

## ORIGINAL ARTICLE

# Reduced Exposure to PM<sub>10</sub> and Attenuated Age-Related Decline in Lung Function

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## ABSTRACT

**BACKGROUND**

Air pollution has been associated with impaired health, including reduced lung function in adults. Moving to cleaner areas has been shown to attenuate adverse effects of air pollution on lung function in children but not in adults.

**METHODS**

We conducted a prospective study of 9651 adults (18 to 60 years of age) randomly selected from population registries in 1990 and assessed in 1991, with 8047 participants reassessed in 2002. There was complete information on lung volumes and flows (e.g., forced vital capacity [FVC], forced expiratory volume in 1 second [FEV<sub>1</sub>], FEV<sub>1</sub> as a percentage of FVC, and forced expiratory flow between 25 and 75% of the FVC [FEF<sub>25-75</sub>]), smoking habits, and spatially resolved concentrations of particulate matter that was less than 10 μm in aerodynamic diameter (PM<sub>10</sub>) from a validated dispersion model assigned to residential addresses for 4742 participants at both the 1991 and the 2002 assessments and in the intervening years.

**RESULTS**

Overall exposure to individual home outdoor PM<sub>10</sub> declined over the 11-year follow-up period (median, -5.3 μg per cubic meter; interquartile range, -7.5 to -4.2). In mixed-model regression analyses, with adjustment for confounders, PM<sub>10</sub> concentrations at baseline, and clustering within areas, there were significant negative associations between the decrease in PM<sub>10</sub> and the rate of decline in FEV<sub>1</sub> (P=0.045), FEV<sub>1</sub> as a percentage of FVC (P=0.02), and FEF<sub>25-75</sub> (P=0.001). The net effect of a decline of 10 μg of PM<sub>10</sub> per cubic meter over an 11-year period was to reduce the annual rate of decline in FEV<sub>1</sub> by 9% and of FEF<sub>25-75</sub> by 16%. Cumulative exposure in the interval between the two examinations showed similar associations.

**CONCLUSIONS**

Decreasing exposure to airborne particulates appears to attenuate the decline in lung function related to exposure to PM<sub>10</sub>. The effects are greater in tests reflecting small-airway function.

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LONG-TERM EXPOSURE TO AIR POLLUTANTS, especially particulate air pollution, has been repeatedly associated with increased mortality<sup>1-5</sup> and with decreased lung function.<sup>6-9</sup> Lung function is known to be one of the strongest determinants of cardiorespiratory health and longevity,<sup>10-13</sup> although the causal pathway is poorly understood.<sup>14</sup> According to a recent report, reduced exposure to concentrations of particulate matter that is less than 2.5  $\mu\text{m}$  in aerodynamic diameter (PM<sub>2.5</sub>) was associated with a reduction in mortality from all causes, from cardiovascular causes, and from lung cancer.<sup>15</sup> Whereas the beneficial effects of smoking cessation on lung function are well established,<sup>16,17</sup> there has been little investigation of the effects of reductions in air pollution on lung function.<sup>18</sup>

A study in California showed that a pollutant-related delay in lung development in children<sup>19</sup> can be attenuated if children move to cleaner geographic areas.<sup>18</sup> In adults in Switzerland, residence in more polluted areas has been associated with reduced lung function.<sup>6</sup> However, it is not known whether the pollution-related effects are a result of lower achieved levels of lung function at the end of the growth period or whether air pollutants can accelerate a decline in lung function during adult life. One study that investigated the effect of air pollution on longitudinal change in lung function showed that a greater decline in the forced expiratory volume in 1 second (FEV<sub>1</sub>) in adults was associated with residence near major roads,<sup>8</sup> indicating that there may be measurable effects during adult life.

The use of air-pollution measurements from a fixed monitoring site to characterize community exposure is being superseded by individual estimates of exposure.<sup>20</sup> Models of concentrations of pollutants according to residence now include interpolation techniques<sup>4</sup> and the use of geographic information system software.<sup>5</sup> Individual estimates permit characterization of exposure differences across and within communities<sup>21</sup> and should improve the statistical power to detect pollution-related effects.

The Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) is a prospective study of a population sample of adults that was designed to investigate long-term health effects of air pollution. Levels of PM<sub>10</sub> (particulate matter with an aerodynamic diameter <10  $\mu\text{m}$ ) have commonly been used to assess exposure to suspended particulate matter in the respirable

range,<sup>22</sup> and the baseline assessment of the SAPALDIA cohort in 1991 showed that average levels of forced vital capacity (FVC) were inversely associated with ambient levels of PM<sub>10</sub> at central sites.<sup>6</sup> We have now assigned individual estimates of ambient PM<sub>10</sub> concentrations to each participant's residence for each year from 1991 to 2002 and hence can estimate exposure for each participant over the 11-year follow-up period. PM<sub>10</sub> concentrations in ambient air have, on average, declined in Switzerland during the past decade.<sup>23</sup> In this article, we examine whether age-related decline in lung function was smaller in participants who had a greater decline in exposure to PM<sub>10</sub>.

