Relation Between Lung Function and RBC Distribution Width in a Population-Based Study*

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Study objectives: **Pulmonary function is dependent not only on smoking, but also on nutritional status. Since an increased RBC distribution width (RDW) has been associated with nutritional deficiencies, we postulated that RDW has an inverse relation to pulmonary function. The purpose of this study was to test this hypothesis.**
Design and setting: **A cross-sectional study was conducted of a random sample of the general population in western New York.**
Participants: **A total of 1,616 subjects of both genders who were aged 35 to 79 years and were free of respiratory disease.**
Interventions: **None.**
Measurements: **Pulmonary function was assessed from FEV_1, FVC, height, body weight, total pack-years of smoking, smoking status, hemoglobin concentration, and hematologic indexes, eosinophil count, education, and blood levels of retinol, β-cryptoxanthin, and vitamin E.**
Results: **We found a direct relation between RDW and the number of pack-years of smoking and smoking status, and an inverse relation between FEV_1 and FVC with RDW, even when potentially confounding variables such as smoking were taken into account. When the variability of FEV_1 due to smoking was used for comparison, an additional 27% of that variability in FEV_1 was explained by variations in antioxidant vitamin levels, and another 24% by RDW.**
Conclusions: **The results confirmed our hypothesis that there is an inverse relation between RDW and pulmonary function, and raise the possibility that RDW may be a biomarker for as-yet unidentified nutrients that affect pulmonary function.** ***(CHEST 2003; 124:494–500)***

Key words: antioxidants; nutrition; pulmonary function tests; spirometry; vitamins

Abbreviations: RDW = RBC distribution width; MCHC = mean corpuscular hemoglobin concentration

Pulmonary function has been shown to be a good predictor of overall mortality in the general population.[1,2] Of the various risk factors affecting lung function, smoking and nutrition are among the most important from a public health perspective because potentially, they are modifiable. The fact that only 15% of smokers develop COPD suggests that other factors may play a role.[3,4] It has been suggested that some of this variability in smoking-related risk may be due to differences in ethnicity, nutrition, or other lifestyle factors.[5–7]

The RBC distribution width (RDW) is the coefficient of variation of mean RBC volume and may be influenced by nutritional factors. No clinical conditions have been associated with values that are below the normal range. The levels are usually normal or elevated. It is known, however, that an increased RDW is associated with nutritional deficiency (*ie*, iron, vitamin B_{12}, and folic acid) and ethnicity.[8–10]

Measurements of nutritional status are complex and unreliable for some micronutrients. Because of the association between RDW and nutritional factors, one might consider RDW as a biomarker for nutritional status of vitamin B_{12}, folic acid, and iron. These micronutrients play an important role in oxidative stress defense mechanisms,[11,12] and oxidative stress is associated with impaired lung function.[13] Prior studies also have suggested that RDW may be a marker for ethnic differences in biological

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Manuscript received April 29, 2002; revision accepted January 29, 2003.

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susceptibility to alcohol abuse. Asians who abuse alcohol and who are thought to have an increased susceptibility to alcohol, as judged by an increase in liver enzyme levels, including γ-glutamyl transpeptidase, also have an increased RDW compared to their European counterparts.[14] Therefore, we hypothesized that RDW may be a biomarker for biological susceptibility of the lung to the effects of smoking, or it may be a biomarker for deficiency of certain nutritional factors that exert an effect on lung function.

To test these hypotheses, we analyzed the relation between RDW and lung function in a general population sample of 1,616 residents of western New York. To our knowledge, no studies to date have investigated the association between RDW and lung function.

Materials and Methods

Study Population

This study was performed in a random sample of the general population from among residents of western New York who were between the ages 35 and 79 years. The details of the study design, random selection of participants, exclusion criteria, laboratory variability, analytical methods, and spirometry have been described previously.[15] One thousand six hundred sixteen participants were included in the analysis. The study was approved by the institutional review board of the University at Buffalo.

Data Collection

A detailed self-administered socioeconomic and medical history questionnaire was given to all participants. A detailed account of education was taken, and a personal interview addressed lifestyle habits that included details on the duration and amount of smoking and the number of years since quitting smoking.

