also assessed the impact of interactions between metabolic syndrome and specific confounders on the association with lung function impairment. The differential relationships between lung function impairment and specific metabolic syndrome variables were investigated by principal component analysis with varimax (orthogonal) rotation. We combined syndrome variables into factors, to quantify the common pathways by which they might influence lung function impairment. Only variables that shared at least 15% of the factor variance, corresponding to a factor loading of at least 0.40, were used in the interpretation of the factors. We identified three factors, subsequently named the “lipids” pattern, the “glucose–blood pressure” pattern, and the “abdominal obesity” pattern, on the basis of a scree test and the interpretability of the results. Individual factor scores were obtained for each pattern by summing the original metabolic syndrome variables multiplied by their factor loadings. We investigated the association between each of the three patterns and lung function impairment, using rotated factor scores as continuous index variables in the logistic regression model predicting lung function impairment. All analyses were performed for the whole cohort and separately for women and men with SAS 9.1 software package (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of Study Participants According to Sex

Men were better educated and less sedentary than women, but had higher frequency of current smoking, heavy drinking, diabetes mellitus, cardiovascular disease history, chronic bronchitis-like symptoms, and lung function impairment (Table 1). The prevalence of metabolic syndrome was 15.0% for the whole cohort and was significantly higher in men than in women (16.8 vs. 11.4%, $P < 0.001$). Comparison for individual components of metabolic syndrome showed women to have higher frequency of abdominal obesity and low HDL cholesterol or specific treatment, whereas men had a higher frequency of high triglycerides or specific treatment, high systolic blood pressure/diastolic blood pressure or antihypertensive treatment, and hyperglycemia or diabetes treatment (Table 1).

Metabolic Syndrome as a Risk Factor for Lung Function Impairment

Higher frequencies of metabolic syndrome (Table 2) and each of its individual components were associated with lung function impairment (FEV₁ or FVC $<$ LLN) (Table E4). After adjustment for age, sex, BMI, smoking status, alcohol consumption, leisure-time physical activity, and cardiovascular history, metabolic syndrome remained independently associated with lung function impairment (adjusted odds ratio [OR_a] [95% confidence interval (CI)], 1.28 [1.20–1.37] for FEV₁ and OR_a, 1.41 [1.31–1.51] for FVC, for the whole cohort). Similar results were obtained for women and men (Table 2). Use of the IDF (15) definition gave similar results (OR_a, 1.30 [1.22–1.40] for FEV₁ and OR_a, 1.46