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## METHODS

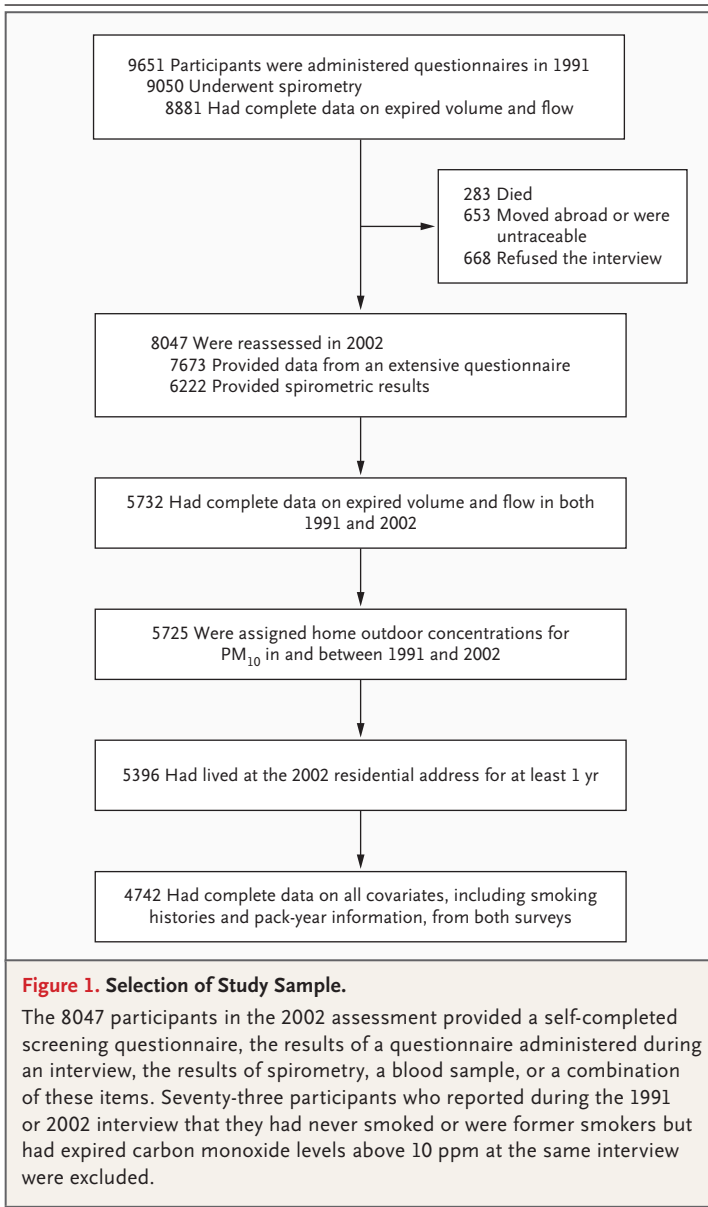
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### STUDY DESIGN AND POPULATION

The methods and selection of the study participants have been described in detail elsewhere.<sup>24,25</sup> The population was a random sample of adults recruited in 1990 with the use of population registries in eight areas of Switzerland. In 1991, health examinations were conducted in 9651 adults who were between 18 and 60 years of age and of whom 51% were women; 8047 participants were reassessed in 2002. Approval of the study was obtained from the Swiss Academy of Medical Sciences and the regional ethics committees, and written informed consent was obtained from all participants. This analysis includes 4742 participants with complete results of spirometry, residential history, smoking history, and PM<sub>10</sub> data from both surveys and the intervening years (Fig. 1). The SAPALDIA team takes responsibility for this report from the study.

### ASSESSMENT OF EXPOSURE TO AIR POLLUTION

The assessment of exposure to PM<sub>10</sub> for individual subjects was performed with the use of a dispersion model (PolluMap, version 2.0) that simulated hourly concentrations of PM<sub>10</sub> with a 200 m by 200 m spatial resolution for 1990 and for 2000<sup>26</sup> (details are in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). We estimated the annual average PM<sub>10</sub> concentrations between 1990 and 2002 for each residential address by developing an algorithm that allowed interpolation of modeled values on the basis of historical trends in central-site measurements between the two years. Thus, each subject was assigned an annual PM<sub>10</sub> concentration every year between 1990 and 2002 according to his or her



residential history. For our exposure indexes, we used the difference in the annual average exposure between 2002 and 1991 and the “interval exposure,” defined as the sum of the annual exposures for each subject for each year of follow-up between their examinations. Just as pack-years represents a cumulative exposure for tobacco smoke, with units of exposure multiplied by time, the units for interval exposure are micrograms per cubic meter-years.

#### SMOKING HABITS AND OTHER RISK FACTORS

Detailed information about current and past smoking habits, exposure to environmental tobacco

smoke, respiratory symptoms, occupational exposure to dust or fumes, and other risk factors was gathered through questionnaires administered during interviews.<sup>27</sup> Subjects classified as never having smoked had smoked fewer than 20 packs of cigarettes and less than 360 g of tobacco in their lifetime. Pack-years smoked before the first examination and those smoked between examinations were assessed. Nonsmoking status was validated by measurement of the carbon monoxide concentration in exhaled breath (EC 50 Micro-Smokerlyzer, Bedfont Scientific).