All anthropometric measurements were taken according to a standardized protocol. Blood samples for vitamin E, β-cryptoxanthin, retinol, total vitamin C, hemoglobin concentration and its indexes, RDW, automated differential cell blood count, and spirometry were conducted in a manner that has been described in detail previously[15] using the same prediction equations for FEV_1 and FVC derived from values of healthy lifelong nonsmokers. To facilitate the comparison of the relative effects of the micronutrients, the absolute blood values of each micronutrient were divided by 1 SD of the micronutrient to obtain a dimensionless ratio.

Statistical Analysis

The relation of RDW to FEV_1 and FVC were explored using multiple linear regression analysis, and were tested for linearity, collinearity, and interactions among the independent variables. Significance was accepted at the 0.05 level, and at the 0.1 level for interaction terms. Mean values and SD for all relevant variables were calculated.

The factors affecting RDW were examined using stratification and regression methods. The following covariates were considered because all have been demonstrated to affect RDW: age; gender; ethnicity; hemoglobin; usual alcohol intake over the past 12 months.[8,9,16,17] In addition, we included smoking status, total number of pack-years of smoking, and body weight because of the adverse effects of smoking and body weight on folate status. We also included measurements of micronutrients that were shown to affect pulmonary function in our previous study.[15]

Initially, a multiple linear regression model that predicts FEV_1 and FVC included the following covariates: total number of pack-years of smoking; present smoking status; blood eosinophil count; education; blood levels of vitamin E (corrected for triglycerides), serum β-cryptoxanthin, and retinol; and weight.[15] Both age and ethnicity are known to influence both RDW and pulmonary function. To avoid separate adjustments of RDW and pulmonary function with the same variables, we developed linear regression equations in which FEV_1 and FVC were expressed in absolute units rather than as the predicted normal values adjusted for age, height, gender, and ethnicity that we had used previously.[15] Serum vitamin C level was not included because it provided no additional explanatory power if serum vitamin E level was included as a covariate.[15] To investigate the contribution of RDW and other hemoglobin indexes, each was added separately to the initial model. We then added RDW to the initial model along with potentially confounding variables.

Results

Study Population

Table 1 shows the baseline characteristics of the 1,616 participants by gender. The age of the subjects ranged from 36 to 80 years. More than one third of men (33.9%) and more than half of women (50.9%) had never smoked. The proportions of former and current smokers are shown in (Table 1). The percentages of current smokers among men and women were only 12.2% and 15%, respectively.

Spirometry, Blood Vitamin Levels, and RBC Indexes

Absolute FEV_1 and FVC were higher in men, but FEV_1 percent predicted was lower in men than in women. Women had higher serum concentrations of vitamin E and β-cryptoxanthin than men. The mean RDW was 12.5 (95% confidence interval, 14.6 to 10.4) with no gender difference. In contrast, hemoglobin level and its indexes were larger in men than in women. RDW was correlated significantly ($p < 0.0001$) with hemoglobin concentration ($r = -0.296$), hematocrit ($r = -0.237$), mean corpuscular volume ($r = -0.293$), mean corpuscular hemoglobin ($r = -0.345$), and mean corpuscular hemoglobin concentration (MCHC) [$r = 0.285$], but the correlation coefficients were low.

Factors Affecting RDW

A multiple linear regression model was used to determine the factors affecting RDW. A log transformation of RDW was used to normalize the distri-

