Eur Respir J
1992, 5, 553–559

# Time trends in repeated spirometry in children

G. Hoek*†, B. Brunekreef*

*Time trends in repeated spirometry in children. G. Hoek, B. Brunekreef.*
**ABSTRACT: In a study on acute health effects of air pollution in the Netherlands, pulmonary function has been measured repeatedly in children aged 7–11 yrs. In study periods of approximately 3 months, 6–10 tests have been made in a group of 1,621 children. The spirometric data have been examined for the presence of trends of pulmonary function with day of study, independent of air pollution.**

**Peak expiratory flow (PEF) increased more than expected from normal lung growth, whereas for maximal mid-expiratory flow (MMEF) a decrease with time was observed. For forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$) a smaller than expected increase with time was observed. The observed deviation from the expected pattern was larger for the children with a one week interval between successive tests than for the children with a three week interval. For FVC and $FEV_1$ a non-linear relationship with time was observed, for PEF and MMEF this relationship was approximately linear.**

**The particular changes of spirometric variables with time need to be taken into account when repeated lung function tests are performed to investigate acute effects of air pollution exposure.**
*Eur Respir J., 1992, 5, 553–559.*

* Dept of Epidemiology and Public Health, and † Dept of Air Pollution, University of Wageningen, Wageningen, The Netherlands.

Correspondence: G. Hoek
Dept of Epidemiology and Public Health
University of Wageningen
P.O. Box 238
6700 AE Wageningen
The Netherlands

Keywords: children
growth
lung function
training

Received: July 24 1991
Accepted after revision January 20 1992

Epidemiological studies of acute health effects of air pollution frequently employ repeated testing of pulmonary function [1]. Spirometry is widely used. These studies are characterized by a limited number of tests, usually 10 or less, in a relatively short time period (typically a few weeks to 2 months). In the statistical analysis of the data from such studies, individual regression analysis is often used [2–4]. For each subject, pulmonary function is regressed on air pollution exposure. In these studies there may be confounding effects due to trends of pulmonary function with time, unrelated to environmental physical, chemical or biological agents [5, 6]. In summer camp studies, with daily measurements of pulmonary function, a decrease of forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$) has been noted during the first 5–6 tests [5]. The initial decrease was followed by an increase [5]. In another summer camp study, an increase of peak expiratory flow (PEF) and a decrease of $FEV_1$ was observed during the first week [6]. In a study of peak flow variability, using mini-Wright peak flow meters between 2–4 times daily during two weeks, significantly lower values were observed on the first two days [7]. In the subsequent analysis the data obtained on these two days were not used [7].

Factors which may contribute to these trends are lung growth in children, lung ageing in adults, learning effects in the performance of the test and decreasing motivation of the subjects performing the test. Even for the typically short study period the effect of lung growth in children can be comparable to the magnitude of health effects observed in earlier air pollution episode studies [8]. The annual decrease of pulmonary function in adults is less than the growth observed in children. Learning and motivation effects can play a role in these studies, due to the short interval between tests and the nature of spirometry. Spirometry depends upon the effort and co-operation of the subject performing the test. Growth and ageing would be expected to lead to approximately linear changes in these short studies. A learning effect would be expected to lead to a larger increase of pulmonary function during the first tests. Decreasing motivation would lead to lower pulmonary function values with time.

This paper presents an evaluation of the occurrence of time trends in spirometric variables in a study of the acute effects of air pollution on pulmonary function of children living in the Netherlands [9]. This epidemiological study is an extension of earlier air pollution episode studies conducted in the Netherlands [8, 10].

## Methods

### *Study design*

Our earlier episode studies consisted of one baseline measurement, followed by measurements during and some time after an episode. To obtain more information about both the variation of pulmonary function independent of air pollution and the time course of an effect during and after an episode, it was decided to perform spirometry more frequently. Pulmonary function was, therefore, measured at regular intervals, independent of the air pollution concentration. When high concentrations of $SO_2$, $NO_2$ or $O_3$ were expected, additional measurements were made. In the first part of the study, each child was tested 10 times, with an interval of 1 week between successive tests. In the second part of the study, 6–10 tests were made with an interval of 2–3 weeks. Finally, at two schools, measurements have been performed according to our earlier protocol [8, 10]. It consisted of one baseline measurement, a sham episode measurement approximately 2.5 months later and a follow-up test approximately 2.5 weeks after the sham episode measurement.