TABLE 1. CHARACTERISTICS OF THE POPULATION STUDY ACCORDING TO SEX

	All (n = 121,965)	Women (n = 41,135)	Men (n = 80,830)	P Value*
Age, yr	45.7 ± 12.3 [†]	45.8 ± 13.7	45.7 ± 11.5	0.32
Women, %	33.7	—	—	
Educational level, %				<0.001
No school or primary	12.4	13.6	11.8	
Lower secondary	23.7	25.1	23.0	
Upper secondary	18.4	21.9	16.6	
Short-term tertiary	11.4	12.7	10.8	
University tertiary (>2 yr)	34.1	26.7	37.9	
Smoking status, %				<0.001
Never	47.0	59.7	40.5	
Former (≥1 yr)	21.3	13.8	25.0	
Current	31.8	26.5	34.5	
Smoking consumption, pack-years				
>20 pack-years, %	13.0	7.3	15.9	<0.001
Alcohol consumption, glass/day, %				<0.001
0	48.7	63.8	40.8	
1–2	34.4	30.6	36.5	
3–4	12.1	4.6	16.0	
>4	4.8	1.1	6.7	
Leisure-time physical activity, time/week, %				<0.001
Never	57.1	62.0	54.6	
1–2	36.3	32.4	38.3	
≥3	6.6	5.6	7.0	
BMI, kg/m ²	25.1 ± 3.9	24.3 ± 4.4	25.5 ± 3.5	<0.001
BMI, % normal	54.0	65.7	48.1	<0.001
Overweight	35.5	23.4	41.6	
Obese	10.5	10.9	10.3	
Waist circumference, cm	85.0 ± 12.0	76.9 ± 10.8	89.2 ± 10.3	<0.001
Cardiovascular disease history, %	3.2	3.0	3.3	0.02
Diabetes mellitus, %	2.6	1.7	3.1	<0.001
Metabolic syndrome, [‡] %	15.0	11.4	16.8	<0.001
Waist circumference ≥ 102/88 [§] cm	13.1	15.7	11.7	<0.001
Low HDL cholesterol < 40/50 [§] mg/dL or specific treatment	14.5	16.2	13.6	<0.001
Triglycerides ≥ 150 mg/dL or specific treatment	18.2	10.7	21.9	<0.001
SBP ≥ 130/DBP ≥ 85 mm Hg or antihypertensive treatment	48.7	39.4	53.5	<0.001
Fasting glucose ≥ 100 mg/dL or diabetes treatment	29.5	17.1	35.9	<0.001
Asthma, %	9.4	10.0	9.1	<0.001
Chronic bronchitis-like symptoms, %	13.1	11.3	13.9	<0.001
FEV ₁ , L	3.1 ± 0.8	2.4 ± 0.5	3.4 ± 0.7	<0.001
FEV ₁ < LLN, %	6.0	5.5	6.2	<0.001
FVC, L	3.8 ± 1.0	2.9 ± 0.6	4.2 ± 0.8	<0.001
FVC < LLN, %	5.0	4.8	5.1	0.007
FEV ₁ /FVC, %	81.3 ± 7.8	81.9 ± 7.8	81.0 ± 7.8	<0.001
FEV ₁ /FVC < LLN, %	6.5	5.8	6.9	<0.001

Definition of abbreviations: DBP = diastolic blood pressure; LLN = lower limit of normal; SBP = systolic blood pressure.

* P value for comparison between sexes from t test and χ² test for continuous and categorical variables, respectively.

[†] Mean ± SD.

[‡] According to the American Heart Association/National Heart, Lung, and Blood Institute statement.

[§] Threshold for men/women.

[1.36–1.57] for FVC, for the whole cohort). The association between lung function impairment and the metabolic syndrome was modified by smoking status (*P*_{interaction} < 0.001), with stronger estimates in former (OR_a, 1.36 [1.17–1.57] and OR_a, 1.54 [1.32–1.80] for FEV₁ and FVC, respectively) and current smokers (OR_a, 1.52 [1.36–1.70] and OR_a, 1.56 [1.38–1.77] for FEV₁ and FVC, respectively) (Table 3). No interaction between metabolic syndrome and BMI was found to affect the association with lung function impairment (Table 3). Findings for interactions were similar for women and men (data available from the authors). Restricting the analysis to subjects without lung diseases (asthma and/or chronic bronchitis-like symptoms), diabetes mellitus, or cardiovascular disease gave similar results (Table 3).

Rotated Factors and Factor Loadings from Factor Analysis of Metabolic Syndrome Variables

Three dominant factors were identified (Table 4). Factor 1, the lipids pattern, included low HDL cholesterol or specific treatment and high triglycerides or specific treatment. Factor 2, the glucose–blood pressure pattern, included fasting glucose or diabetes treatment and high BP or antihypertensive treatment. Factor 3, the abdominal obesity pattern, included large WC (≥102 cm in men and ≥88 cm in women). No variable loaded in more than one factor. The total variance explained by these three factors was 74.0%. The factor scores for these three factors were used to analyze the independent associations between the factors and lung function impairment.