Table 1—*Characteristics of the Study Population

Characteristics	Men (n = 777)	Women (n = 839)
Age, yr	60.6 (10.9)†	59.3 (10.4)
Height, m	1.75 (0.07)‡	1.62 (0.06)
Weight, kg	87.2 (14.6)‡	72.9 (16.1)
FVC, L	4.54 (0.64)‡	3.29 (0.498)
FEV_1, L	3.35 (0.80)‡	2.50 (0.55)
FVC, %	97.8 (15.7)	98.9 (14.7)
FEV_1, %	95.3 (17.2)‡	97.7 (15.5)
Plasma vitamin C, mg/dL	1.19 (0.58)‡	1.33 (0.64)
Plasma vitamin E, μg/mL	13.91 (6.28)‡	15.00 (7.00)
Plasma β-cryptoxanthin, μg/mL	0.093 (0.066)‡	0.103 (0.073)
Plasma retinol, μg/mL	0.587 (0.142)‡	0.548 (0.152)
Eosinophil count, cells/μL	3.4 (1.9)†	3.0 (1.8)
African American, %	6.8	6.9
Never-smoker, %	33.9‡	50.9
Current smoker, %	12.2	15
Ex-smoker, %	53.9‡	34.1
Smoking, pack-yr (entire sample)	19.6 (26.0)‡	10.3 (18.5)
RDW	12.52 (1.05)	12.47 (1.06)
Hemoglobin, g/dL	15.06 (1.135)‡	13.67 (1.036)
Hematocrit, %	45.0 (3.36)‡	41.0 (3.09)
Mean corpuscular volume, fL	91.5 (5.04)‡	90.7 (5.50)
Mean corpuscular hemoglobin, pg	30.6 (1.82)‡	30.3 (2.08)
Mean corpuscular hemoglobin concentration, g/dL	33.44 (0.69)‡	33.35 (0.71)
Usual alcohol intake in the past year, oz	176.80 (300.64)‡	69.25 (150.36)

*Values given as mean (SD).
†$p < 0.05$.
‡$p \leq 0.01$.

Table 2—*Coefficients of Multiple Linear Regression for Predictors of Log RDW Added Simultaneously

Independent Variables	β Statistic	p Value
Age, yr	0.0124 (0.0023)	< 0.001
Hemoglobin concentration, g/dL	−0.2808 (0.0211)	< 0.001
Ethnicity†	0.1702 (0.0459)	< 0.001
Weight, kg	0.0067 (0.0015)	< 0.001
Gender:hemoglobin concentration	0.0722 (0.0208)	< 0.001
Smoking status‡		
Linear term	0.1903 (0.0600)	0.002
Quadratic term	0.1519 (0.0407)	< 0.001
Gender§	−0.8715 (0.2995)	0.004
Smoking, total pack-yr	0.0035 (0.0012)	0.005
Usual alcohol intake in past year, oz	−0.0001 (0.0001)	0.194
Retinol‖	−0.0268 (0.0229)	0.242
Education	−0.0087 (0.0084)	0.298
Eosinophils	0.0001 (0.0002)	0.450
Vitamin E‖¶	−0.0112 (0.0236)	0.636
β-cryptoxanthin‖	0.0098 (0.0242)	0.686

*Values given as mean (SE), unless otherwise indicated. : = indicates an interaction.
†Ethnicity is coded as follows: white, −1 African American, 1.
‡Smoking status was coded as an ordered factor as follows: nonsmoker, − 1; ex-smoker, 0; and current smoker, 1.
§Gender is coded as follows: female, −1; male, 1.
‖Values given as mean (SD).
¶Blood levels of vitamin E were adjusted for triglyceride levels (μg/mg triglyceride per deciliter of serum), retinol, and β-cryptoxanthin.

bution of residuals. The effects of smoking on RDW were confirmed. Table 2 shows that age, hemoglobin concentration, ethnicity, weight, gender, total number of pack-years of smoking, and smoking status were significantly associated with RDW. Alcohol intake clearly did not attain statistical significance. None of the coefficients of known important micronutrients that affect pulmonary function (*ie*, blood levels of vitamin E, retinol, and β-cryptoxanthin) achieved statistical significance.

Relation Between Pulmonary Function and RDW

The initial regression models are shown in Table 3 for FEV_1 and FVC as the dependent variables. There are small differences in the coefficients compared with our previous analysis because we expressed spirometric values in absolute units rather than as the predicted normal values. The interaction terms for age, gender, and ethnicity were used in the analysis so that the results can be presented in a single regression model, rather than presenting sex-specific and race-specific analyses of pulmonary function. All of the analyzed residuals appeared to be normally distributed.

