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Relationship Between Acute Ozone Responsiveness and the Chronic Loss of Lung Function in Residents Exposed to Recurrent Oxidant Air Pollution

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY



**AIR RESOURCES BOARD
Research Division**

**RELATIONSHIP BETWEEN ACUTE OZONE RESPONSIVENESS
AND THE CHRONIC LOSS OF LUNG FUNCTION IN RESIDENTS
EXPOSED TO RECURRENT OXIDANT AIR POLLUTION**

**Final Report
Contract No. A6-158-33**

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RELATIONSHIP BETWEEN ACUTE OZONE RESPONSIVENESS AND THE CHRONIC LOSS OF
LUNG FUNCTION IN RESIDENTS EXPOSED TO RECURRENT OXIDANT AIR POLLUTION

ABSTRACT

We tested the hypothesis that persons with acute respiratory responsiveness to ozone (O_3) are at high risk of chronic lung injury from repeated exposure to oxidant air pollution. Nonsmoking, chronically oxidant-exposed adult residents ($n = 164$) of Glendora, California underwent lung function measurements in the field during 1986-87 (time 3) as a followup of larger-scale field studies in 1977-78 (time 1) and 1982-83 (time 2). Although these 164 subjects showed a large annual decrease in forced expired volume in one second (FEV_1) between time 1 and time 2, they did not show continued decline in lung function between time 2 and time 3. Forty-five members of the time 3 group were studied in the laboratory in 1989 (time 4) and showed statistically significant but mild acute reductions in FEV_1 and forced vital capacity (FVC) during 2-hour controlled chamber exposures to 0.4 ppm ozone (O_3), in comparison with exposures to clean air. Post-exposure bronchial responsiveness to inhaled methacholine was not statistically significantly different between O_3 and clean air exposures at time 4. Lung function (FEV_1 and FVC) responses to acute O_3 exposures at time 4 correlated poorly with longer-term FEV_1 or FVC changes (possibly influenced by chronic ambient oxidant exposure), as measured over the previous time intervals (times 1-3). These results do not support the hypothesis that acute lung function responses to ozone exposure can predict chronic effects in typical middle-aged nonsmokers residing in oxidant-polluted communities, or that such people experience unusually rapid long-term lung function decline.

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DISCLAIMER

The statements and conclusions in this report are those of the contractor and not necessarily those of the California Air Resources Board and the U.S. Environmental Protection Agency. The mention of commercial products, their source or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products.

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I. SUMMARY AND CONCLUSIONS

Nonsmoking, chronically oxidant-exposed adult residents ($n = 164$) of Glendora, California underwent lung function measurements in the field during 1986-87 as a followup of the UCLA Population Studies of Chronic Obstructive Respiratory Disease (CORD Studies). These 164 subjects previously demonstrated a large annual decrease of 60 mL/yr in forced expired volume in one second (FEV_1) between 1977-78 (time 1) and 1982-83 (time 2). The lung function measurements in the field during 1986-87 (time 3) did not demonstrate continued decline in annualized lung function for this subset of the original sample. The outcome at time 3 was contrary to the investigators' and sponsors' expectations based on results of the previous larger-scale study at times 1 and 2.

Forty-five Glendora residents (27% of the time 3 group) were studied in the laboratory in 1989 (time 4) and showed statistically significant but mild acute reductions in lung function [FEV_1 and forced vital capacity (FVC)] with 2-hour controlled chamber exposures to 0.4 ppm ozone (O_3), in comparison with clean air controls.

Post-exposure nonspecific bronchial responsiveness, as measured by challenge with inhaled methacholine, was not statistically significantly different between O_3 and clean air exposures at time 4.

Lung function (FEV_1 and FVC) responses to acute O_3 exposures at time 4 correlated poorly with longer-term FEV_1 or FVC changes (possibly influenced by chronic ambient oxidant exposure), as measured over the previous time intervals. Because of the unexpectedly negative findings at time 3, the investigation's power to test relationships between acute and longer-term responses to O_3 /oxidants was less than expected. Nevertheless, the results raise considerable doubt that acute lung function responses to ozone exposure can predict chronic effects in typical middle-aged nonsmokers residing in oxidant-polluted communities.

II. RECOMMENDATIONS

This study's results are somewhat reassuring, in that this subgroup of oxidant-exposed middle-aged Glendora residents from the CORD studies did not appear to have rapidly declining lung function (in contrast to earlier CORD findings), and did not exhibit unusual physiologic responses to controlled O_3 exposure. Possible public-health problems from long-term ambient oxidant exposure deserve continued attention, however. The unexpectedly negative findings at times 3 and 4 may reflect a reduction of O_3 responsiveness due to aging, attenuated physiologic response to O_3 after repeated ambient oxidant exposures, a "healthy resident" phenomenon (ongoing selective migration of O_3 -responsive individuals out of Glendora), other selection biases, and/or other still-unrecognized factors. In any event, these physiological findings do not exclude long-term adverse effects of chronic oxidant exposure on lung anatomy or biochemistry of susceptible individuals, which might become clinically manifest later in life. That possibility can be tested by epidemiologic studies which relate late-life cardiorespiratory disability and/or premature death with oxidant exposure history. Also, these findings do not rule out a close relationship

between acute and chronic lung function responses to O_3 /oxidants in younger subjects. That possibility can be tested by combining acute clinical O_3 exposure studies with longitudinal epidemiologic studies of lung physiology and biochemistry in younger populations. Another possibility to be considered is that variations in spirometer calibration contributed to the different results between t1-t2 and later time intervals, despite rigorous quality control procedures. Efforts to further reduce random and nonrandom instrument variability should be encouraged in current and future epidemiologic studies.