TABLE 2. ASSOCIATION BETWEEN METABOLIC SYNDROME AND LUNG FUNCTION IMPAIRMENT (FEV₁ OR FVC < LOWER LIMIT OF NORMAL) IN THE WHOLE COHORT AND BY SEX

	FEV ₁		FVC	
	≥LLN	<LLN	≥LLN	<LLN
Whole cohort				
Metabolic syndrome*				
%	14.5	23.2 [†]	14.5	24.7 [†]
Age- and sex-adjusted OR, (95% CI)	1 (Ref)	1.60 (1.51–1.70)	1 (Ref)	1.84 (1.73–1.96)
OR _a [‡] (95% CI)	1	1.28 (1.20–1.37)	1	1.41 (1.31–1.51)
Women				
Metabolic syndrome				
%	10.9	19.9 [†]	10.9	22.4 [†]
Age-adjusted OR (95% CI)	1	1.87 (1.66–2.09)	1	2.24 (1.99–2.52)
OR _a [‡] (95% CI)	1	1.18 (1.04–1.34)	1	1.31 (1.15–1.50)
Men				
Metabolic syndrome				
%	16.3	24.7 [†]	16.3	25.8 [†]
Age-adjusted OR (95%CI)	1	1.52 (1.41–1.62)	1	1.71 (1.58–1.84)
OR _a [‡] (95% CI)	1	1.34 (1.24–1.45)	1	1.47 (1.35–1.60)

Definition of abbreviations: CI = confidence interval; LLN = lower limit of normal; OR = odds ratio; OR_a = adjusted odds ratio; Ref = reference.

* According to the American Heart Association/National Heart, Lung, and Blood Institute statement.

[†] P value < 0.001 for all comparisons between FEV₁ or FVC categories.

[‡] Adjusted for age, sex (when applicable), body mass index, leisure-time physical activity, smoking status, alcohol consumption, educational level, and cardiovascular disease history.

Association between Factors, Based on Factor Analysis and Lung Function Impairment

All three factors were independently associated with lung function impairment in the multiple adjusted model (Table 5). Lung function impairment was predominantly linked to abdominal obesity (OR_a, 1.94 [1.80–2.09] for FEV₁ and OR_a, 2.11 [1.95–2.29] for FVC, for the whole cohort), and in both women and men (Table 5). Smoking status had no significant modifying effect on the association between the abdominal obesity and lung function impairment (OR_a, 1.64 [1.46–1.85]; OR_a, 1.73 [1.44–2.07]; OR_a, 2.06 [1.78–2.38] for FEV₁ and OR_a, 1.93 [1.71–

2.17]; OR_a, 2.19 [1.80–2.66]; OR_a, 2.00 [1.70–2.35] for FVC, in never, former, and current smokers, respectively). The abdominal obesity component was associated with greater lung function impairment risk in all BMI categories (OR_a, 2.93 [2.03–4.24]; OR_a, 1.83 [1.64–2.04]; OR_a, 1.53 [1.29–1.81] for FEV₁ and OR_a, 3.23 [2.18–4.80]; OR_a, 2.06 [1.83–2.31]; OR_a, 1.61 [1.34–1.93] for FVC, in normal, overweight and obese individuals, respectively).

Association between Metabolic Syndrome, Factors, and Ventilatory Patterns

Metabolic syndrome and the three factors identified in factor analysis, including abdominal obesity in particular, were independently associated with the restrictive ventilatory pattern (Table 6). When FVC%predicted was used in place of FVC less than LLN, a similar inverse relationship between FVC and WC in sex-specific quintiles was shown (Figure 1). No association was found between metabolic syndrome glucose–blood pressure component or the lipids component and obstructive ventilatory pattern. However, the abdominal obesity component was independently related to obstructive pattern (Table 6), the severity of which was found to depend on the abdominal obesity component (OR_a, 2.46 [1.96–3.08] for the moderate-to-severe obstructive category) and the glucose–blood pressure component (OR_a, 1.45 [1.23–1.72] for the moderate-to-severe obstructive category). Similar results were obtained for both sexes (data available from the authors).