#### PULMONARY FUNCTION AND ATOPY

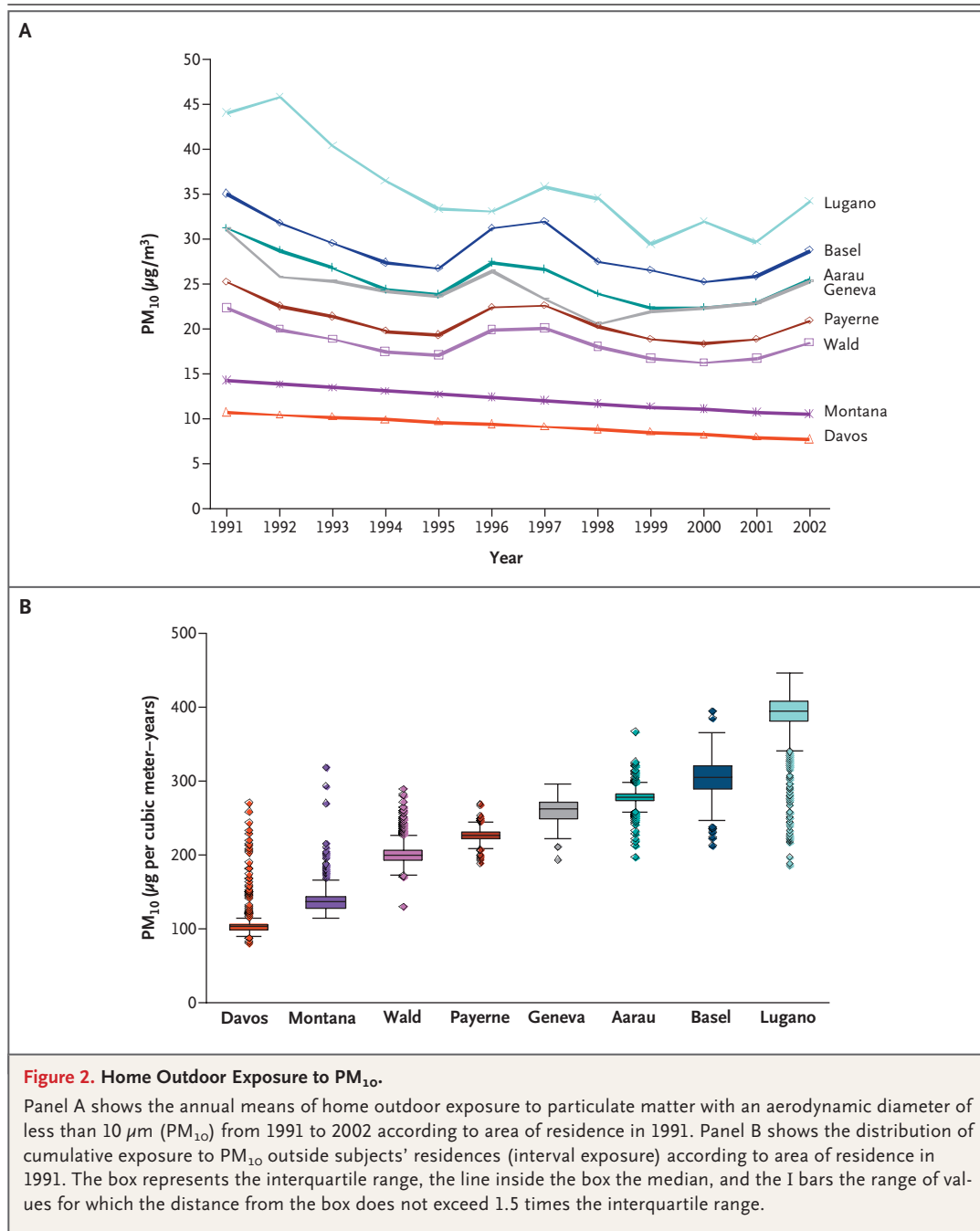
The same spirometers (SensorMedics 2200 SP, SensorMedics) were used in 1991 and 2002. Experimental cross-comparisons of spirometer performance were conducted before and after examination periods. (Spirometers were taken to one place and compared with one another; the same test subjects were used.<sup>28,29</sup>) The protocol for the measurement of expired volumes and flows was outlined in the European Community Respiratory Health Survey and complied with American Thoracic Society recommendations.<sup>27,30</sup> FVC, FEV<sub>1</sub>, and forced expiratory flow between 25% and 75% of the FVC (FEF<sub>25-75</sub>) were recorded. The rate of change in lung function was defined as the difference in each variable between the two examinations, divided by the follow-up time for the participant.

Skin-prick tests were conducted in 1991.<sup>24,27</sup> Participants were classified as having atopy if a wheal developed in response to one or more of the eight inhalant allergens tested (cat, timothy grass, parietaria, birch, house-dust mite, *Alternaria tenuis*, *Cladosporium herbarum*, and dog), with a mean diameter at least 3 mm greater than the mean diameter of the wheal for the negative control.

#### STATISTICAL ANALYSIS

Descriptive analyses of the lung-function variables, PM<sub>10</sub>, smoking status, and other covariates were performed initially. Subsequently, our main goal was to determine whether improvements in air quality or interval exposure were associated with reductions in the annual decline in lung function when controlling for air-pollution concentrations at baseline. Although interval exposure has some theoretical attractiveness, it was highly correlated with change in exposure ( $R^2 > 0.9$ ), which limited our ability to distinguish between them.