III. PROJECT REPORT

A. INTRODUCTION

The long-term health effects of oxidant air pollution in man remain unclear despite extensive data from chronic animal studies and acute human exposures to ozone (O_3). The UCLA Population Studies of Chronic Obstructive Respiratory Diseases (CORD Studies) evaluated lung function longitudinally in a large nonsmoking population living in four regions of Southern California, including Glendora, a community 25 miles east of downtown Los Angeles which experiences some of the highest short-term peak and annual average concentrations of ambient O_3 in the United States. The lung function of more than 1,000 Glendora residents was initially measured in 1977-78 (time 1 or t1) and was remeasured in 1982-83 (time 2 or t2) [Detels et al., 1987]. During this 5-year interval (t1-t2) the average (\pm SEM) change in FEV_1 in healthy Caucasian nonsmokers was -50 ± 6 mL/yr for males and -47 ± 2 mL/yr for females who were between the ages of 25 and 59 years at t1. (Note that these average changes differ slightly from the values published by Detels et al. [1987], because the latter include subjects down to age 19.) The annual declines in FEV_1 in the Glendora nonsmokers were comparable to those reported in smokers and occupationally-exposed groups elsewhere. (The normal rate of decline in FEV_1 is approximately 25-35 mL/yr in adult nonsmokers as judged from cross-sectional surveys in individuals of diverse ages, and less than that as judged from longitudinal studies of young to middle-aged adults [Knudson et al., 1983; Burrows et al., 1986; Xu et al., 1992].) The primary purpose of the Detels et al. [1987] investigation was to compare longitudinal changes in lung function between Glendora and the less polluted community of Lancaster. Differences were comparatively small, but some lung function variables showed statistically significantly greater decrements in Glendora. Even apart from the comparison with Lancaster, findings in the Glendora cohort may be interpreted as representing accelerated decline in lung function, directly related to their recurrent exposures to community oxidant pollution.

1. Hypothesis

We tested the hypothesis that lung function responses to acute O_3 exposure correlate with chronic lung function changes in individuals repeatedly exposed to high oxidant air pollution; i.e., that individuals in the Glendora cohort with larger year-to-year FEV_1 losses also show larger hour-to-hour FEV_1 losses during controlled O_3 exposure. Confirmation of that hypothesis would imply that the acute lung insult from oxidants, and the body's immediate response to it, are directly related to the long-term development of chronic respiratory disease. Furthermore, it would imply that people most at risk from long-term exposures could be identified (or predicted) by an acute O_3 challenge. Protective measures, as well as further research to elucidate biological mechanisms of oxidant response, could then target this high-risk subgroup.

2. Specific Aims

The apparent accelerated decline in FEV_1 in the Glendora cohort warranted further study, since the confirmation of long-term health effects from ambient oxidants has major public health and regulatory implications. Definitive confirmation would have required retesting a large percentage of subjects from

Glendora and from the cleaner comparison community (Lancaster), which was not economically feasible. Thus, we conducted a followup evaluation of a relatively small subset of the Glendora population studied at t1-t2, in two phases:

- a. Re-testing of lung function in 1986-87 (time 3 or t3) to further characterize the longitudinal course of FEV₁. (Since only a minority of the population was tested, this would provide only limited evidence concerning continued long-term function decline in the population. More importantly, it would improve the precision of individual long-term FEV₁ change measurements, to be correlated with individual short-term O₃ responses.)
- b. Measurement of acute responses to controlled O₃ (0.4 ppm) exposure in 1989 (time 4 or t4) to evaluate the potential relationship between acute and chronic changes in lung function due to O₃/oxidants.

B. METHODS

1. Field Tests of Lung Function -- Time 3

a) Subjects.

A cohort of 208 persons (71 men, 137 women) was invited for repeat lung function testing during 1986-87. Nearly all still lived in or near Glendora, but two individuals who had moved to more distant, lower-oxidant locations also participated. These prospective subjects were selected from 1,117 white, non-Hispanic, nonsmoking individuals analyzed over the t1-t2 interval, who represented 58% of the Glendora residents originally studied at t1 and who were demographically and physiologically similar to the original group. The t3 cohort was selected according to the following criteria:

- 1) Age 30-44 years at t1;
- 2) Completion of t1 and t2 lung function measurements; and
- 3) Continued abstinence from tobacco smoking.

This cohort showed an average (\pm SD) change in FEV₁ of -51 ± 48 mL/yr for the group, -58 ± 62 mL/yr for males, and -48 ± 39 mL/yr for females between t1 and t2. Invitations were made by letter from the CORD study director, Dr. Roger Detels, followed up by telephone contacts.

b) Protocol.

The protocol was approved by the UCLA Human Subject Protection Committee. All participants gave written informed consent.

Subjects were evaluated during a single visit to the Mobile Lung Function Laboratory located in Glendora, CA. This mobile laboratory was the same facility used during t1 and t2 in Glendora. The laboratory consists of a 40-foot air-conditioned mobile trailer with separate interviewing and testing rooms. Physiologic testing equipment included a 12-liter rolling-seal electronic spirometer (Ohio Medical Products, model 780), a voltage-to-frequency converter (Vidar Corporation, model 260), a digital stepping recorder (Digi-Data Corporation, model DSR-1440H), a data converter (Wang Laboratories, model 2268), 1.5- and 4.0-liter calibration syringes, and a calibrator spirometer (Ohio Medical Products, model 781) with a Scotch-Yoke mechanism to deliver 6 liters reciprocally at 10 liters/second peak flow. In addition, a 9.5-liter rolling-seal spirometer (Spirotech, Inc., model S400) was used for cross-calibration and backup purposes. This spirometer fulfills the specifications of the American Thoracic Society for reliable use in high-volume screening [American Thoracic Society, 1987].