### *Population*

From October, 1987 until March, 1990, 17 primary schools were entered in the study sequentially. All children of grades 4 to 7 (age 7–11 yrs) were invited to participate. Out of 1,693 children eligible for the study, 1,621 children (96%) participated. The children were living in four different towns in the Netherlands. Deurne and Venlo are non-industrial communities in the south-east of the country, Enkhuizen is a non-industrial community in the north-west. In Nijmegen, a city of 150,000 inhabitants in the east of the country, a school in the inner city was selected.

### *Pulmonary function measurements*

Spirometry was performed in the schools of the participating children according to the criteria of the European Community for Coal and Steel (ECCS) [11]. Briefly, a Vicatest-5 dry spirometer was used to obtain volume and (through differentiation) flow parameters of a forced expiratory manoeuvre. The spirometer was connected with automatic data acquisition equipment. For each child at least three acceptable efforts had to be collected. The highest forced vital capacity (FVC), forced expiratory volume in one second ($FEV_1$) and peak expiratory flow rate (PEF) were selected from the available curves. The highest maximal mid-expiratory flow (MMEF) was selected from a manoeuvre with a FVC within 5% or 100 ml of the highest FVC. The lung function technician evaluated the volume time curves on a paper recorder and the automatically calculated pulmonary function variables of the present and previous manoeuvres. A more detailed description of the protocol has been published previously [12]. The tests were performed between 8.30 am and 4 pm. The order of testing of the different school grades was the same each test day. In this paper only FVC, $FEV_1$, PEF and MMEF will be discussed.

### *Statistical methods*

The relationship between pulmonary function and day of study was analysed by individual linear regression. For each child a linear regression model was calculated, with a pulmonary function variable as the dependent, and day of study as the independent variable. The distribution of individual regression coefficients was then evaluated. Deviation of the mean of the distribution of individual regression coefficients from zero has been tested with a t-test. Two-sided significance levels are reported in this paper. Day of study was entered as the number of days since the start of the study for the child. A linear regression analysis was performed, because the expected change is a small, linear increase with time due to lung growth. The distribution of coefficients was evaluated separately for children measured with an interval of 1 week and children measured with an interval of 2 or 3 weeks between successive tests. To obtain some stability of the estimated individual regression coefficients, only children with more than four measurements were included in the analysis.

These analyses were repeated taking into account two measures of the quality of the information obtained from an individual child. Each coefficient was weighted with the inverse of the standard error of the regression coefficient or the root mean square error of the individual regression model. The distribution of the weighted coefficients was compared to the unweighted distribution.

The observed changes with time have been compared with data obtained from a longitudinal study, in which children were measured four times over a 2.5 yr period [13]. In that study, children aged 6–11 yrs were tested with the same equipment and protocol [12]. The study was designed to evaluate respiratory effects of indoor air pollution. A more detailed description of the study has been published previously [14]. The lung growth data from that study have been shown to agree closely with regression coefficients of cross-sectional analyses of pulmonary function on age in the same age group [8].

The appropriateness of the linear trend assumption was investigated by repeating the regression analysis without the first and the first two tests, respectively. Moreover, plots of group mean pulmonary function level *versus* day of study were made. Since interindividual variation of pulmonary function is large, the same group of children has been compared for the different days of study. Therefore, only children with valid measurements for all tests were included in the graphical analysis.

Finally, the distribution of regression slopes has been investigated in subgroups defined by sex, age and presence or absence of chronic respiratory symptoms, respectively. The group of children with chronic respiratory symptoms comprised children with doctor diagnosed asthma ever, wheeze in the last year, shortness of breath in the last year or attacks of shortness of breath with wheeze in the last year, as reported by the parents of the children on a self-completion version of the World Health Organization (WHO) children's questionnaire [15]. The independent influence of these three variables has been evaluated by performing a multiple linear regression analysis, with the regression slope as the dependent variable and sex, age and symptom status as independent variables.