We then added either RDW, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, or MCHC as additional independent variables in the initial model. Table 4 shows that the dominant significant effect on FEV_1 and FVC is with RDW. Hemoglobin concentration had a lower order significant effect on FVC only.

When RDW is adjusted for variables that were not already included in the initial model (*ie*, hemoglobin concentration and the interaction term between gender and hemoglobin concentration), the coefficient for RDW is unaffected with either FEV_1 or FVC as the dependent variable (Table 5).

We found that there were no significant interaction effects between RDW and smoking expressed in terms of total number of pack-years, smoking status, and both total number of pack-years and smoking status. The stratification of the data by smoking status indicated that the mean (± SE) coefficient for RDW in the multiple linear regression model for FEV_1 was -0.0513 ± 0.00166 for never-smokers, -0.0525 ± 0.0217 for ex-smokers, and -0.0421 ± 0.0353 for current smokers. A significant interaction term was found with gender ($p < 0.048$). The stratification of the data by gender indicated that the mean (± SE) coefficients for RDW in the multiple linear regression model remained significant, as follows: women, -0.039 ± 0.0132 ($p = 0.003$); men,

Table 3—*Coefficients for Initial Multiple Linear Regression Models Added Simultaneously

Independent Variables	FEV_1, L		FVC, L	
	β Statistic	p Value	β Statistic	p Value
Age, yr	−0.0349 (0.0012)	< 0.001	−0.0370 (0.0015)	< 0.001
Height, m	3.1617 (0.1928)	< 0.001	4.9041 (0.2373)	< 0.001
Gender	0.5419 (0.0721)	< 0.001	−0.6083 (0.0887)	< 0.001
Smoking, total pack-yr	−0.0050 (0.0006)	< 0.001	−0.0031 (0.0008)	< 0.001
Smoking status				
Linear term	−0.1232 (0.0311)	< 0.001	−0.0920 (0.0383)	0.016
Quadratic term	−0.0920 (0.0212)	< 0.001	−0.0888 (0.0261)	< 0.001
Ethnicity	−0.1816 (0.0235)	< 0.001	−0.2563 (0.0289)	< 0.001
Age: gender	−0.0053 (0.0011)	< 0.001	−0.0054 (0.0010)	< 0.001
Eosinophil	−0.0004 (0.0001)	0.001	−0.0003 (0.0001)	0.018
Retinol	0.0316 (0.0120)	0.009	0.0295 (0.0148)	0.046
Education	0.0114 (0.0044)	0.010	0.0103 (0.0054)	0.057
Ethnicity: gender	−0.0522 (0.0230)	0.021	−0.0505 (0.0283)	0.074
Weight, kg	−0.0019 (0.0008)	0.023	−0.0054 (0.0010)	< 0.001
β-cryptoxanthin	0.0280 (0.0126)	0.027	0.0373 (0.0155)	0.016
Vitamin E	0.0266 (0.0124)	0.033	0.0518 (0.0153)	< 0.001

*Values given as mean (SE), unless otherwise indicated. See Table 2 for definitions of terms.

-0.0753 ± 0.0244 ($p < 0.001$). When the model was restricted to whites only, the mean coefficient for RDW -0.0640 ± 0.0142 remained significant.

To assess the relative contribution of the independent variables for predicting FEV_1 and FVC, we used analysis of variance to determine the marginal increase in the mean sum of squares associated with that variable (or group of variables) when it is added to the rest of the model. We used the models shown in Table 5 but eliminated variables with $p < 0.1$. Of the potentially modifiable predictor variables (*ie*, smoking, RDW, micronutrients, eosinophil count, education, and weight) of FEV_1, smoking (*ie*, total number of pack-years of smoking and smoking status) had the greatest influence (Fig 1). The variability due to RDW was 27% of that due to smoking, compared to 26% for eosinophil count, 24% for known micronutrient levels (*ie*, vitamin E, β-cryptoxanthin, and retinol), 9% for educational grade, and 5% for weight. Of the potentially modifiable predictor variables of FVC, RDW had the greatest influence (Fig 2).