Each subject completed a respiratory-demographic questionnaire like those administered at t1 and t2, which incorporated symptom questions from the National Heart, Lung, and Blood Institute respiratory disease questionnaire [Detels et al., 1987], along with questions on residence history, environmental and occupational exposure history, and smoking history. He/she then performed maximal forced expiratory spirometry before and after inhaling a bronchodilator (two puffs of albuterol from a metered-dose inhaler). Five or more spirometric maneuvers each were recorded in pre- and post-bronchodilator testing sessions, and the best single blow from each session was selected by a computer algorithm

[Detels et al., 1975]. The laboratory, instrumentation, and personnel employed at t3 were essentially identical to those used during t1 and t2 [Detels et al., 1979, 1987], except for the addition of post-bronchodilator spirometry and the deletion of body plethysmography and single-breath nitrogen test.

2. Laboratory Tests of Ozone Response -- Time 4

a. Modifications to Research Plan in Response to Time 3 Results.

Because of the unexpected results at t3 (see Results section), the investigators and funding agencies postponed the O₃ chamber exposure studies (t4) in order to re-check and validate the subjects' data from t1, t2, and t3. The validation included a restudy of lung function in 63 (38%) of the 164 subjects from t3, performed at the Pulmonary Function Laboratory, UCLA Medical Center. After the restudy showed a high correlation between field (Glendora) and laboratory (UCLA) results for FEV₁ ($r = 0.97$; $p < 0.001$), the investigators and the CARB decided to continue with controlled exposures to O₃ during the winter-spring of 1989. That season was chosen to minimize intercurrent ambient O₃ exposures, and also to maximize the potential for acute O₃ responses. (Although evidence is limited, O₃ responsiveness appears to vary seasonally in Los Angeles area residents [Linn et al., 1988].)

b. Subjects.

All Glendora residents who completed measurements at t1, t2, and t3 were invited to participate in three visits to the UCLA Environmental Exposure Laboratory during the Winter-Spring of 1989. Subjects who had moved during the interim were also located and invited to participate. (Most of those who moved remained in the San Gabriel Valley area, so that their ambient oxidant exposures should have remained much the same after leaving Glendora.) However, subjects who had developed a major medical condition in the interim were excluded from this phase.

c. Protocol.

The protocol was approved by the UCLA Human Subject Protection Committee. All participants gave written informed consent prior to the study.

Each subject underwent a medical screening examination during the first laboratory visit to rule out medical contraindications for participation. The screening evaluation included a cardiopulmonary physical examination, 12-lead resting electrocardiogram, spirometry, exercise stress test, and completion of a questionnaire like those administered at t1-t3. During the second and third visits, each subject underwent 2-hour exposures in random order (at least one week apart) to clean air with O₃ (0.4 ppm) and clean air alone, under single-blind conditions. The chamber was maintained at 20° C and 50% relative humidity during each exposure. Subjects exercised on a stationary bicycle (Corival, model 400) to achieve an exercise minute ventilation of 30 L/min for 15 minutes of each half hour throughout each exposure. All exposures were conducted with unencumbered breathing except for intermittent measurements of ventilation with a mouthpiece and a ventilation analyzer (Alpha Technologies, model VMM2). Spirometry (Spirotech, Inc., model S400) was performed immediately before

exposure began, and again 5 min after exposure ended. If post-exposure FEV₁ was at least 80% of pre-exposure FEV₁, the subject underwent a measurement of bronchial reactivity via a standardized challenge [Chai et al., 1975] with inhaled methacholine (maximum concentration 200 mg/ml), Rosenthal-French dosimeter, and DeVilbiss 646 nebulizer. A dose-response slope was calculated for each methacholine test to avoid censoring of data in nonasthmatic subjects [O'Connor et al., 1987]. If post-exposure FEV₁ was less than 80% of pre-exposure FEV₁, bronchial reactivity testing was postponed. Spirometry was repeated at 15 min post-exposure, and every 15 min thereafter for up to one hour, until FEV₁ had recovered to more than 80% of its pre-exposure level. The methacholine challenge was then performed. The aforementioned Spirotech S400 spirometer was used for all t4 testing, and was calibrated with the same syringes as used at t3.

d. Exposure Facility.

The controlled exposures took place in a double-walled Plexiglas environmental chamber approximately 12 m³ in size, equipped with a dedicated air conditioning and air purification unit [Weymer et al., 1994]. Air supplied to the chamber was passed through permanganate/ alumina chemisorbent (Purafil) and particulate filters (Farr 30/30, HP100, and HEPA 99.97). Ozone was produced from medical grade oxygen using a corona discharge generator (Sanders model IV), and metered into the chamber air supply via a mixing box. Clean air with or without O₃ was supplied to the chamber at a rate allowing 15 changes per hour. Chamber ozone was monitored continuously with two photometric analyzers (Dasibi Environmental Corporation, models 1003-AH and 1003-PC). Chamber temperature and humidity were continuously monitored with thermocouples.

3. Quality Control

Continuity of personnel and equipment was maintained from t1 and t2 through t3 and t4 studies insofar as possible. Investigators and staff members involved with the t1 and t2 CORD studies (Michael Simmons, James Sayre, Donald Tashkin, M.D., Roger Detels, M.D., and Edward Otoupalik) continued to participate or to consult during the t3 testing. Questionnaires administered were essentially identical from t1 through t4. Instrumentation used for the majority of t3 tests (Ohio spirometer and associated data processing equipment) was the same as used in t1-t2. The Spirotech spirometer, cross-calibrated with the Ohio, was used for some t3 testing, as well as for all t4 testing in the exposure laboratory.