DISCUSSION

This large-scale study demonstrates that abdominal obesity is the key determinant of the association between metabolic syndrome and lung function impairment. This association was both strong and consistent in women and men. It was also independent of major cardiovascular risk factors and persisted after the exclusion of individuals with a history of cardiovascular or respiratory diseases. The course of chronic obstructive pulmonary disease is inversely related to body weight (30), but we found that abdominal obesity was positively related to both obstructive and restrictive ventilatory patterns, regardless of BMI. To our knowledge, only two cross-sectional population-based studies conducted in Asians (21, 22), have assessed the relationship

TABLE 3. ASSOCIATION BETWEEN METABOLIC SYNDROME AND LUNG FUNCTION IMPAIRMENT (FEV₁ OR FVC < LOWER LIMIT OF NORMAL) BY STRATIFICATION VARIABLES IN THE WHOLE COHORT

	n	FEV ₁		FVC	
		≥LLN	<LLN	≥LLN	<LLN
Metabolic syndrome					
Smoking status					
Never	57,260	1 (Ref)	1.08 (0.98–1.20)	1 (Ref)	1.27 (1.14–1.41)
Former	25,921	1	1.36 (1.17–1.57)	1	1.54 (1.32–1.80)
Current	38,784	1	1.52 (1.36–1.70)	1	1.56 (1.38–1.77)
BMI					
Normal	65,896	1	1.27 (1.10–1.46)	1	1.34 (1.14–1.57)
Overweight	43,276	1	1.31 (1.19–1.44)	1	1.44 (1.30–1.59)
Obese	12,793	1	1.17 (1.03–1.33)	1	1.27 (1.11–1.45)
Without diabetes mellitus	118,771	1	1.23 (1.15–1.32)	1	1.33 (1.24–1.44)
Without asthma or chronic bronchitis-like symptoms	96,489	1	1.28 (1.19–1.39)	1	1.42 (1.31–1.54)
Without cardiovascular disease	118,086	1	1.30 (1.21–1.39)	1	1.42 (1.32–1.53)

Definition of abbreviations: BMI = body mass index; CI = confidence interval; LLN = lower limit of normal; OR = odds ratio; OR_a = adjusted odds ratio; Ref = reference.

* Adjusted when applicable for age, sex, body mass index, leisure-time physical activity, smoking status, alcohol consumption, educational level, and cardiovascular disease history.

TABLE 4. FACTORS AND FACTOR LOADINGS FROM FACTOR ANALYSIS OF VARIABLES RELATED TO METABOLIC SYNDROME

Variable	Factor 1: Lipids	Factor 2: Glucose–Blood Pressure	Factor 3: Abdominal Obesity
Waist circumference ≥ 102/88* cm	−0.04	−0.18	0.90
Low HDL cholesterol < 40/50* mg/dL or treatment	0.64†	−0.15	−0.06
Triglycerides ≥ 150 mg/dL or treatment	0.56	0.09	−0.06
SBP ≥ 130/DBP ≥ 85 mm Hg or treatment	−0.12	0.44	0.36
Fasting glucose ≥ 100 mg/dL or treatment	0.00	0.81	−0.24
Eigenvalue	1.73	1.09	0.85
% Total variance	0.35	0.22	0.17
% Cumulative variance	0.35	0.57	0.74

Definition of abbreviations: DBP = diastolic blood pressure; HDL = high-density lipoprotein; SBP = systolic blood pressure.

* Threshold for men/women according to the American Heart Association/National Heart, Lung, and Blood Institute statement.