## Results

At the first eight schools, tests were performed once a week. Air pollution levels were low during all test sessions at seven of the eight schools. Therefore, only the data from these seven schools were further analysed for evaluation of time trends. At the other nine schools pulmonary function tests were made every two or three weeks. There were insufficient numbers of children measured with a two weeks interval who experienced low air pollution during the whole test period. There were three schools which were visited every three weeks with low air pollution levels during and before all test sessions. Therefore, only these three schools were included in subsequent analyses. At these three schools, six test sessions were performed. In table 1 a description of the populations used for the presented analyses is given. The three winters included in the study were mild with only a few days with minimum temperatures slightly below 0°C. Daily average $SO_2$ concentration during the pulmonary function test days ranged from 2–81 $\mu g \cdot m^{-3}$, well below concentration levels at which health effects can be expected [16].

In table 2 the results of the linear regression analysis of pulmonary function on day of study are shown. All regression coefficients have been transformed in estimated changes per year. The observed mean change with day of study was different for the various pulmonary function variables. For PEF an increase was observed, for MMEF a decrease was observed. For FVC and $FEV_1$ the results were more mixed. There

Table 1. – Population characteristics of air pollution acute pulmonary function effects study, the Netherlands; children included in analysis of trends of pulmonary function

| | 1 week interval | | 3 week interval | |
|---|---|---|---|---|
| | Mean (SD) | Range | Mean (SD) | Range |
| Age yrs | 9 (1.2) | 6.8–12.4 | 9 (1.2) | 7–12.4 |
| Valid tests n | 9 (1.3) | 5–10 | 6 (0.5) | 5–6 |
| Children with >4 valid tests n (%) | 679 | (95%)* | 244 | (80%)* |

*: percentage of all participating children. SD: standard deviation.

Table 2. – Mean change of pulmonary function with day of study, in relation to the interval between repeated tests

| Interval | Unweighted | | Weighted by 1/SE(B) | | Weighted by 1/RMSE | |
|---|---|---|---|---|---|---|
| **1 week (n=679)** | | | | | | |
| FVC $ml \cdot yr^{-1}$ | 27† | (25)†† | 28 | (21) | 12 | (23) |
| $FEV_1$ $ml \cdot yr^{-1}$ | -38 | (22) | -39* | (18) | -44* | (19) |
| PEF $ml \cdot s^{-1} \cdot yr^{-1}$ | 2218* | (115) | 2030* | (102) | 2051* | (108) |
| MMEF $ml \cdot s^{-1} \cdot yr^{-1}$ | -265* | (62) | -317* | (46) | -302* | (49) |
| **3 weeks (n=224)** | | | | | | |
| FVC $ml \cdot yr^{-1}$ | 79* | (22) | 71* | (21) | 65* | (21) |
| $FEV_1$ $ml \cdot yr^{-1}$ | 30 | (22) | 43* | (20) | 35 | (21) |
| PEF $ml \cdot s^{-1} \cdot yr\text{-}1$ | 729* | (121) | 665* | (110) | 668* | (111) |
| MMEF $ml \cdot s^{-1} \cdot yr^{-1}$ | -148* | (66) | -120* | (51) | -130* | (50) |
| **6 weeks (n=75)** | | | | | | |
| FVC $ml \cdot yr^{-1}$ | 54 | (39) | -58 | (103)# | -51 | (93)# |
| $FEV_1$ $ml \cdot yr^{-1}$ | 51 | (42) | 137* | (44) | 132* | (40) |
| PEF $ml \cdot s^{-1} \cdot yr^{-1}$ | 543* | (251) | 784* | (282)## | 803* | (316)## |
| MMEF $ml \cdot s^{-1} \cdot yr^{-1}$ | -54 | (112) | 372* | (176)## | 383* | (179)## |

†: mean of individual regression coefficients; ††: standard error (SE) of the mean of individual regression coefficients; 1/SE(B): coefficients weighted with the inverse of the standard error of the coefficients; 1/RMSE: coefficients weighted with the inverse of the root mean square error of the individual regression model; #: without one extreme negative outlier mean (SE) were 43 (26) and 40 (29), respectively; ##: several positive outliers, not present in the unweighted distribution; *: $p<0.05$ (two-sided t-test); FVC: forced vital capacity; $FEV_1$: forced expiratory volume in one second; PEF: peak expiratory flow; MMEF: maximal mid-expiratory flow.