Prior to t3 field studies, the spirometers and electronic equipment underwent electronic maintenance, and the Ohio 781 calibrator was tested against a standard water-sealed spirometer (13.5-L Stead Wells type). In the field, the calibrator was used to test the study spirometer before, during, and after each day's testing.

As described earlier, spirometry was repeated in randomly selected subjects at UCLA Medical Center, and their results from the mobile laboratory and the Medical Center showed a high correlation for FEV₁ ($r = 0.97$, $p < 0.001$). In addition, spirometry was performed by 58 non-cohort subjects at the Glendora field site to compare the Ohio and Spirotech spirometers. The two spirometers' FEV₁ readings showed a high correlation ($r = 0.99$, $p < 0.001$). Overall, Ohio readings averaged 4 mL higher than the Medical Center readings on the cohort

subjects, and 45 mL higher than Spirotech readings on the non-cohort subjects.

The Spirotech S400 spirometer was used during t4 measurements and was calibrated with 1.5- and 4.0-liter syringes, as described above.

4. Ambient Air Quality

Ambient air quality in the Glendora area was monitored by a fixed monitoring station located four miles upwind of the Glendora study area. This station continuously measured levels of total oxidants, nitric oxide, nitrogen dioxide, total oxides of nitrogen, total hydrocarbons, and sulfur dioxide. In addition, 24-hour totals for total suspended particulates and sulfates (at six-day intervals) were monitored. Quality control for the air quality data in Southern California is maintained by the California Air Resources Board and the Air and Industrial Hygiene Laboratory of the California Department of Health Services. A summary of local air quality data during 1972-82 was presented previously [Detels et al., 1987]. Monitoring data in the Glendora area during 1983-89 [CARB, 1983-89] continued to indicate high ambient levels of O₃ (Table 1).

TABLE 1. 1983-89 AMBIENT OZONE (PPM) DATA FOR GLENDORA

<u>Year</u>	<u>Daily Maximum O₃</u>		<u>All Hours</u>
	<u>Highest</u>	<u>Annual Avg.</u>	<u>Annual Avg.</u>
1983	.38*	.120*	.044*
1984	.34*	.134*	.041*
1985	.39	.123	.041
1986	.35	.118	.044
1987	.33	.109	.042
1988	.34	.113	.042
1989	.34	.103	.039

*Incomplete data.

5. Statistical Analysis

In both protocols, conventional linear regression analyses, t tests, and repeated-measures analyses of variance were performed with commercial statistical software (SAS Institute, Cary, NC; BMDP Statistical Software, Los Angeles). Specific analyses are described in the Results section.

C. RESULTS

1. Field Lung Function Tests -- Time 3

Of the 208 invited subjects from t1-t2, 164 (79%) underwent re-testing during fall 1986 - winter 1987 (t3). The 164 subjects (56 males and 108 females) were 36 ± 4 years of age at t1 and 45 ± 4 years at t3. The t3 participants had a calculated mean change in FEV₁ of -60 mL/yr between t1 and t2. Thus, the 164 t3 participants averaged similar or slightly greater FEV₁ loss over the t1-t2 interval in comparison with the 208 invitees, who themselves averaged slightly greater loss than did the entire t1-t2 population, as indicated on pp. 7 and 9. None of the participants reported the development of asthma or other active respiratory symptoms or disorders between t2 and t3.

The results of lung function measurements at t1, t2, and t3 (pre-bronchodilator) are summarized in Figure 1. The mean FEV₁ rose slightly from t2 to t3 (from 3.24 to 3.26 L, difference not significant), in contrast to the significant decline in mean FEV₁ between t1 and t2 (3.49

The FEV₁ data at t3 indicated a decline in FEV₁ of -25 between t1 and t3, less than half the rate of decline at t2. Mean FVC showed essentially the same pattern of 12 L at t1, 3.86 L at t2, and 3.93 L at t3. However, the relatively consistent rate of decline (expected with age 85.5% at t1, 84.4% at t2, and 83.3% at t3. These were significant overall ($p < 0.0001$ by anova). Pairwise the change in FEV₁/FVC was significant ($p < 0.05$) between t1 and t2. This contrasts with the findings for FEV₁, in which the t1-t2 interval accounted for all the

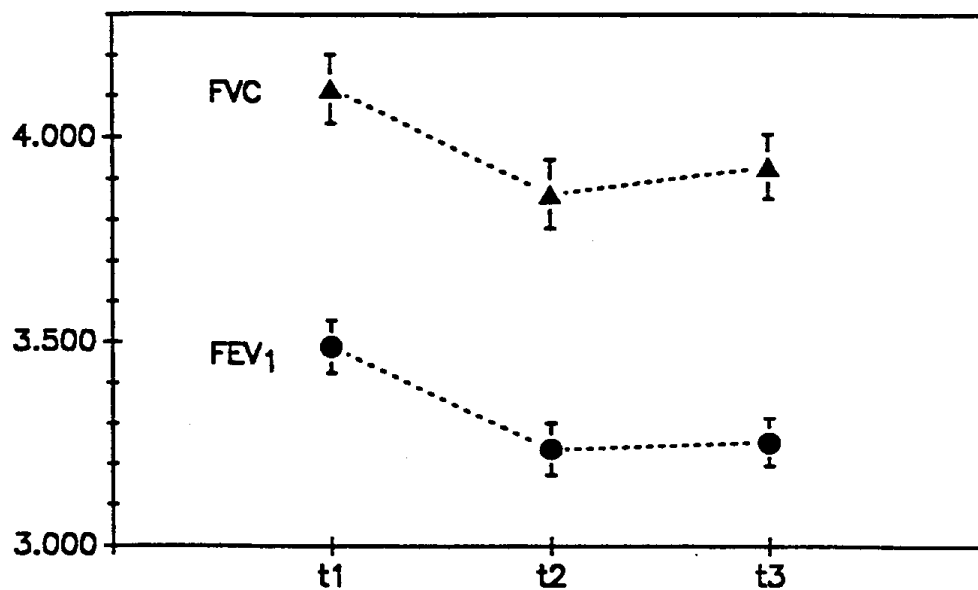
change in FEV₁ at 15 minutes after bronchodilator. The change was $+0.8\% \pm 2.7\%$ (mean \pm sd), with median of +0.9% and 1%. Thus, as expected in a healthy population, there was no significant change in FEV₁ after bronchodilator inhalation on average.