Mixed-model regression analyses of the effect of change in exposure and interval exposure to



PM<sub>10</sub> on the rate of change in lung function were adjusted for clustering of residuals within areas; the models were controlled for baseline PM<sub>10</sub>. Covariates selected a priori included age, age squared, sex, height, parental smoking status, seasonal effects (sine and cosine function of day of examination), level of education and change in level, nationality (Swiss or other), the presence or absence of occupational exposure to dust or fumes

at both examinations, smoking status in 2002 (never smoked, formerly smoked, currently smoke), pack-years up to and since 1991, cigarettes per day in both surveys, presence or absence of atopy, baseline body-mass index (BMI) and change in BMI, and the interaction between BMI at baseline and change in BMI. The covariates were included in all reported models except the model for subjects who had never smoked, in which the smok-

<b>Table 1. Characteristics of Participants.*</b>					
	<b>Participants</b>		<b>Nonparticipants (N = 3309)‡</b>	<b>P Value§</b>	
	Included in Analysis (N = 4742)	Excluded from Analysis (N = 999)†		Included vs. Excluded (N = 999)	Included vs. Nonparticipants (N = 3309)
Female sex (%)	54.1	46.8	49.2	<0.001	<0.001
Age in 1991 (yr)	41.5±11.3	38.5±11.7	41.3±12.1	<0.001	0.42
Height (cm)	168.7±8.9	170.1±9.0	168.9±9.2	<0.001	0.35
<b>BMI¶</b>					
In 1991	23.7±3.6	23.8±3.7	24.4±4.2	0.32	<0.001
Change	2.1±2.2	2.0±2.4	NA	0.18	<0.001
<b>Smoking status (%)</b>					
Never smoked, 1991	47.9	41.8	38.5	<0.001	
Never smoked, 2002	46.7	28.1	NA	<0.001	
Current smoker, 1991	29.7	31.3	39.6	0.32	<0.001
Current smoker, 2002	22.3	37.1	NA	<0.001	
<b>No. of pack-years for current smokers in 2002</b>			NA		
Median	26.6	16.0		<0.001	
Interquartile range	13.8 to 42.0	7.6 to 33.0			
<b>No. of cigarettes per day for current smokers in 1991</b>					
Median	20	15	20	<0.001	0.004
Interquartile range	10 to 25	10 to 20	14 to 30		
<b>No. of cigarettes per day for current smokers in 2002</b>			NA		
Median	15	7		<0.001	
Interquartile range	6 to 20	1 to 20			
<b>Father or mother smoked (%)</b>	54.0	54.1	56.8	0.94	0.01
<b>Workplace exposure to dust or fumes (%)</b>					0.001
1991	30.0	30.9	33.6	0.59	
2002	26.3	31.4	NA	<0.001	
<b>Swiss nationality (%)  </b>	87.5	85.5	74.7	0.09	<0.001
<b>Further or professional education by 2002 (%)</b>	27.7	32.5	NA	0.009	
<b>Educational level increased between surveys (%)</b>	17.7	19.7	NA	0.14	
<b>Atopy in 1991 (%)</b>	22.5	25.9	23.4	0.02	0.41
<b>Exposure to ETS in those who had never smoked (%)</b>					
1991	26.7	36.1	32.4	<0.001	<0.001
2002	15.2	13.0	NA	0.37	
<b>Change in PM<sub>10</sub> (µg/m<sup>3</sup>)</b>			NA		
Median	-5.3	-5.6		0.17	
Interquartile range	-7.5 to -4.1	-8.4 to -4.1			
<b>Interval PM<sub>10</sub> (µg/m<sup>3</sup>-yr)</b>			NA		
Median	238	260		0.003	
Interquartile range	197 to 287	200 to 297			
<b>FVC in 1991 (ml)</b>					
Women	3818±612	3887±597	3689±659	0.02	<0.001
Men	5270±822	5314±806	5121±887	0.28	<0.001

Table 1. (Continued.)

	Participants		Nonparticipants (N=3309)‡	P Value§	
	Included in Analysis (N=4742)	Excluded from Analysis (N=999)†		Excluded (N=999)	Nonparticipants (N=3309)
FEV <sub>1</sub> in 1991 (ml)					
Women	3060±542	3149±551	2959±581	0.001	<0.001
Men	4096±723	4167±704	3989±823	0.04	<0.001
FEV <sub>1</sub> >70% of FVC in 1991 (%)					
Women	92.7	94.2	88.7	0.32	<0.001
Men	86.1	89.3	81.3	0.10	<0.001
FEF <sub>25-75</sub> in 1991 (ml/sec)					
Women	3060±1004	3213±1045	2998±1043	0.003	0.06
Men	3776±1297	3923±1324	3731±1426	0.02	0.34

\* Plus-minus values are means ±SD. ETS denotes environmental tobacco smoke, FEF<sub>25-75</sub> forced expiratory flow between 25% and 75% of forced vital capacity (FVC), FEV<sub>1</sub> forced expiratory volume in 1 second, NA not available, and PM<sub>10</sub> particulate matter with an aerodynamic diameter of less than 10 μg.

† Excluded participants had spirometry performed at both visits but were not included in the final analysis because of missing covariate data.

‡ Nonparticipants had spirometry performed in 1991 but either did not have spirometry performed in 2002 or did not participate in the 2002 assessment.

§ P values are for the comparison between participants in the model and excluded participants and for the comparison between participants in the model and nonparticipants. P values were calculated with the use of Fisher's exact test, t-test, or the Wilcoxon rank-sum test.

¶ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

|| Nationality was assessed with a questionnaire administered by the interviewer.

ing variables were replaced with variables for baseline exposure to environmental tobacco smoke and exposure to environmental tobacco smoke between surveys, including the number of hours exposed per day. To assess the linearity of the relationship between the interval exposure to PM<sub>10</sub> and the annual rate of decline in lung function, the mixed model was refitted with the use of a penalized spline of interval exposure allowing up to 10 degrees of freedom for the curve (i.e., a penalty was imposed on the spline coefficients to achieve a smooth fit).

