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Longitudinal and Cross-sectional Analyses of Lung Function in Toluene Diisocyanate Production Workers

Mei Lin Wang, MD, MPH, Eileen Storey, MD, MPH, Laura D. Cassidy, PhD, MS, Brent Doney, PhD, MS, MPH, Patrick R. Conner, MD, James J. Collins, PhD, Michael Carson, DO, MPH, and Don Molenaar, MD

Objective: The aim of this study was to investigate lung function among toluene diisocyanate (TDI) production workers. **Methods:** One hundred ninety-seven U.S workers performed spirometry from 2006 through 2012. Results were compared within the study cohort and with U.S. population measures. A mixed-effects model assessed factors affecting repeated forced expiratory volume in 1 second (FEV_1) measurements. **Results:** The cohort's mean FEV_1 and forced vital capacity (FVC) percent reference values, although greater than 90%, were significantly lower and the prevalence of abnormal spirometry (predominantly restrictive pattern) was significantly higher than in the U.S. population. Differences in lung function among workers with higher cumulative TDI exposure were in the direction of an exposure effect, but not significant. **Conclusion:** We found little evidence of an adverse effect of TDI exposure on longitudinal spirometry in these workers. The association between TDI exposure and the increasing prevalence of a restrictive pattern needs further exploration.

Toluene diisocyanate (TDI) is recognized as a respiratory toxicant capable of causing pulmonary impairment and immunologic disturbances in exposed persons.[1] Since the 1950s, numerous studies have been conducted in facilities that produce or utilize TDI.[1–5] These studies have led to a better understanding of the respiratory effects of TDI exposure, which range from self-limited respiratory irritant effects to chronic effects, such as induction of bronchial asthma, hypersensitivity pneumonitis, and possibly an accelerated loss of pulmonary function.[1–5] Some previous studies of working populations exposed to TDI have shown both acute pulmonary effects and excess chronic loss of pulmonary function,[6–9] while other studies showed no significant long-term TDI-related effect on forced expiratory volume in 1 second (FEV_1).[10–12]

Spirometry measurements are an integral part of medical monitoring programs, which, when combined with effective industrial hygiene assessments and early removal of sensitized employees from subsequent TDI exposure, may preserve long-term pulmonary health. This study reports on lung function parameters and spirometry-defined patterns of abnormality among a cohort of potentially exposed TDI workers monitored for up to 6 years. This study tested the null hypothesis that lung function parameters [forced vital capacity (FVC), FEV_1, and the ratio of FEV_1/FVC] among TDI workers would not differ from those of comparable unexposed members of the U.S. general population, and that the TDI cohort would not show a greater rate of annual FEV_1 decline than the rate observed for the U.S. general population.

METHODS

Participants

The study population and the data collection methods have been reported elsewhere and are briefly reviewed here (L. Cassidy, B. Doney, M.L. Wang, et al, in preparation). A multidisciplinary team from industry, government, labor, and academia collaborated to conduct medical monitoring and exposure assessment in three U.S. TDI production plants from 2006 through 2012. A study site coordinator in each plant registered all eligible workers (excluding contract workers), those who performed job tasks that required them to work in areas of potential exposure to TDI during any given year and who were able to participate fully in the on-site medical surveillance program. Of 269 eligible workers, 197 participants completed a questionnaire and performed at least one spirometry test during the study period. Approval was obtained from both the National Institute for Occupational Safety and Health and Dow Chemical Company Institutional Review Boards.