Discussion

The present study examined the relation between RDW and lung function in a sample of individuals from the general population of western New York. The RDW is the width of the frequency distribution curve of the RBC volume (one SD) divided by the mean RBC volume.[18] Only increased levels of RDW have been associated with pathologic states. For example, both microcytic and macrocytic anemias have contrasting effects on mean corpuscular volume, but both conditions increase RDW. It has little diagnostic utility because it lacks both specificity and sensitivity for anemias due to nutritional deficiency. Nevertheless, the fact that it is measured easily renders it a suitable candidate as a marker for susceptibility to the effects of smoking on the lung and for nutritional impairment.

The results of the study show that the RDW is independently and negatively associated with lung function, after adjusting for known important con-

Table 4—*Coefficients for Hemoglobin Indices Added Separately to Initial Model

Independent Variables	FEV_1, L		FVC, L	
	β Statistic	p Value	β Statistic	p Value
RDW	−0.0538 (0.0124)	< 0.001	−0.0535 (0.0153)	< 0.001
Hemoglobin	0.0237 (0.0143)	0.099	0.0372 (0.0177)	0.035
Hematocrit	0.0200 (0.0141)	0.157	0.0331 (0.0174)	0.057
MCV	0.0081 (0.0122)	0.506	0.0052 (0.0150)	0.727
MCH	0.0095 (0.0121)	0.429	0.0069 (0.0148)	0.641
MCHC	0.0071 (0.0121)	0.560	0.0072 (0.0149)	0.631

*Values given as mean (SE), unless otherwise indicated. All coefficients were all expressed as 1 SD change. MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin.

Table 5—*Coefficients for Revised Multiple Linear Regression Models Added Simultaneously

Independent Variables	FEV_1, L		FVC, L	
	β Statistic	p Value	β Statistic	p Value
Age, yr	−0.0341 (0.0012)	< 0.001	−0.0361 (0.0015)	< 0.001
Height, m	3.1508 (0.1918)	< 0.001	4.8922 (0.2365)	< 0.001
Gender	0.3463 (0.1757)	0.049	0.3654 (0.2166)	0.092
Smoking, total pack-yr	−0.0049 (0.0006)	< 0.001	−0.0030 (0.0008)	< 0.001
RDW	−0.0535 (0.0131)	< 0.001	−0.0495 (0.0162)	0.002
Smoking status				
Linear term	−0.1160 (0.0312)	< 0.001	−0.0875 (0.0385)	0.023
Quadratic term	−0.0863 (0.0213)	< 0.001	−0.0854 (0.0263)	0.001
Ethnicity	−0.1663 (0.0239)	< 0.001	−0.2379 (0.0295)	< 0.001
Eosinophil	−0.0004 (0.0001)	< 0.001	−0.0003 (0.0001)	0.021
Retinol	0.0308 (0.0120)	0.010	0.0291 (0.0148)	0.049
Education	0.0109 (0.0044)	0.013	0.0098 (0.0054)	0.070
β-cryptoxanthin	0.0286 (0.0126)	0.023	0.0379 (0.0155)	0.015
Vitamin E	0.0269 (0.0124)	0.030	0.0528 (0.0153)	< 0.001
Weight, kg	−0.0015 (0.0008)	0.067	−0.0051 (0.0010)	< 0.001
Hemoglobin	0.0031 (0.0117)	0.7882	−0.0147 (0.0144)	0.309
Age:gender	−0.0049 (0.0011)	< 0.001	−0.0049 (0.0014)	< 0.001
Ethnicity:gender	−0.0522 (0.0232)	0.025	−0.0505 (0.0286)	0.079
Hemoglobin:gender	0.0118 (0.0111)	0.288	0.0139 (0.0137)	0.308

*Values given as mean (SE), unless otherwise indicated. See Table 2 for definitions of terms.

founding variables. Each of the confounders had independent associations with FEV_1 and FVC. The confounders with a negative association included smoking,[19] eosinophil count,[20] and weight,[21] and those with a positive association included education[16] and blood levels of known antioxidants,[22] which are in agreement with previously published studies.