† Boldface indicates loadings ≥ 0.40.

between lung function impairment and metabolic syndrome. In accordance with our findings, both reported metabolic syndrome to be significantly associated with the restrictive ventilatory pattern, but not with the obstructive pattern. A similar finding was obtained in a small study of elderly patients (23). However, in these previous studies (21–23), the association between lung function impairment and each individual component of the syndrome was not tested independently of the others. As metabolic syndrome is unlikely to be a homogeneous entity, we need to be able to estimate the relative roles of each of its components in lung function impairment. The frequency of the AHA/NHLBI-defined (26) metabolic syndrome in our study was consistent with published findings for a French population (31) and the frequencies of the ventilatory patterns were similar to those reported from a population-based study (22). Nonetheless, our study was subject to certain limitations. The cross-sectional design of our study precluded the drawing of conclusions about the temporal relationship between lung function impairment and metabolic syndrome. Restrictive ventilatory defect was defined on the basis of a low FVC alone, rather than the gold standard total lung capacity measurement. Finally, the potential selection

bias associated with not including subjects for whom lung function test results were not available may have altered the association between lung function impairment and metabolic syndrome. However, the large size of this community-based study and the extensive data available for potential confounders increased estimate precision and allowed for multiple statistical adjustments for separate analyses in women and men, across a wide age range.

The nature of the metabolic syndrome, including details of the underlying pathologic process, remains unclear. It is widely thought that there is a complex interaction between obesity and insulin resistance that is modified by social, environmental, ethnic, and genetic factors (32). The role of diet in the origin of metabolic syndrome remains unclear, but an inverse relationship has been reported between a “prudent” dietary pattern and the prevalence of metabolic syndrome, each of its individual components (33), and annual change in WC (34). We did not aim to determine whether insulin resistance (18) or abdominal obesity (35) was the driving force behind metabolic syndrome. We used the principal component method with factor analysis to simplify the complex cluster of interrelated variables with high collinearity in metabolic syndrome and to estimate the roles of these variables in lung function impairment. The three principal components identified were consistent with previous findings (36, 37).

Lung Function Impairment and Abdominal Obesity

No previous study has investigated the independent relationship between lung function impairment and abdominal obesity as part of metabolic syndrome. Nevertheless, an inverse relationship between abdominal obesity and lung function has been reported in a few studies, mostly cross-sectional (38–44), of middle-aged subjects. We found that abdominal obesity was strongly associated with lung function impairment, independently of the other two components and major risk factors, including BMI. Similar estimates of the relationship between lung function impairment and metabolic syndrome were obtained if the AHA/NHLBI (26) definition was replaced by the IDF (15) definition, which identifies abdominal obesity as the core component of the syndrome. This association may result from the mechanical effects of truncal obesity and/or the metabolic effects of adipose tissue (12). Abdominal obesity may mechanically affect the diaphragm and chest wall compliance with decreased lung volumes (45). Lower levels of ventilation at

TABLE 5. ASSOCIATION BETWEEN FACTORS FROM FACTOR ANALYSIS AND LUNG FUNCTION IMPAIRMENT (FEV₁ OR FVC < LOWER LIMIT OF NORMAL), IN THE WHOLE COHORT AND BY SEX

	FEV ₁		FVC	
	≥ LLN	< LLN	≥ LLN	< LLN
	OR	OR _a * (95% CI)	OR	OR _a * (95% CI)
Whole cohort				
Lipids	1 (Ref)	1.10 (1.03–1.17)	1 (Ref)	1.17 (1.09–1.25)
Glucose–blood pressure	1	1.23 (1.16–1.30)	1	1.31 (1.23–1.40)
Abdominal obesity	1	1.94 (1.80–2.09)	1	2.11 (1.95–2.29)
Women				
Lipids	1	1.07 (0.96–1.20)	1	1.15 (1.02–1.30)
Glucose–blood pressure	1	1.21 (1.09–1.36)	1	1.27 (1.13–1.43)
Abdominal obesity	1	2.13 (1.87–2.44)	1	2.27 (1.97–2.61)
Men				
Lipids	1	1.12 (1.04–1.21)	1	1.19 (1.09–1.29)
Glucose–blood pressure	1	1.24 (1.16–1.32)	1	1.33 (1.24–1.43)
Abdominal obesity	1	1.88 (1.72–2.06)	1	2.06 (1.86–2.27)

For definition of abbreviations, see Table 2.

* Adjusted for the three factors, and age, sex (when applicable), body mass index, leisure-time physical activity, smoking status, alcohol consumption, educational level, and cardiovascular disease history.