Individuals' FEV₁ changes in mL/year for t2-t3, as a function of the corresponding changes for t1-t2, along with the least-squares regression line are shown in Figure 2. The t2-t3 changes showed a small significant correlation with the t1-t2 changes ($r = -0.28$, $p < 0.01$). This finding suggests the possibility of a highly susceptible subgroup with a decline over the entire followup period. (If such a subgroup exists, its members should show larger-than-average negative FEV₁ changes at t2-t3, and at t1-t2, in which case there should be more points in the lower right of Figure 2, and the correlation coefficient and intercept should be highly positive.)

Figure 1.

LUNG FUNCTION (POINT = MEAN, FLAG = SEM)
FOR 164 SUBJECTS AT 3 FIELD EVALUATIONS

LITERS



FEV₁/FVC RATIO (POINT = MEAN, FLAG = SEM)
FOR 164 SUBJECTS AT 3 FIELD EVALUATIONS

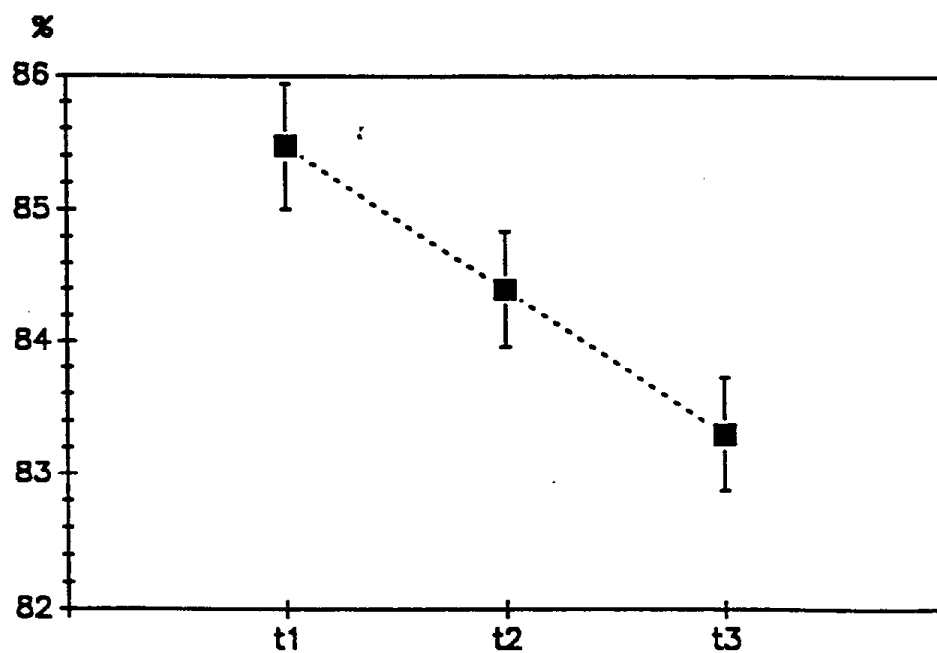
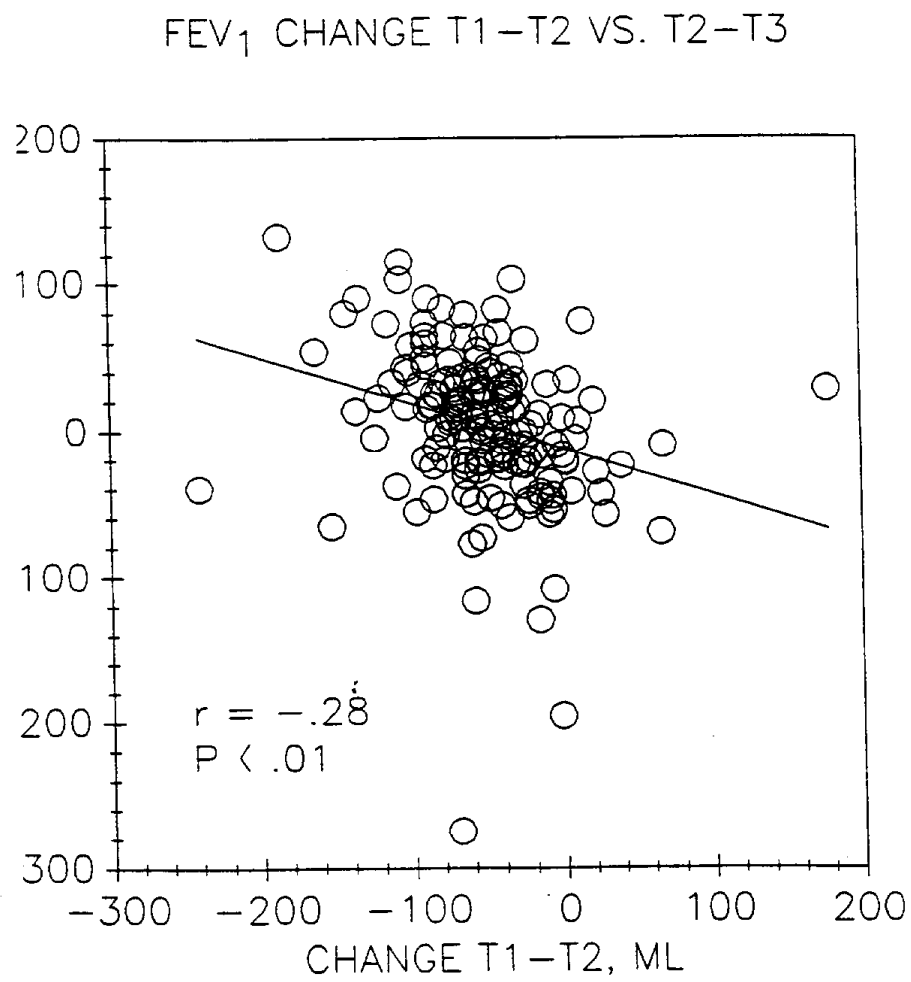