Spirometry Testing

Spirometry testing was conducted by technicians trained by NIOSH staff at three plants producing TDI. The tests were done with a SensorMedics dry-rolling seal spirometer, model #922 (Occupational Marketing, Inc., Houston, TX), software version 5.05.12, and tests were conducted and interpreted in accordance with the 2005 American Thoracic Society/European Respiratory Society guidelines.[13,14] The height measurement methods for some participants differed from the guidelines and these difference in methods will be discussed later. Tests with at least two acceptable curves showing maximum effort were included for analysis. Using prediction equations developed on the basis of data from the Third National Health and Nutrition Examination Survey (NHANES III), lower limit of normal (LLN) and the percent reference values (%Ref) were calculated for FEV_1, FVC, and their ratio (FEV_1/FVC).[15] The LLN approximated the one-sided 95% confidence limit for the expected value based on the NHANES III prediction equations. Percent reference values were determined using NHANES III spirometry data from healthy, nonsmoking individuals as the reference.[15] The observed spirometry value from a participant was divided by the predicted value from the corresponding reference and then multiplied by 100.

Patterns of spirometry abnormality were defined as follows:

(1) Obstructive abnormality was characterized by narrowing of the airways during exhalation leading to a decline in FEV_1/FVC

From the National Institute for Occupational Safety and Health, Morgantown, West Virginia (Drs Wang [former affiliation], Storey, Doney); Medical College of Wisconsin, Milwaukee, Wisconsin (Dr Cassidy); BASF-The Chemical Company, Florham Park, New Jersey (Dr Conner [former affiliation]); DOW Chemical Company, Midland, Michigan (Drs Collins, Carson [former affiliations]); Saginaw Valley State University, University City, Michigan (Dr Collins); and Covestro LLC (formerly known as Bayer MaterialScience LLC), Pittsburgh, Pennsylvania (Dr Molenaar [former affiliation]).

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Address correspondence to: Eileen Storey, MD, MPH, Surveillance Branch, Respiratory Health Division, NIOSH/CDC, 1095 Willowdale Road MS HG900, Morgantown, WV 26508 (EStorey@cdc.gov).

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and a disproportionate reduction in FEV_1 compared with FVC: $FEV_1/FVC < LLN$; $FVC > LLN$; and $FEV_1 < LLN$.
(2) Restrictive abnormality was characterized by reduced lung compliance causing a decline in total lung capacity: $FEV_1/FVC > LLN$; and $FVC < LLN$.
(3) Mixed abnormality was characterized by both obstructive and restrictive abnormalities: $FEV_1/FVC < LLN$; and $FVC < LLN$.

Statistical Analysis

Data analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Cross-sectional analyses included comparisons of %Ref values and the proportion of abnormal spirometry between the study population and the U.S. general population, and also within the study population. For the U.S. population, we used the NHANES combined 2007 to 2010 datasets collected by the National Center for Health Statistics (NCHS). For NHANES 2007 to 2010, study participants were selected using a complex, multistage, probability sampling design. Participants were interviewed in their homes and asked to attend an examination in the mobile examination center that included spirometry for those 6 to 79 years of age. NHANES 2007 to 2010 was approved by the NCHS Research Ethics Review Board. The NHANES website offers detailed information about the surveys.[16]

For the purpose of comparing the spirometry results for the TDI study participants with the U.S. general population, we used spirometry, demographic information, height, weight, and smoking history from NHANES 2007 to 2010, and documentation explaining the database from the NCHS website using the methods recommended by NCHS.[17] Only those persons 20 to 69 years of age at the time of examination were included. Eight datasets were combined and converted to SAS datasets for further analysis and the proper sample weights were used according to NCHS analytic and reporting guidelines to account for the NHANES complex sample survey.[18] SAS PROC SURVEYMEANS and SAS PROC SURVEYFREQ were used to obtain the variance estimations and 95% confidence intervals (95% CIs) for the means of spirometry indices and the proportions of abnormal lung function stratified by age, gender, race/ethnicity, and smoking status that accounted for weighting. Means obtained from the TDI study cohort and NHANES 2007 to 2010 were compared using the corresponding 95% CI obtained from NHANES 2007 to 2010. If the TDI mean fell into the NHANES 95% CI, there was no significant evidence of difference between the TDI study cohort and the U.S. general population.