Heterogeneity of effects across study areas was explored with the use of random slopes at the geographic-area level. Since the effect of interval exposure on the rate of decline in lung function may depend on the initial PM<sub>10</sub> concentration, we examined interaction terms between baseline PM<sub>10</sub> concentration and interval exposure. Sensitivity analyses that were conducted included the computation of parsimonious models without covariates for socioeconomic characteristics and atopy and analyses restricted to participants who remained in the area of the 1991 assessment throughout the follow-up period. The potential bias from nonpar-

ticipation in the 2002 assessment was examined by fitting weighted regression models of the data, with weights that were inversely proportional to the probability of participating in the 2002 assessment, given the baseline characteristics of the subjects. Potential modifications of effects according to sex, presence or absence of asthma, and smoking status were also assessed with the use of interaction terms.

Analyses were conducted with the use of SAS 9.1, Stata SE 8.2, and R 2.4 software. P values less than 0.05 and P values less than 0.10 were interpreted as statistically significant for main and interaction effects, respectively.

## RESULTS

Of the participants, 87% were living in the same area in 2002 as they had been in 1991, and 54% had the same address. In general, home outdoor concentrations of PM<sub>10</sub> declined (Fig. 2). The median decline between examinations was 5.3 μg per cubic meter (interquartile range, 4.1 to 7.5), and the decline was greatest for participants living in urban areas and least for those in alpine areas.<sup>26</sup>

The mean interval exposure over the 11-year follow-up period was 238  $\mu\text{g}$  per cubic meter-years (interquartile range, 197 to 287) (Table 1, and Table E1 in the Supplementary Appendix).

Participants in the follow-up were more likely to be women and less likely to be smokers than were nonparticipants (i.e., those who underwent spirometry in 1991 but either did not undergo spirometry in 2002 or did not participate in the 2002 assessment) (Table 1). Participants tended to gain weight, give up smoking, and reduce their exposure to dust or fumes at work and to environmental tobacco smoke.

Lung function declined least in those who had never smoked (Table E2 in the Supplementary Appendix). There was significant heterogeneity in the rate of decline of lung function across areas ( $P < 0.001$ ) (Tables E3 and E4 in the Supplementary Appendix).

In analyses of mixed models adjusted for covariates and baseline exposure, a decrease of 10  $\mu\text{g}$  per cubic meter in the annual average  $\text{PM}_{10}$  concentration between examinations was associated with a 9% decrease in the annual rate of decline in  $\text{FEV}_1$  (i.e., by 3.1 ml; 95% confidence interval [CI], 0.03 to 6.2), a decrease of 0.06 (95% CI, 0.01 to 0.12) in the annual rate of decline in  $\text{FEV}_1$  as a percentage of FVC, and a 16% decrease in the annual rate of decline in  $\text{FEF}_{25-75}$  (i.e., by 11.3 ml per second; 95% CI, 4.3 to 18.2) (Table 2). A similar pattern was seen with interval exposure in models adjusted for baseline exposure, with significant associations with a decline in  $\text{FEV}_1$  ( $P = 0.005$ ) and in  $\text{FEF}_{25-75}$  ( $P = 0.01$ ). A reduction in interval exposure of 109  $\mu\text{g}$  per cubic meter-years (equivalent to a reduction of 10  $\mu\text{g}$  per cubic meter in the annual average during the mean follow-up time of 10.9 years) was associated with a reduction of 6.9 ml (95% CI, 2.1 to 11.7) in the annual decline in  $\text{FEV}_1$  and a 22% reduction in the annual decline in  $\text{FEF}_{25-75}$  (i.e., by 14.0 ml per second; 95% CI, 3.1 to 24.8) (Table 2). In assessing the linearity of the dose-response curve, the mixed model was refitted with the use of a penalized spline of interval exposure. Generalized cross-validation essentially chose a linear fit (Fig. 3).

Observed associations between longitudinal changes in lung-function variables and exposure to  $\text{PM}_{10}$  did not vary significantly across study areas (Tables E5 and E6 in the Supplementary Appendix). No significant modification according to baseline exposure was seen for FVC,  $\text{FEV}_1$ , or  $\text{FEV}_1$

as a percentage of FVC; however, a significant interaction was seen for  $\text{FEF}_{25-75}$  ( $P = 0.04$ ). In all cases, the signs of the interaction indicated that there was less improvement in decline in lung function for the same absolute reduction in interval exposure if the baseline exposure had been higher. For the significant association with  $\text{FEF}_{25-75}$ , the model indicated that a reduction in interval exposure of 109  $\mu\text{g}$  per cubic meter-years would lower the annual rate of decline in this variable by 13.5 ml per second if the assessment started from a baseline exposure of 30  $\mu\text{g}$  per cubic meter, but by 22.4 ml per second if the assessment started from a baseline of 15  $\mu\text{g}$  per cubic meter. No significant interactions were found with sex, presence or absence of atopy, or smoking status.

Similar effects were observed when the analysis was confined to subjects who never smoked, with significant associations for changes in the  $\text{PM}_{10}$  concentration with  $\text{FEF}_{25-75}$  ( $P = 0.03$ ) and marginally significant associations, but with larger effect sizes, for the other lung-function variables ( $P < 0.10$ ). For interval exposure, the effect estimates were larger in subjects who never smoked for all measures of lung function except  $\text{FEV}_1$  as a percentage of FVC and were significant for  $\text{FEV}_1$  ( $P = 0.006$ ) and  $\text{FEF}_{25-75}$  ( $P = 0.047$ ). The analysis that was weighted to account for nonparticipation had results that were similar to those of the main analysis (Table E7 in the Supplementary Appendix).