Figure 2.



2. Controlled Ozone Exposures -- Time 4

In late 1988, the 164 subjects who participated in t3 were invited to participate in acute exposure studies during the winter of 1989. The responses to these invitations are summarized in Table 2.

TABLE 2. DISPOSITION OF SUBJECTS STUDIED AT TIME 3

Time 4 Protocol completed	45 subjects	27.4%
Dropouts or investigator-terminated	7	4.3
Subject refused	53	32.3
No response (after several inquiries)	45	27.4
Unable to locate	<u>14</u>	<u>8.6</u>
Total:	164 subjects	100.0%

The 45 participants at t4 consisted of 16 males and 29 females with an average age of 45 ± 4 years (range 38-53 years). Their average decline in FEV₁ was -61 mL/yr (t1-t2), -8 mL/yr (t2-t3), and -29 mL/yr (t1-t3). The 45 subjects were not statistically different from the 119 nonparticipants in their age, FEV₁ at t3, and annual declines in FEV₁ during t1-t2, t2-t3, and t1-t3 ($p > 0.05$ by 2-sample t tests); nor in the proportions of males and females ($p > 0.05$ by chi-square test). Although the differences were non-significant, the subjects had slightly more negative FEV₁ changes than the nonparticipants over the earlier time intervals. Results from acute O₃ exposure studies are summarized in Table 3. The average loss in lung function after exposure to 0.4 ppm O₃ was modest, but the post-O₃-exposure mean was statistically significantly lower than the pre-O₃-exposure mean, and the pre-to-post-exposure changes in O₃ were significantly more negative than the minimal lung function changes during clean-air control studies. Bronchial reactivity to methacholine inhalation was not significantly increased after O₃ exposures, relative to clean air controls.

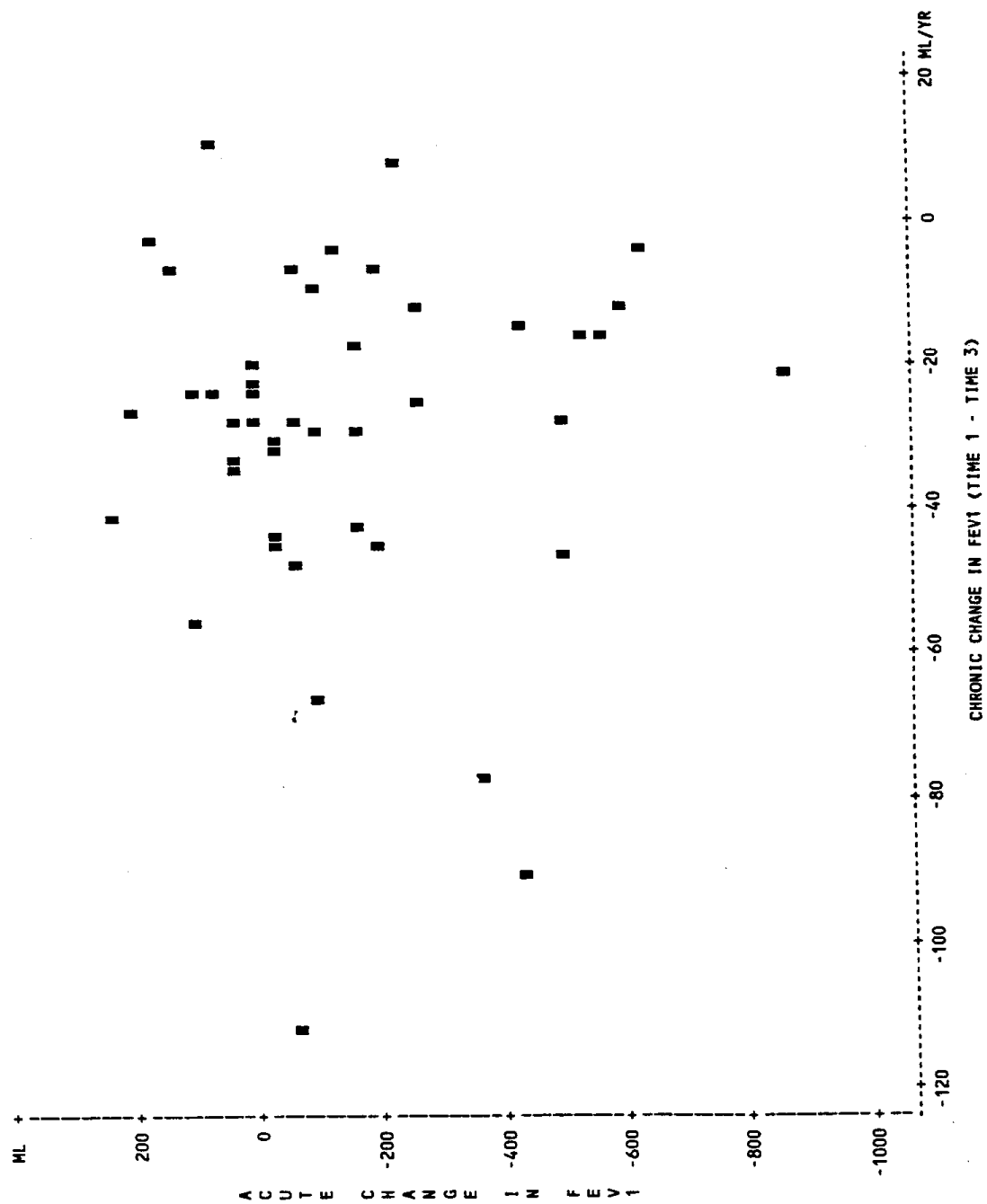
Figure 3 illustrates the relationship between acute and chronic FEV₁ changes. (The acute response is expressed as FEV₁ change during O₃ exposure, minus the corresponding change during the clean air control study.) Acute and chronic changes were compared for FEV₁, FVC, and their ratio. Chronic effects were expressed as the actual measured changes t1-t3 (as in Figure 3), and also as linear regression slopes derived from t1, t2, and t3 measurements. No matter how they were expressed, correlations between chronic function changes and acute responses to O₃ were low and not statistically significant. For example, for the acute FEV₁ change versus the chronic FEV₁ slope, $r = -0.02$, $p = 0.89$. For corresponding FVC data, $r = -0.05$, $p = 0.75$; for FEV₁/FVC, $r = -0.20$, $p = 0.18$.