were some remarkable differences between the results for the group with weekly measurements and the group with measurements every three weeks. The increase in PEF was much less for the children measured every three weeks. For FVC and $FEV_1$ increases were observed in the three weeks group. The MMEF decrease was lower in the three weeks group. The results of the weighted and unweighted regression slopes were similar. In general, the standard errors were slightly lower for the weighted coefficients. However, when the number of test days was small, several extreme outliers occurred in the weighted analyses. This appeared to be caused by children with low variability of pulmonary function. Adjustment for the potential effect of air pollution on the observed time trends by including daily average $SO_2$ concentration of the test day in the individual regression models, did not materially change the presented associations. For example, the mean (SE) of adjusted coefficients for the children measured every week were 21 (29), -31 (25), 2,260 (124) and -240 (67) $ml \cdot s^{-1}$ per year for FVC, $FEV_1$, PEF and MMEF, respectively.

In table 3 the estimated changes from this study are compared with data from a longitudinal study [13] in the same age group made at our department with the same equipment and protocol. The observed PEF increase in this study was much larger than would be expected from normal lung growth. The observed change in FVC and $FEV_1$ was less than expected for all groups. Clearly, the change in MMEF is contrary to what would be expected from lung growth. The PEF changes observed for the children measured three times in a three months study period, were only slightly larger than the expected change. The changes for FVC, $FEV_1$ and MMEF were still less than expected.

The time trends were similar for boys and girls, the youngest and the oldest children, and for children with and without chronic respiratory symptoms. In table 4 the results of multiple linear regression analysis with the regression slopes as the dependent variable and sex, age and symptom status and a dummy variable defining the interval between tests as independent variables, are shown. None of the variables was significantly related to the observed change of pulmonary function with time, except the time interval between tests, which was significantly related to the increase of PEF with time.

To adjust for potential training effects, sometimes the first or first two tests are not included in the analysis. In table 5 the results of individual regression analysis of pulmonary function on day of study are shown for all test days, all days without the first test and all days except the first two tests, respectively. For PEF and MMEF the coefficients do not change much, but in the 1 week interval group the coefficients for FVC and $FEV_1$ do change drastically, indicating non-linearity of their changes with time.

Table 3. – Mean change of pulmonary function observed with different intervals of repeated measurements, compared to expected lung growth

| | 1 week | 3 weeks | 6 weeks* | 2.5 yrs** |
|---|---|---|---|---|
| FVC $ml \cdot yr^{-1}$ | 27 (25) | 79 (22) | 54 (39) | 233 (3) |
| $FEV_1$ $ml \cdot yr^{-1}$ | -38 (22) | 30 (22) | 51 (42) | 182 (3) |
| PEF $ml \cdot s^{-1} \cdot yr^{-1}$ | 2218 (115) | 729 (121) | 543 (251) | 459 (10) |
| MMEF $ml \cdot s \cdot yr^{-1}$ | -265 (62) | -148 (66) | -51 (112) | 150 (5) |
| n | 679 | 224 | 75 | 420 |

Data are presented as mean (SE). *: children from 2 schools with 3 tests in a 3 months period (baseline, sham episode and follow-up test); **: observed in a longitudinal study of children [13]. For abbreviations see legend to table 2.

Table 4. – Association of observed change of pulmonary function with personal characteristics of the child

| | Sex† | Age†† yrs | Respiratory# symptoms | Interval## |
|---|---|---|---|---|
| FVC $ml \cdot yr^{-1}$ | 25 (40) | 21 (17) | 45 (55) | -55 (47) |
| $FEV_1$ $ml \cdot yr^{-1}$ | -3 (36) | 0 (15) | 38 (50) | -67 (43) |
| PEF $ml \cdot s^{-1} \cdot yr^{-1}$ | 327 (187) | -72 (78) | -193 (259) | 1506* (219) |
| MMEF $ml \cdot s^{-1} \cdot yr^{-1}$ | -111 (102) | -76 (42) | 64 (142) | -102 (120) |

Data are presented as mean of individual regression coefficients (SE). *: $p<0.05$ (two-sided t-test); †: boy=0, girl=1; ††: age in years, calculated from the exact day of birth and the start day of the study for the child; #: presence of one or more chronic respiratory symptoms coded as 1, absence of these symptoms as 0 (text); ##: one week interval coded as 1, three week interval as 0. For abbreviations see legend to table 2.