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## DISCUSSION

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Our data show that improvement in air quality may slow the annual rate of decline in lung function in adulthood. The finding suggests that important changes in the rate of decline in pulmonary function occur across the range of exposures seen in Switzerland, where particle concentrations are relatively low. The old standard of the U.S. Environmental Protection Agency for annual average  $\text{PM}_{10}$ , for example, was 50  $\mu\text{g}$  per cubic meter, and the new European Union limits for  $\text{PM}_{2.5}$  are consistent with  $\text{PM}_{10}$  concentrations in the upper range of those shown in Figure 2, suggesting that further reductions in these standards are likely to improve pulmonary health.

The strongest beneficial effects of a reduction in  $\text{PM}_{10}$  were in the small airways, with a reduction in interval exposure of 109  $\mu\text{g}$  per cubic meter-years associated with a 22% reduction in the

**Table 2. Estimated Effect of Change in PM<sub>10</sub> and of Interval Exposure to PM<sub>10</sub> on Annual Change in Lung Function.\***

Variable	No. of Participants	Decrease in PM <sub>10</sub> of 10 µg/m <sup>3</sup> between 1991 and 2002		Decrease in Interval Exposure of 109 µg/m <sup>3</sup> -yr	
		Effect (95% CI)	P Value	Effect (95% CI)	P Value
<b>All participants</b>	4742				
FVC (ml)		-0.2 (-4.3 to 3.9)	0.91	5.3 (-1.1 to 11.7)	0.10
FEV <sub>1</sub> (ml)		3.1 (0.03 to 6.2)	0.045	6.9 (2.1 to 11.7)	0.005
FEV <sub>1</sub> as a percentage of FVC		0.06 (0.01 to 0.12)	0.02	0.05 (-0.04 to 0.13)	0.27
FEF <sub>25-75</sub> (ml/sec)		11.3 (4.3 to 18.2)	0.001	14.0 (3.1 to 24.8)	0.01
<b>All participants who never smoked</b>	2213				
FVC (ml)		2.2 (-3.4 to 7.9)	0.43	9.9 (1.3 to 18.4)	0.02
FEV <sub>1</sub> (ml)		4.2 (-0.3 to 8.5)	0.06	9.3 (2.6 to 16.0)	0.006
FEV <sub>1</sub> as a percentage of FVC		0.05 (-0.03 to 0.13)	0.18	0.03 (-0.08 to 0.15)	0.59
FEF <sub>25-75</sub> (ml/sec)		11.3 (1.4 to 21.2)	0.03	15.4 (0.2 to 30.6)	0.047

\* Estimates were made after controlling for baseline PM<sub>10</sub>, age, age squared, sex, height, parental smoking status, sine and cosine function of day of examination to control for seasonal effects, level of education in 1991, change in level of education, nationality, self-reported occupational exposure to dust or fumes in 1991 and in 2002, smoking status in 2002 (never smoked, former smoker, or current smoker), pack-years up to 1991, pack-years between 1991 and 2002, number of cigarettes per day in 1991 and in 2002, presence or absence of atopy, body-mass index (BMI) in 1991, change in BMI between 1991 and 2002, and clustering within area. FEF<sub>25-75</sub> denotes forced expiratory flow between 25% and 75% of forced vital capacity (FVC), FEV<sub>1</sub> forced expiratory volume in 1 second, and PM<sub>10</sub> particulate matter with an aerodynamic diameter of less than 10 µg.

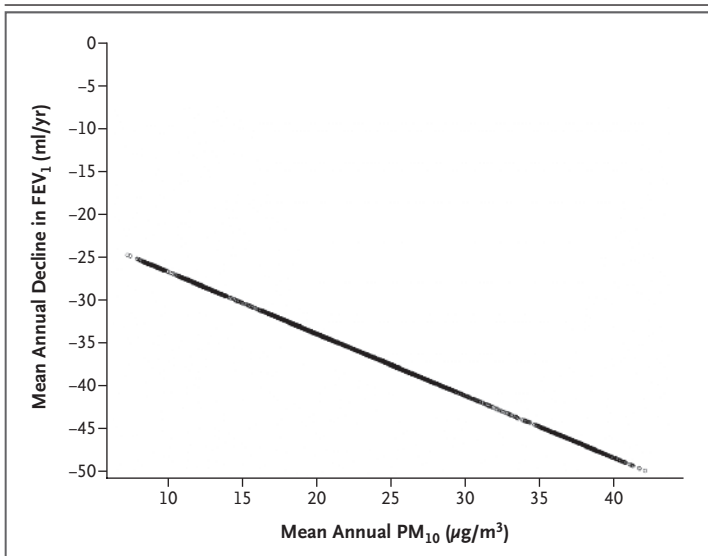
rate of decline of FEF<sub>25-75</sub>, but effects were also observed for FEV<sub>1</sub>. We also found evidence of some persistence of the effect of the baseline level of air pollution on the subsequent annual decline in flow rates. Subjects whose baseline level was higher had a smaller improvement in the rate of decline in FEF<sub>25-75</sub> than did subjects whose baseline level of exposure was lower. This implies some long-lasting effect of historical exposure. Because of the high correlation ( $R^2 > 0.9$ ) between change in PM<sub>10</sub> and interval exposure, we were unable to single out one or the other as the superior measure.