Factors Affecting RDW

Our results are also similar to those of prior studies that have shown age-related and gender-related changes in the RDW.[16] Ethnic variations in RDW also have been described. African Americans have higher RDW compared to their white counterparts.[8] Individuals from south Asia who abuse alcohol to the same extent as Europeans have higher RDW.[14] It is well-established that a low hemoglobin level is associated with an increase in RDW.[9,23] In our study, we found a similar relation. An increased RDW also has been associated with alcohol abuse,[10] but we found no significant relation with alcohol consumption. This result is in accordance with that of a previous study,[17] in which only 29.8% of alcoholics showed high RDW values.

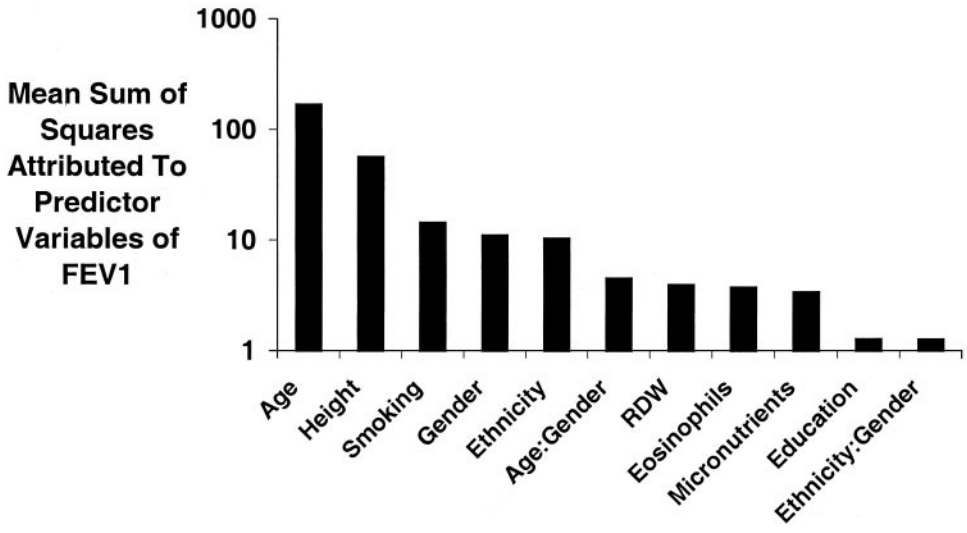

FIGURE 1. Bar chart of the mean sum of squares of FEV_1 for each of the predictor variables of the revised multiple linear regression model with terms that were not statistically significant having been removed. Not shown is the residual mean sum of squares (0.21).

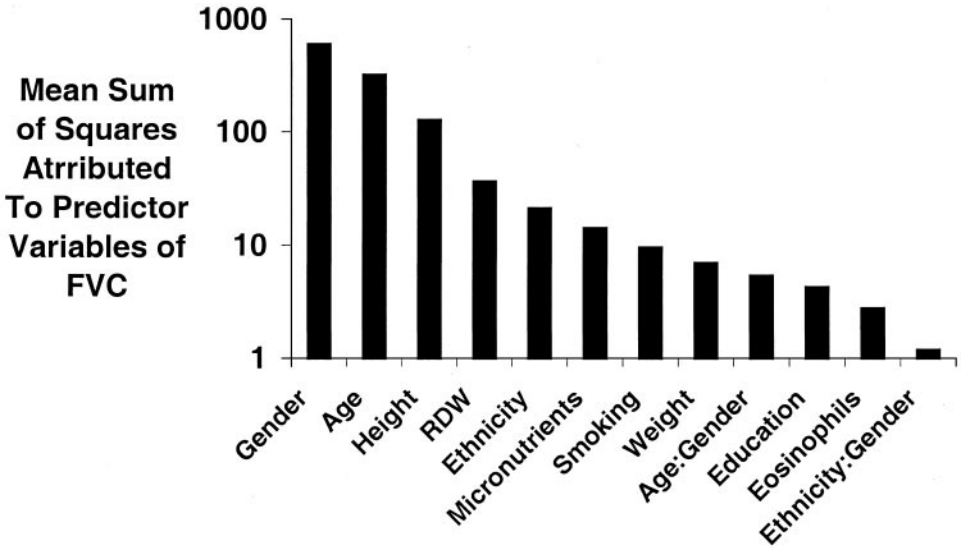

FIGURE 2. Bar chart of the mean sum of squares of FVC for each of the predictor variables of the revised multiple linear regression model with terms that were not statistically significant having been removed. Not shown are the mean sum of squares for weight and the residual mean sum of squares (0.69 and 0.32, respectively).