TABLE 3. LUNG FUNCTION RESULTS (Mean \pm SD) FROM CONTROLLED EXPOSURES AT TIME 4
(N = 45 SUBJECTS)

	Ozone (0.4 ppm)			Clean Air		
	Pre	Post	% Change	Pre	Post	% Change
FEV ₁ , L	3.17 \pm 0.69	2.96* \pm 0.73	-6.8	3.17 \pm 0.66	3.12 \pm 0.69	-1.5
FVC, L	3.87 \pm 0.88	3.64* \pm 0.88	-5.9	3.85 \pm 0.81	3.82 \pm 0.87	-1.0
Methacholine dose- response slope		1.08 \pm 2.92			0.90 \pm 3.39	

* $p < 0.05$, pre vs. post and O₃ vs. air, by paired t test.

FIGURE 3. ACUTE FEV₁ CHANGE WITH O₃ EXPOSURE, VS. CHRONIC FEV₁ CHANGE



D. DISCUSSION

Our results do not support the hypothesis that individuals with rapid long-term lung function decline are especially sensitive to controlled O_3 exposure in the short term. Our results also unexpectedly fail to support the CORD studies' previous finding of unusually rapid long-term function decline in Glendora residents. (We had only limited power to test that finding, however, because we could study only a small minority of the CORD population.) That is, most of our subjects did not appear to have unusually rapid long-term lung function loss, and their individual rates of long-term loss did not appear to have any relationship with their individual short-term responses to controlled O_3 exposure. To guide public-health policy appropriately, further investigation will be needed to determine whether our results are valid for the general population in high-oxidant communities, or are misleading due to experimental design problems and/or interfering factors. No firm conclusions are possible at present. However, considerable relevant information is available from other recent studies.

Besides the CORD studies, the only other large-scale long-term epidemiologic investigation of nonsmoking adults in California is the AHSMOG component of the Adventist Health Study [Abbey et al., 1993, 1995]. From questionnaire responses, validated by review of medical records when practical, the AHSMOG investigators found an association between the risk of developing chronic obstructive airway symptoms and long-term exposure to poor ambient air quality. No lung function measurements are available for AHSMOG subjects; but individuals who have chronic symptoms may have subnormal lung function, and likely have experienced faster-than-usual FEV_1 decline for years before the onset of symptoms. The AHSMOG data associate the risk of obstructive airway symptoms with particulate pollution more strongly than with O_3 ; however, ambient particulate levels as well as O_3 levels are high in Glendora. Thus, in a general but not a specific sense, the AHSMOG findings agree with the original CORD findings in predicting that rapid function loss is plausible and should be observable in Glendora. Lung function testing has been added to the AHSMOG study recently [D.E. Abbey, private communication], and may eventually provide further insights.

The lack of measurable changes in FEV_1 and FVC between t_2 and t_3 is very difficult to explain in biological terms, especially in light of the large negative changes observed between t_1 and t_2 . Previous longitudinal studies suggest that the rate of lung function loss should, if anything, accelerate rather than decline with increasing age [Burrows et al., 1986; Xu et al., 1992]. A third key lung function variable, FEV_1/FVC ratio, behaved more in line with a priori expectations and may offer an explanation of the other results. From cross-sectional data on healthy nonsmokers without extreme ambient pollution exposures, FEV_1/FVC appears to decrease with age between 0.10 and 0.17 percent per year in men and between 0.19 and 0.29 percent per year in women, depending on what other variables are included in regression models [Knudson et al., 1983]. For the predominantly female Glendora group studied at t_3 , the decline in FEV_1/FVC averaged near 0.22 percent per year from t_1 to t_2 , and 0.25 percent per year from t_2 to t_3 -- in reasonable agreement with the previous findings by Knudson et al. [1983] and consistent with the expectation of a steady or increasing rate of decline with advancing age.