The evidence of long-term effects on lung health of relatively low levels of exposure to air pollution has increased substantially during the past decade.<sup>15,31</sup> Deposition and accumulation of particles in the airways are related to lung anatomy and particle size,<sup>32,33</sup> and the smaller components of PM<sub>10</sub> can penetrate the periphery of the lungs.<sup>14</sup> Inhalation of smoke and other particulates has been associated with increased airway and systemic inflammation,<sup>14,34</sup> as well as with oxidative stress.<sup>35</sup> Animals that were exposed to Boston air and were moved into filtered air had a continuous reduction in oxidative stress in the lung, measured by means of an *in vivo* chemiluminescence assay.<sup>36</sup> An accelerated decline in lung function in persons with higher exposure to air

pollution, as compared with persons with lower exposure, may represent a step toward increased mortality risk.<sup>37</sup>

Exposure to air pollution has been associated with smoking and other socioeconomic factors that are predictors of respiratory health.<sup>38</sup> To address possible confounding, our reported associations were adjusted for a wide range of factors. Since nonparticipants in the second survey differed in a range of characteristics from participants in both surveys, we conducted weighted analyses and found essentially identical results. Also, baseline lung function was not predictive of change in the exposure to PM<sub>10</sub>, suggesting that our exposure variable was not associated with baseline lung health. The strongest effects observed were on lung flows, which are less commonly assessed than expired volumes in studies of respiratory health, because of greater intersubject variability.<sup>39</sup> In longitudinal studies, variability is reduced because each subject serves as his or her own control. Nevertheless, our findings need to be repeated elsewhere or in another follow-up study.

We were able to assign annual estimates of individual exposure to home outdoor PM<sub>10</sub>.<sup>26</sup> The predictions of the dispersion model provide an improvement over predictions based on fixed monitors, because they capture within-area vari-



**Figure 3.** Estimated Effect of Interval Exposure between 1991 and 2002 (Expressed as Mean Annual PM<sub>10</sub>) on Mean Annual Decline in FEV<sub>1</sub>.

The mixed model was refitted with a penalized spline and the use of generalized cross-validation. Interval exposure has been converted to mean annual exposure during the interval for ease of interpretation. PM<sub>10</sub> denotes particulate matter with an aerodynamic diameter of less than 10 µm, and FEV<sub>1</sub> forced expiratory volume in 1 second.

ations in the exposure variable and increase the statistical power. We used PM<sub>10</sub> outside individual residences to estimate exposure, since outdoor exposures at home have been shown to be the most important factor in predicting individual exposure to particulate matter<sup>40,41</sup> and may be a surrogate of interrelated urban pollutants, including fine particles (i.e., PM<sub>2.5</sub>).<sup>22,42</sup> PM<sub>2.5</sub> makes up nearly 80% of PM<sub>10</sub> in most Swiss areas, and nearly 80% of PM<sub>2.5</sub> readily infiltrates indoors.<sup>43-45</sup>

In the 1991 SAPALDIA analysis, we found that an increase of 10 µg per cubic meter in PM<sub>10</sub> was associated with a 3.4% decline in predicted FVC and with evidence of a negative effect on FEV<sub>1</sub>.<sup>6</sup> A negative association between FEV<sub>1</sub> and long-term exposure to PM<sub>10</sub> has been reported in a cross-sectional analysis of the California Adventist Health Study cohort.<sup>9</sup> However, our new results complement the intervention-like study of lung-function development and air-pollution change in children in California,<sup>18</sup> where beneficial effects of moving to cleaner areas were strongest for lung flow (i.e., FEF<sub>25-75</sub> and peak flow). In our study, levels of PM<sub>10</sub> decreased mostly as a result of air-quality interventions in Switzerland and Europe.

In conclusion, our findings provide further support for a causal role of exposure to air pollution in respiratory health. Relatively small reductions in exposure to PM<sub>10</sub> have measurable benefits for lung function, suggesting that a decline in air pollution, even from low levels, may have positive consequences for public health.

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#### APPENDIX

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#### REFERENCES

1. Dockery DW, Pope CA III, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 1993;329:1753-9.
2. Abbey DE, Nishino N, McDonnell WF, et al. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am J Respir Crit Care Med* 1999;159:373-82.
3. Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002;287:1132-41.
4. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Nether-