Longitudinal rate of decline in an individual's FEV_1, often called "FEV_1 slope," was calculated for study participants by linear regression of FEV_1 measurements over time. The resulting FEV_1 slope was then used as the outcome variable in the two-stage analysis comparing average slopes across the various groups of interest within the study cohort, including age group, gender, race/ethnicity, smoking status, and TDI exposure categories. The cross-sectional comparisons of %Ref values of FEV_1, FVC, and FEV_1/FVC ratio were evaluated using *t* tests or analysis of variance (ANOVA). The comparisons of spirometry indices were also made within the TDI cohort, by age group, smoking status, and among four TDI exposure groups by quartiles of ml95.

Exposure Assessment

The development of exposure estimates is described in the study by Middendorf et al[19] and those that are used in this paper are summarized here. Exposure assessment was conducted at the three plant locations. Employees who perform similar tasks that had the potential to produce similar time-weighted average (TWA) TDI exposures, based on detailed discussions of job descriptions, were grouped into plant-level similar exposure groups (Plant/SEGs). Air samples representing shift length duration TWA exposures were collected. Samples were collected and analyzed using the Covestro LLC (formerly known as Bayer MaterialScience LLC; Leverkusen, Germany) Industrial Hygiene Laboratory Method. All employees in a SEG were eligible for sampling whether or not they participated in the study.

TWA Exposures

A method was developed to combine Plant/SEGs that had been determined using job titles and professional judgment into data-derived cross-facility SEGs (SuperSEGs), which are comprised of one or more Plant/SEGs. For example, Plant/SEGs included TDI loading of trucks or railcars, TDI field unit operations, and maintenance in the TDI unit. A total of 1594 TWA air samples collected during the study were used to represent exposures for participants in each SEG. To develop the SuperSEGs, the TWA exposure results, without regard to the use of respirators for each Plant/SEG, were categorized into one of the following groups: less than 0.1 ppb; 0.1 to <0.5 ppb; 0.5 to <2 ppb; 2 to <5 ppb; and at least 5 ppb. The bounding categories (<0.1 and ≥5 ppb) were chosen because 0.1 ppb is approximately the limit of quantification (LOQ), and 5 ppb was the 8-hour TWA-threshold limit value (TLV)® at the time of this study.

Cumulative Exposures

Cumulative TWA exposure estimates for individuals were developed on the basis of the log means for the TWA exposure clusters and the length of exposure.[19]

Peak Exposures

The estimated 95th percentiles for the TWA exposures were used as an index for the potential peak exposures. The 95th percentile for the TWA ("ml95") was determined for each worker by assigning that worker's highest estimate of the 95th percentile among the Plant/SEGs in which the worker was employed. It was calculated using a censored regression model, assuming a log-normal distribution.

A linear mixed-effects model approach was also used to analyze the longitudinal spirometry data.[20] The health outcome variable was the repeated measurement of FEV_1. Multiple factors potentially affecting the measurements of FEV_1 were evaluated as fixed (time-independent) covariables, including baseline age, height, weight, gender, race/ethnicity, plant (Plant A, B, or C), and smoking status. Also evaluated in the mixed effects model were time-dependent covariables, including the interval years from the initial test to each follow-up test, the individual's estimated cumulative TWA exposure from the initial test to each follow-up testing date,[19] and the change from baseline in body weight, with values recorded at the time of each test.