Although it is entirely speculative, and although we cannot rule out other explanations given the large loss to followup, the following scenario may partially explain the available t1-t3 field results: The Glendora population studied at t3 experienced a reasonably normal rate of decline in lung function between t1 and t3. Before t2, the spirometer calibration shifted in some manner such that volume readings were $\approx 3\%$ - 4% lower than at t1. After t2 but before t3, the spirometer calibration was restored to approximately the same condition as at t1. The shift at t2 depressed FVC and FEV₁ equally (making it appear that both had declined about twice as much between t1 and t2 as they actually had), but thereby had no effect on the FEV₁/FVC ratio. Calibration shifts of this magnitude might have occurred despite the CORD study's quality control measures. Such shifts are allowable even in newer model spirometers which meet professional standards for accuracy established after the CORD study [American Thoracic Society, 1987]. Current standards allow shifts of $\pm 3\%$ from designated reference instruments (not widely available today and unavailable at the time of the CORD study), and thus allow differences up to $\approx 6\%$ between measurements from different acceptable spirometers (or the same spirometer at different times). In another recent large-scale field spirometry project, calibration shifts of about 2% were detected in more modern spirometers of the same basic design as the CORD spirometer [Linn et al., 1994]. This finding was in part fortuitous, and depended on the availability of multiple spirometers plus calibration-checking technology which had not existed during the CORD study. Thus, from this later indirect evidence it is possible that calibration shifts like those hypothesized above could have occurred during the CORD study, and gone undetected by quality control measures then available. Of course, if we assume that calibration shifts could occur at all, we must assume that they could have biased measurements at t3, as well as at t2, in comparisons against t1. However, the simplest hypothesis which fits these data and other data on longitudinal lung function change is that the important shift affected t2 only.

If the above speculations are approximately correct, then the rapid function loss reported from the CORD study between t1 and t2 may be at least partly spurious, and the stable function between t2 and t3 likewise. The finding of an essentially normal rate of FEV₁ loss between t1 and t3 might or might not be valid, depending on the actual magnitude and timing of the calibration shifts. In any event, the t1-t3 function change is likely to be estimated more accurately than the t1-t2 or t2-t3 changes, given the longer time base. Thus, this study's results are not consistent with the possibility of rapid long-term lung function decline in Glendora residents, but suggest that their long-term decline is similar to that of other populations less exposed to ambient pollution. However, firm conclusions are not warranted, since this study dealt with only a fraction of the original oxidant-exposed CORD population, and provided no comparisons with a less-exposed group.

The average FEV₁ loss attributable to controlled O₃ exposure at t4 was within the range found previously, albeit less than would be predicted by composite dose-response curves derived from multiple previous controlled studies [Hazucha, 1987]. This relatively slight response might be explained by our subjects' being somewhat older than typical subjects in the studies reviewed by Hazucha [1987]. Exclusively middle-aged groups such as ours apparently have not been studied previously, but increasing age has been found to correlate with

decreasing acute O_3 responsiveness in younger adults [McDonnell et al., 1993], and elderly subjects have shown comparatively little response [Bedi et al., 1988; Reisenauer et al., 1988]. Another possibility may be the development of attenuated physiologic response to O_3 after repeated ambient oxidant exposures [Linn et al., 1988], although this possibility was partially minimized with O_3 challenges during winter-spring. Thus, our subjects did not appear unusual in their acute responses to controlled O_3 exposure, relative to other subjects studied previously in Southern California and elsewhere. It remains possible that a relationship between short- and long-term responses does exist in younger people more acutely responsive to O_3 exposure, or in some particular "high-risk" subgroup of the middle-aged or older adult population which was not well represented among our subjects. However, for middle-aged Glendora residents and possibly Southern Californians in general, these results suggest that acute responses to O_3 have poor power to predict chronic air-pollution-related respiratory effects.

Apart from questions concerning spirometer calibration changes, the major limitations in interpretation of these results relate to the question of how the successively smaller subsets studied at t2, t3, and t4 relate to the original Glendora population studied at t1. In principle, we cannot accurately determine what happened to the original study population (or would have happened had they all continued to live in Glendora) from followup observations on non-randomly-selected subgroups. The portion of the population with poorer respiratory health (whether or not caused by ambient pollution) might be expected to migrate selectively away from a smoggy environment like Glendora. Thus, observance of "normal" long-term lung function changes might be misleading; it might result from a "survivor effect", in which most of those individuals whose function was truly affected by ambient exposures were lost to observation. As the original CORD investigators indicated [Detels et al., 1987], that probably did not happen between t1 and t2, because (a) there appeared to be rapid function decline, and (b) the cohort available at t2 was not greatly different from the original t1 population in any relevant health or demographic characteristic among those measured. Point (b) is also true for our subject groups tested at t3 and t4. For these much smaller groups, some kind of selection bias, relative to the t2 or t1 group, would be likely. That is, it is unlikely that self-selection, which brought about the t3 and t4 subject groups, would yield an unbiased sample of the t2 (let alone the t1) population. Nevertheless, our subjects' original lung function levels and their rates of lung function change from t1 to t2 were similar to those of the other subjects. Any differences were in the direction of more rapid long-term decline in the t3 or t4 subjects, compared to the much larger group who were not studied at those times. Thus, spuriously negative results due to a "survivor effect" cannot be ruled out, but seem unlikely on the basis of available information. As stated previously, if spirometer calibration shifts were important, they might have falsely increased the rate of lung function decline measured at t2, but might also have falsely decreased the rate of decline measured at t3. Thus, the question of excess chronic lung function loss in individuals living in high-oxidant regions of Southern California remains open.

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V. PREVIOUS PUBLICATIONS

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