- lands: a cohort study. *Lancet* 2002;360:1203-9.
5. Nafstad P, Håheim LL, Wisløff T, et al. Urban air pollution and mortality in a cohort of Norwegian men. *Environ Health Perspect* 2004;112:610-5.
  6. Ackermann-Lieblich U, Leuenberger P, Schwartz J, et al. Lung function and long term exposure to air pollutants in Switzerland. *Am J Respir Crit Care Med* 1997;155:122-9.
  7. Tashkin DP, Detels R, Simmons M, et al. The UCLA population studies of chronic obstructive respiratory disease: XI. Impact of air pollution and smoking on annual change in forced expiratory volume in one second. *Am J Respir Crit Care Med* 1994;149:1209-17.
  8. Sekine K, Shima M, Nitta Y, Adachi M. Long term effects of exposure to automobile exhaust on the pulmonary function of female adults in Tokyo, Japan. *Occup Environ Med* 2004;61:350-7.
  9. Abbey DE, Burchette RJ, Knutsen SF, McDonnell WF, Lebowitz MD, Enright PL. Long-term particulate and other air pollutants and lung function in nonsmokers. *Am J Respir Crit Care Med* 1998;158:289-98.
  10. Tockman MS, Pearson JD, Fleg JL, et al. Rapid decline in FEV<sub>1</sub>: a new risk factor for coronary heart disease mortality. *Am J Respir Crit Care Med* 1995;151:390-8.
  11. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996;313:711-5.
  12. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* 2005;127:1952-9.
  13. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003;58:388-93.
  14. Donaldson K, Stone V, Seaton A, MacNee W. Ambient particle inhalation and the cardiovascular system: potential mechanisms. *Environ Health Perspect* 2001;109:Suppl 4:523-7.
  15. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med* 2006;173:667-72.
  16. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645-8.
  17. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease: the Lung Health Study. *Am J Respir Crit Care Med* 2000;161:381-90.
  18. Avol EL, Gauderman WJ, Tan SM, London SJ, Peters JM. Respiratory effects of relocating to areas of differing air pollution levels. *Am J Respir Crit Care Med* 2001;164:2067-72.
  19. Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057-67. [Erratum, *N Engl J Med* 2005;352:1276.]
  20. Jerrett M, Arain A, Kanaroglou P, et al. A review and evaluation of intraurban air pollution exposure models. *J Expo Anal Environ Epidemiol* 2005;15:185-204.
  21. Jerrett M, Buzzelli M, Burnett RT, DeLuca PF. Particulate air pollution, social confounders, and mortality in small areas of an industrial city. *Soc Sci Med* 2005;60:2845-63.
  22. Brunekreef B, Forsberg B. Epidemiological evidence of effects of coarse airborne particles on health. *Eur Respir J* 2005;26:309-18.
  23. Modelling of PM<sub>10</sub> and PM<sub>2.5</sub> ambient concentrations in Switzerland 2000 and 2010. Bern, Switzerland: Swiss Agency for the Environment, Forests and Landscape SAEFL, 2003. (Accessed November 9, 2007, at <http://www.dehaan.ch/pubs/EnvDoc169.pdf>.)
  24. Martin BW, Ackermann-Lieblich U, Leuenberger P, et al. SAPALDIA: methods and participation in the cross-sectional part of the Swiss Study on Air Pollution and Lung Diseases in Adults. *Soz Präventivmed* 1997;42:67-84.
  25. Ackermann-Lieblich U, Kuna-Dibbert B, Probst-Hensch NM, et al. Follow-up of the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA 2) 1991-2003: methods and characterisation of participants. *Soz Präventivmed* 2005;50:245-63.
  26. Liu L-JS, Curjuric I, Keidel D, et al. Characterisation of source-specific air pollution exposure for a large population-based Swiss cohort (SAPALDIA). *Environ Health Perspect* 2007;115:1638-45.
  27. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-60.
  28. Künzli N, Ackermann-Lieblich U, Keller R, Perruchoud AP, Schindler C. Variability of FVC and FEV<sub>1</sub> due to technician, team, device and subject in an eight centre study: three quality control studies in SAPALDIA. *Eur Respir J* 1995;8:371-6.
  29. Künzli N, Kuna-Dibbert B, Keidel D, et al. Longitudinal validity of spirometers — a challenge in lung function follow-up studies. *Swiss Med Wkly* 2005;135:503-8.
  30. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107-36.
  31. Dockery DW, Brunekreef B. Longitudinal studies of air pollution effects on lung function. *Am J Respir Crit Care Med* 1996;154:S250-S256.
  32. Pinkerton KE, Green FH, Saiki C, et al. Distribution of particulate matter and tissue remodeling in the human lung. *Environ Health Perspect* 2000;108:1063-9.
  33. Kim CS, Hu SC. Regional deposition of inhaled particles in human lungs: comparison between men and women. *J Appl Physiol* 1998;84:1834-44.
  34. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004;59:574-80.
  35. Nel A. Atmosphere: air pollution-related illness: effects of particles. *Science* 2005;308:804-6. [Erratum, *Science* 2005;309:1326.]
  36. Evelson P, González-Flecha B. Time course and quantitative analysis of the adaptive response to 85% oxygen in the rat lung and heart. *Biochim Biophys Acta* 2000;1523:209-16.
  37. Engström G, Lind P, Hedblad B, et al. Lung function and cardiovascular risk: relationship with inflammation-sensitive plasma proteins. *Circulation* 2002;106:2555-60.
  38. Finkelstein MM, Jerrett M, DeLuca P, et al. Relation between income, air pollution and mortality: a cohort study. *CMAJ* 2003;169:397-402.
  39. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991;144:1202-18.
  40. Rojas-Bracho L, Suh HH, Koutrakis P. Relationships among personal, indoor, and outdoor fine and coarse particle concentrations for individuals with COPD. *J Expo Anal Environ Epidemiol* 2000;10:294-306.
  41. Liu L-JS, Box M, Kalman D, et al. Exposure assessment of particulate matter for susceptible populations in Seattle. *Environ Health Perspect* 2003;111:909-18.
  42. Sarnat JA, Schwartz J, Catalano PJ, Suh HH. Gaseous pollutants in particulate matter epidemiology: confounders or surrogates? *Environ Health Perspect* 2001;109:1053-61.
  43. Mathys P, Stern WB, Oglesby L, et al. Elemental analysis of airborne particulate matter by ED-XRF within the European EXPOLIS study. *ICP Information Newsletter* 2001;27(3):190-5.
  44. Oglesby L, Künzli N, Rössli M, et al. Validity of ambient levels of fine particles as surrogate for personal exposure to outdoor air pollution — results of the European EXPOLIS-EAS Study (Swiss Center Basel). *J Air Waste Manag Assoc* 2000;50:1251-61.
  45. Larson T, Gould T, Simpson C, Liu L-JS, Claiborn C, Lewtas J. Source apportionment of indoor, outdoor, and personal PM<sub>2.5</sub> in Seattle, Washington, using positive matrix factorization. *J Air Waste Manag Assoc* 2004;54:1175-87.

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