Table 5. – Mean change of pulmonary function with day of study; effect of excluding the first or first two tests

| Interval | All tests | Test 1 excluded | Test 1 and 2 excluded |
|---|---|---|---|
| **1 week (n=679)** | | | |
| FVC ml·yr⁻¹ | 27 (25) | 115 (29) | 187 (32) |
| $FEV_1$ ml·yr⁻¹ | -38 (22) | 30 (25) | 75 (29) |
| PEF ml·s⁻¹·yr⁻¹ | 2218 (115) | 2283 (130) | 2208 (152) |
| MMEF ml·s⁻¹·yr⁻¹ | -265 (62) | -175 (70) | -185 (84) |
| **3 weeks (n=224)** | | | |
| FVC ml·yr⁻¹ | 79 (22) | 66 (30) | 40 (39) |
| $FEV_1$ ml·yr⁻¹ | 30 (22) | 29 (29) | 2 (38) |
| PEF ml·s⁻¹·yr⁻¹ | 729 (121) | 686 (149) | 578 (198) |
| MMEF ml·s⁻¹·yr⁻¹ | -148 (66) | -159 (77) | -43 (93) |

Data are presented as mean of individual regression coefficients (SE). For abbreviations see legend to table 2.

After exclusion of the first two measurements, approximately the expected growth rate is observed for FVC. The increase of $FEV_1$ is still less than expected from lung growth. In figures 1 and 2 the mean pulmonary function *versus* day of study is shown for the group of children having valid test results for all days of study. These plots confirm the results shown in table 5.

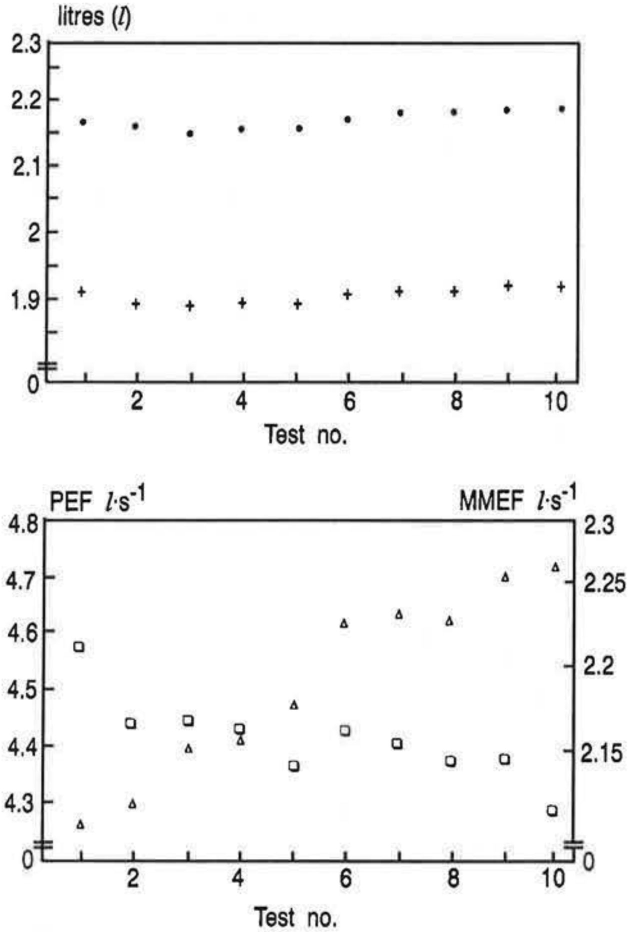


Fig. 1. – Group mean pulmonary function and test number: 1 week interval (n=334). ●: FVC; +: $FEV_1$; Δ: PEF; □: MMEF. FVC: forced vital capacity; $FEV_1$: forced expiratory volume in one second; PEF: peak expiratory flow; MMEF: maximal mid-expiratory flow.