TABLE 6. ASSOCIATION BETWEEN METABOLIC SYNDROME, FACTORS FROM FACTOR ANALYSIS, AND VENTILATORY PATTERNS

	Normal	Obstructive Pattern*	Restrictive Pattern†
	OR	OR _a (95% CI) [‡]	OR _a (95% CI) [‡]
Whole cohort			
Metabolic syndrome	1 (Ref.)	0.94 (0.88–1.02) [‡]	1.40 (1.31–1.51) [‡]
Factors			
Lipids	1	0.96 (0.89–1.02) [§]	1.18 (1.10–1.26) [§]
Glucose–blood pressure	1	0.96 (0.91–1.02)	1.29 (1.21–1.38)
Abdominal obesity	1	1.13 (1.04–1.22)	2.13 (1.96–2.32)
Women			
Metabolic syndrome	1	0.92 (0.79–1.08) [‡]	1.33 (1.16–1.52) [‡]
Factors			
Lipids	1	0.94 (0.83–1.07) [§]	1.15 (1.01–1.30) [§]
Glucose–blood pressure	1	1.03 (0.92–1.16)	1.27 (1.12–1.44)
Abdominal obesity	1	1.19 (1.03–1.38)	2.37 (2.05–2.74)
Men			
Metabolic syndrome	1	0.96 (0.88–1.04) [‡]	1.46 (1.34–1.60) [‡]
Factors			
Lipids	1	0.96 (0.89–1.04) [§]	1.20 (1.10–1.31) [§]
Glucose–blood pressure	1	0.95 (0.89–1.01)	1.31 (1.21–1.41)
Abdominal obesity	1	1.11 (1.01–1.22)	2.03 (1.83–2.26)

For definition of abbreviations, see Table 2.

* FEV₁/FVC < LLN.

† FVC < LLN with FEV₁/FVC ≥ LLN.

‡ For the metabolic syndrome estimates: adjusted for age, sex (when applicable), body mass index, leisure-time physical activity, smoking status, alcohol consumption, educational level, and cardiovascular disease history.

§ For the factors estimates: adjusted for the three factors, age, sex (when applicable), body mass index, leisure-time physical activity, smoking status, alcohol consumption, educational level, and cardiovascular disease history.

the lung base may lead to the closure of peripheral lung units, ventilation-to-perfusion ratio abnormalities, and arterial hypoxemia, particularly in the supine position (12). We observed that the abdominal obesity component was strongly and inversely related to both the restrictive and obstructive ventilatory patterns, suggesting a role for mechanisms unrelated to lung volumes. WC is correlated with both subcutaneous adipose tissue and intraabdominal adipose tissue, but it is a better predictor of intraabdominal adipose tissue—deleterious fat deposition—than BMI (46). Adipose tissue is an active endocrine organ, the mass of which correlates positively with circulating levels of the proinflammatory adipocytokines, IL6,

tumor necrosis factor- α , and leptin, and negatively with levels of adiponectin, which regulates insulin sensitivity and could exert antiinflammatory activities (47). The excretion of adipocytokines by adipose tissue in chronic respiratory diseases may be stimulated by chronic or intermittent hypoxia (48). The role of adipose tissue in the pathogenesis of chronic respiratory diseases remains poorly understood, but adipose tissue may act as an additional source of systemic inflammation (48). Systemic inflammation may also be involved in the association between impaired pulmonary function and cardiovascular diseases (49). Increased levels of serum C-reactive protein, a marker of systemic inflammation, have been positively associated with lung function decline (50), obstructive and restrictive lung diseases (51), and visceral obesity (52). An inverse relationship has also been reported between high levels of serum C-reactive protein and FVC in subjects with metabolic syndrome (53), in which WC has been found to be the main determinant of high serum C-reactive protein (54). We found a strong relationship between lung function impairment and abdominal obesity, even in normal-weight individuals. Serum leptin levels have also been shown to be positively associated with serum C-reactive protein levels and negatively associated with lung function in nonobese subjects (55).