The other variables that were associated significantly with RDW in our study were total number of pack-years of smoking and body weight. Searches of electronic databases did not show any prior study examining these associations directly. However, reports that both smoking and high BMI are associated with suboptimal folate status might explain, at least in part, their relation to RDW.[5,24–26]

RDW and Pulmonary Function

It is unlikely that RDW *per se* has any direct effect on pulmonary function. The association that we have found is most likely due to RDW acting as a marker for some other biological process. There were no interaction effects between RDW and smoking, and, therefore, it seems unlikely that RDW is a measure of the biological susceptibility of the lung to the effects of smoking.

Since RDW is affected by ethnicity, it can be argued that the relation of RDW with lung function is related to ethnic factors. However, we adjusted for ethnicity, so it is unlikely to explain our findings. Furthermore, the relation between RDW and pulmonary function remained even when the data were restricted to whites only. The RDW is increased in individuals who have experienced an early deficiency of iron, folate, and vitamin B_{12}, and is an overall marker of iron, folate, and vitamin B_{12} deficiency.[9,10,27] In comparison, the importance of other nutrients such as iron, folate, and vitamin B_{12} on spirometry has not yet been examined directly. No blood levels of these nutrients were available in this population.

Since smoking is related to both nutrition and lung function, it could confound these associations. However, the relation between RDW and lung function remains strong in the never-smokers, therefore residual confounding by smoking is an unlikely explanation for this observation.

The strengths of this study are that detailed information on several important lifestyle factors related to pulmonary function were obtained and adjusted for in the analysis. This study is unique because there have been no prior studies examining the relation between RDW and lung function. Only one other study[28] has shown a relation between RBC indexes (*ie*, MCHC) and spirometry. Although this observation is consistent with our results, since a low MCHC is associated with an increase in RDW, we were unable to find a relation between MCHC and spirometry values after adjusting for confounding variables.

Our study has some limitations. First, the number of current smokers was limited. Second, the cross-sectional nature of this study prevents us from drawing any conclusions about a cause-effect relation. Third, the study population was limited to residents of western New York. Fourth, we adjusted the RDW for all known factors that affect it but not for the nutrients (*ie*, iron, folate, and vitamin B_{12}) since these data were unavailable.

Given these limitations, the results of our study appear to suggest that some other nutritional factors than those previously described may be important predictors of lung function. The variability in FEV_1 due to RDW is 27% of that due to smoking, com-

pared with 24% for the known micronutrients (*ie*, vitamin E, β-cryptoxanthin, and retinol). Among the potentially modifiable predictor variables of FVC, RDW has the greatest influence. The nutritional factors related to RDW are most probably iron, folate, and/or vitamin B_{12}. Whatever the factors are that relate RDW to lung function, the strength of association appears to be of a similar order of magnitude as that of the known micronutrients. An increase of 1 SD in RDW (about 1.06) is associated with a 54-mL decrease in FEV_1. This decline in FEV_1 is equivalent to the decline associated with 11 pack-years of smoking or 1.5 years of aging. Further studies that are needed to clarify the independent and interactive influences among these nutrients, ethnicity, and smoking on lung function in the general population.

In summary, we have reported the following two new findings: (1) smoking increases RDW; and (2) RDW is inversely related to lung function. The association between RDW and lung function appears to be independent of smoking, ethnicity, and levels of the known important micronutrients (*ie*, vitamin C, vitamin E, β-cryptoxanthin, and retinol).[15] The association may be related to nutritional factors that have not been reported previously, such as the levels of iron, vitamin B_{12}, and/or folic acid.

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