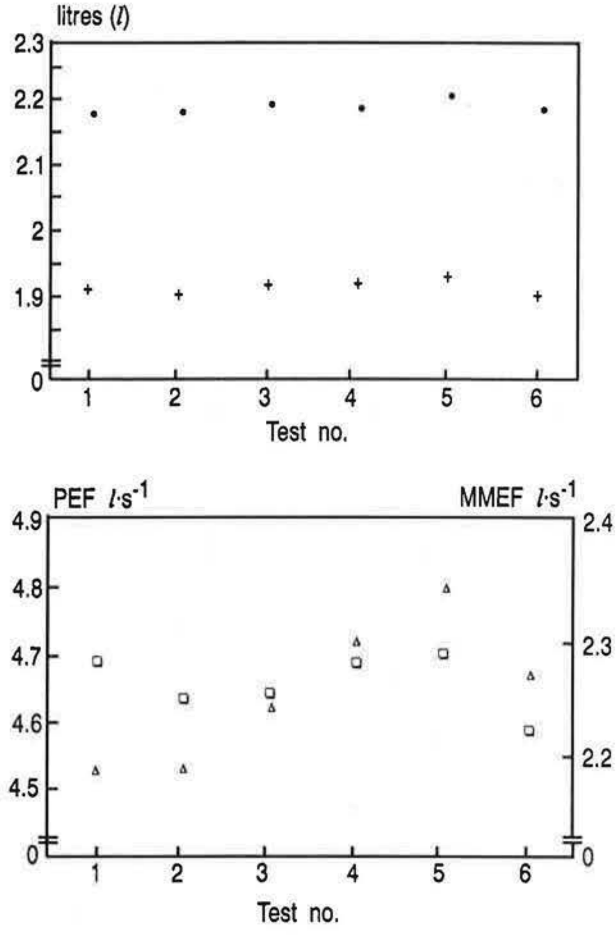


Fig. 2. – Group mean pulmonary function and test number: 3 week interval (n=155). ●: FVC; +: $FEV_1$; Δ: PEF; □: MMEF. For abbreviations see legend to figure 1.

## Discussion

This study has shown that repeated pulmonary function testing with short time intervals between successive tests yielded estimated changes of pulmonary function with time which were different from those expected from normal lung growth. Peak flow increased more than expected. For MMEF a decrease with time was observed. For FVC and $FEV_1$ a smaller than expected increase with time was observed. The observed deviation from the pattern expected from normal lung growth was larger for the children with a one week interval between successive tests than for the children with a three week interval. The changes with day of study for PEF and MMEF could be described by a linear relationship. For FVC and $FEV_1$ this was only possible after ignoring the first two tests.

When exposure variables of interest are also associated with time since start of the study, the observed relationship between pulmonary function and exposure can be biased. An example of this may be a study of the acute health effects of ambient ozone pollution, in which ozone concentrations may be higher or lower at the end of the study due to meteorological factors. Adjustment for this bias has to take into account the observed patterns with time. The presented analyses suggest that PEF and MMEF can be detrended by including a linear relationship with time since the start of the study. For FVC and $FEV_1$, either a non-linear relationship with time needs to be modelled or, probably more appropriately, the first two observations need to be ignored.

Training effects in repeated pulmonary function testing have been described previously [5–7]. In a number of summer camp studies, with daily measurements of pulmonary function, a decrease of FVC and $FEV_1$ and MMEF during the first 5–6 tests has been noted. The initial decrease was followed by an increase [5, 17]. In one of the three study populations described, an increase of peak flow was observed in the latter phase of the two week study period [17]. In another summer camp study, an increase of PEF and a decrease of $FEV_1$ was observed during the first week [6]. This pattern is almost identical to the pattern in our study. In two other studies made at our department, mini-Wright peak flow meters were used for repeated testing, with an interval of approximately one week between successive tests [9, 18]. In these studies no unexpectedly large increase with time was observed [18]. In a panel study of 73 children with chronic respiratory symptoms, peak flow was measured at home twice daily with mini-Wright peak flow meters during two months. Preliminary analyses suggest significant training effects during the first few days. This latter observation is consistent with the results from a study of daily peak flow variability over a period of two weeks [7]. Differences between these studies are not readily explainable. It may be that training effects are less pronounced with mini-Wright meters due to the simpler equipment or a somewhat different technique of performing the test. Different study settings (interval between tests, presence of a lung function technician) may also explain differences.