We found a significant interaction between metabolic syndrome and smoking status, with estimated lung function impairment risk being higher in former and current smokers than in those who had never smoked. Metabolic abnormalities tend to be more frequent in smokers (56), but previous studies conducted in nonsmokers showed a highly significant relationship between abdominal adiposity and a dysmetabolic profile (19). We found that the abdominal obesity was positively and strongly associated with lung function impairment, regardless of smoking status.

Lung Function Impairment and Diabetes

A weak link was found between lung function impairment and glucose–blood pressure, which was more closely related to impaired glycemia control. Insulin resistance is a common feature of impaired glucose metabolism and blood pressure homeostasis (18). Restricting our analysis to subjects with no diabetes history did not modify the association between lung function impairment and metabolic syndrome. Conflicting results have been published concerning the relationship between lung function impairment

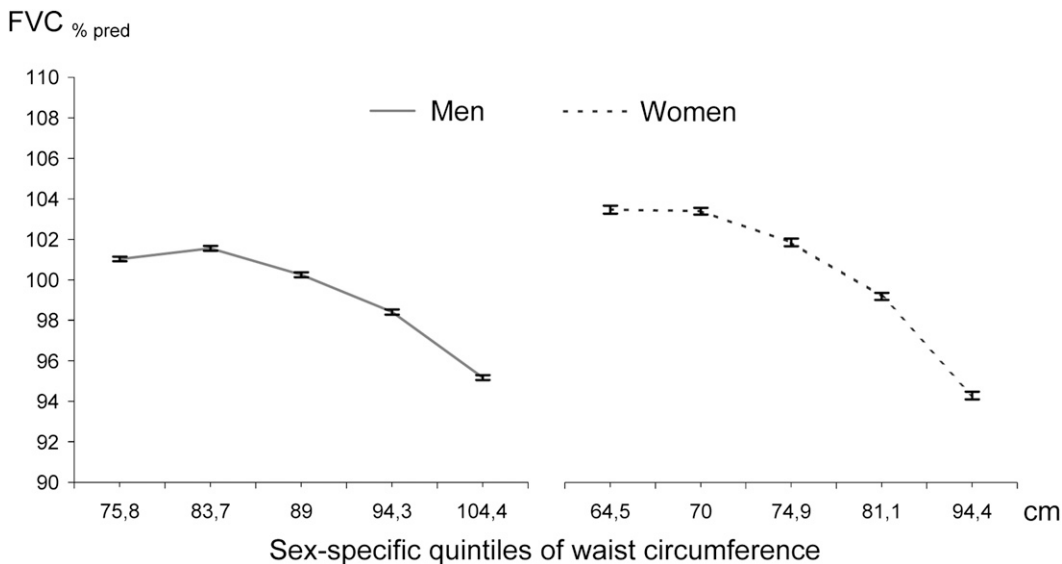


Figure 1. FVC% predicted according to sex-specific quintiles of waist circumference.

and diabetes mellitus. Lung function impairment, including restrictive ventilatory defect in particular, has been reported to be associated with developing high risk of diabetes (7). However, other studies have reported diabetes to be frequently comorbid with chronic obstructive pulmonary disease (57) or faster lung function decline in diabetic individuals than in other subjects (9).

We found a positive independent relationship between lung function impairment and metabolic syndrome due mainly to abdominal obesity. As abdominal obesity has recently been related to a higher risk of respiratory death, regardless of BMI (58), our study raises potential concerns about how the possible impact of the increase in WC reported in the United States (59) and, to a lesser extent, in France (60) on future adverse health outcomes should be considered when assigning resources in respiratory care. Prospective studies are needed, to determine the temporal relationship between lung function impairment and metabolic syndrome, including abdominal adiposity in particular. Mechanistic studies are also required to clarify the underlying physiopathological pathways.

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