The physiological interpretation of the observed results is not simple. We believe that the following mechanisms play a role in explaining the patterns observed in this study: training effect of PEF, negative effort dependence and lung growth. We believe the observed pattern of PEF is the driving force of the changes noted in the other variables, since the pattern noted for PEF is most consistent for different schools and subgroups. It appears that the children were able to increase their maximal effort in the course of the study. Maybe some physiological training of (the control over) respiratory muscles occurs, resulting in higher peak flows at later tests. This hypothesis is supported by the larger increase of PEF observed in the group of schools with an interval of one week. In a short-term ventilatory muscle training programme including 30 min of forced expiratory and inspiratory manoeuvres, large increases (55%) of expiratory and inspiratory maximal pressures were observed. Only a modest (4%) increase of VC was noted [19, 20]. There are several examples of pulmonary function technicians improving their own pulmonary function by performing regular pulmonary function tests themselves [20].

The pattern for FVC, $FEV_1$ and MMEF might be explained by negative effort dependence [19, 21–23]. Negative effort dependence is partly an artifact of measuring lung volumes by exhaled volumes at the mouth. Higher efforts cause higher alveolar pressures, leading to compression of the airway gas. When lung volumes are measured at the mouth, the compression part of the change in actual lung volume is not measured. A second mechanism is denoted as true effort dependence [19, 21] and has been related to dynamic compression of the airways [19]. Submaximal efforts, therefore, lead to higher flows in the effort independent portion of the flow volume curve [19, 21, 23]. The magnitude of the effect has been illustrated in a number of studies. Krowka *et al.* [21] noted that in a large group of adult patients FVC, $FEV_1$, MMEF and $MEF_{50\%}$ were, respectively, 2.3, 2.7, 3.5 and 3.4% less for maximal efforts compared to the value from the highest $FEV_1$-curve. Medinger [22] noted in a group of 121 adult patients a significantly lower $FEV_1$ from curves with the highest PEF. Consistent with this hypothesis is that the deviance from growth-predicted increase in this study with time is larger for $FEV_1$ than for FVC. This is not consistent with less inspiration or earlier termination of the manoeuvre. After removing the first two tests for FVC an increase close to expected from normal growth was observed. For $FEV_1$, the observed increase is still less than expected from growth. This may be a result of the larger impact of the described mechanism on $FEV_1$. The observed decrease of MMEF may also result from the larger influence of negative effort dependence on this variable. Lung growth apparently was not sufficiently large to compensate for this effect in the relatively short study periods.

In summary, this study has shown unexpected changes of spirometric pulmonary function with day of study, when children were tested repeatedly in a short period. The analyses presented here, suggest the necessity of taking into account potential confounding effects of patterns of pulmonary function with time.

*Acknowledgements:* This study would not have been possible without the co-operation of the schools, the children and their parents. M. Ridder, S. van der Zee, J. Douwes, S. de Wind, F. Cottaar, P. Kosterink, E. Timmer and F. in 't Veld contributed to the pulmonary function measurements. The helpful comments of P.H. Quanjer (University of Leiden) and M. Raizenne (Health and Welfare, Ottawa, Canada) on an earlier version of this manuscript are greatly appreciated.

## References

1. Lippmann M. – Health effects of ozone. A critical review. *J Air Pollut Control Assoc*, 1989; 39: 672–695.
2. Spektor DM, Lippmann M, Lioy PJ *et al.* – Effects of ambient ozone on respiratory function in active, normal children. *Am Rev Respir Dis*, 1988; 137: 313–320.
3. Lioy PJ, Wollmuth TA, Lippmann M. – Persistence of peak flow decrement in children following ozone exposures exceeding the national ambient air quality standard. *J Air Pollut Control Assoc*, 1985; 35: 1068–1071.
4. Higgins ITT, D'Arcy JB, Gibbons DI, Avol EL, Gross KB. – Effect of exposures to ambient ozone on ventilatory lung function in children. *Am Rev Respir Dis*, 1990; 141: 1136–1146.
5. Raizenne ME, Haines DA. – Trends in repeated spirometry (Abstract). *Am Rev Respir Dis*, 1990; 141 (Suppl.): A331.
6. Avol EL, Trim SC, Little DE *et al.* – Time-related and ozone-related lung function changes in children attending a Southern California summer camp (Abstract). *Am Rev Respir Dis*, 1990; 141 (Suppl.): A69.
7. Quackenboss JJ, Lebowitz MD, Krzyzanowski M. – The normal range of diurnal changes in peak expiratory flow rates. *Am Rev Respir Dis*, 1991; 143: 323–330.
8. Brunekreef B, Lumens M, Hoek G, Hofschreuder P, Fischer P, Biersteker K. – Pulmonary function changes associated with an air pollution episode in January 1987. *J Air Pollut Control Assoc*, 1989; 39: 1444–1447.
9. Lebret E, Hoek G, Aardema JB. – A study on the effects of air pollution episodes on pulmonary function and respiratory symptoms in children and adults. *In*: Brasser LJ, Mulder WC, Eds. Proceedings of the World Clean Air Congress 1989. The Hague, 1989; vol. 1; pp. 19–24.
10. Dassen W, Brunekreef B, Hoek G *et al.* – Decline in children's pulmonary function during an air pollution episode. *J Air Pollut Control Assoc*, 1986; 36: 1223–1227.
11. Quanjer PH. – Standardized lung function testing. *Bull Eur Physiopathol Respir*, 1983; 19 (Suppl.): 1–95.
12. Houthuijs D, Remijn B, Brunekreef B, Koning R de. – Estimation of maximum expiratory flow-volume variables in children. *Pediatric Pulmonol*, 1989; 6: 127–132.
13. Smeets M, Brunekreef B, Dijkstra L, Houthuijs D. – Lung growth of pre-adolescent children. *Eur Respir J*, 1990; 3: 91–96.
14. Dijkstra L, Houthuijs D, Brunekreef B, Akkerman I, Boleij JSM. – Respiratory health effects of the indoor environment in a population of Dutch children. *Am Rev Respir Dis*, 1990; 142: 1172–1178.
15. Florey C du V, Leeder SR. – Methods for cohort studies of chronic airflow limitation. WHO Regional Publications, European series no. 12, Copenhagen, 1982.
16. World Health Organization. – Air quality guidelines for Europe. WHO Regional Publications. European Series no. 23. Copenhagen, 1987.
17. Raizenne ME, Burnett RT, Stern B, Franklin CA, Spengler JD. – Acute lung function responses to ambient acid aerosol exposures in children. *Environ Health Perspect*, 1989; 79: 179–185.
18. Kosterink P, Berg R van den, Hoek G, Brunekreef B. – The impact of elevated ambient ozone concentrations on pulmonary function of exercising children (in Dutch). *Ned Tijdschr Geneeskd*, 1990; 134: 2343–2347.
19. Miller A. – Spirometry and maximum expiratory flow-volume curves. *In*: Miller A, Ed. Pulmonary function tests in clinical and occupational lung disease. New York, Harcourt Brace Jovanovich, Publishers, 1986.
20. Leith DL, Bradley M. – Ventilatory muscle strength and endurance training. *J Appl Physiol*, 1976; 41: 508–516.
21. Krowka MJ, Enright PL, Rodarte JR, Hyatt RE. – Effect of effort on measurement of forced expiratory volume in one second. *Am Rev Respir Dis*, 1987; 136: 829–833.
22. Medinger AE. – Should largest $FEV_1$ be reported from spirometric trials? (Abstract). *Am Rev Respir Dis*, 1990; 141 (Suppl.); A223.
23. Ingram RH, Schilder DP. – Effect of gas compression on pulmonary pressure, flow and volume relationship. *J Appl Physiol*, 1966; 21: 1821–1826.