Mixed-model methodology offers additional capabilities in analyzing longitudinal data. Historically, missing data have caused serious problems in the statistical analysis of repeated measures, but such problems do not generally arise with the mixed-model approach, as long as the missing data are random.[20] In this study, 197 participants had from 1 to 12 tests in 1 to 6 years of follow-up; and the interval between two tests also varied. However, we did not detect any patterns or specific reasons for missing results. Most absences were not due to health problems and it appeared that failure to attend a health survey was a random event, as stated in the study by Cassidy et al (L. Cassidy, B. Doney, M.L. Wang, et al, in preparation) SAS PROC MIXED provides a rich assortment of covariance structures, including those applicable to unequally spaced data.[21]

The MIXED model procedure was fitted using the pure RANDOM effective statement. Mixed-model methods also permit modeling the covariance structure of the data, which is especially important for analysis of repeated measures. The selection of the

appropriate type of covariance structure was accomplished by choosing the smallest Akaike Information Criterion (AIC) after fitting models with alternative covariance structures.[22] The final MIXED model procedure was fitted using an unstructured covariance to account for random variation between individuals in the intercept and slope (the longitudinal rate of change in FEV_1 obtained from the mixed models for repeated measurements). This structure specifies an intersubject random effect for differences between individuals.

Two additional mixed models were performed, the first including only white males, and the second model including an addition of a dichotomous marker variable for overweight [body mass index (BMI) $\geq$25 kg/m^2, yes or no][23] to further explore the association between weight gain and the decline in FEV_1. An interaction was evaluated in white males regarding being overweight at the time of the spirometry test and the effect of weight gain on FEV_1.

RESULTS

Of the 197 participants, there were 18 participants with one test, 19 with two, 16 with three, 22 with four, 24 with five, 34 with six, 37 with seven, 19 with eight, four with nine, two with 10, and two with 12 tests. The mean number of tests for each participant in this study was 5.1. There were 1007 valid spirometry test results included in the data analysis (45 tests for 12 females, 962 tests for 185 males). Years of follow-up ranged from less than 1 to 6 years, with an average follow-up time of 3.6 years.

Table 1 summarizes the population characteristics and spirometry indices at the initial test by gender. The average age at the initial spirometry test was approximately 42 years. The age ranged from 21 to 62 years at the initial test and from 24 to 67 years at the final test (Table 2). Approximately 64% of the workers were never smokers. The means of %Ref FEV_1 and %Ref FVC at initial and final tests for males and females were all greater than 90% (Table 2). When compared with the mean %Ref FEV_1 (98%) for the U.S. general population, the TDI cohort's initial (102%) and final (99%) mean %Ref FEV_1 were significantly higher for females. The initial mean %Ref FVC was significantly higher than the U.S. general population (100%) and the final mean %Ref FVC was significantly lower. In males, the mean %Ref FEV_1 and FVC were 94% and 93% at the initial test and 93% and 91% at the final test and were significantly lower than the 96% and 99% for the U.S. population. The %Ref FEV_1/FVC ratio was significantly higher among TDI study participants for both females and males. The mean BMI for the TDI study population was significantly lower than the U.S. population (Table 2). Additional comparisons between the TDI study cohort and the U.S. population were made, stratified by both age and smoking for white males only. The results were very similar to the whole TDI study cohort, which are presented in Table 3.

TABLE 1. Population Characteristics and Spirometry Indices at the Initial Test by Gender ($n = 197$)

	Females ($n = 12$)	Males ($n = 185$)
Characteristic*		
Age, years	39.8 (5.8, 32–50)	42.1 (9.7, 21–62)
Height, cm	167.0 (7.0, 155–178)	177.4 (6.8, 160–203)
Weight, kg	74.3 (17.1, 46–99)	81.0 (15.2, 43–131)
BMI, kg/m^2	26.7 (6.2, 18–36)	25.7 (4.4, 16–41)
Race/ethnicity		
White (n)	8 (66.7%)	129 (69.7%)
Black (n)	2 (16.7%)	29 (15.7%)
Hispanic (n)	2 (16.7%)	27 (14.6%)
Smoker status		
Ever (n)	4 (33.3%)	66 (64.3%)
Never (n)	8 (66.7%)	119 (35.7%)
Spirometry index*		
FEV_1, mL	3157 (370, 2,599–3,688)	3779 (663, 1,535–5,905)
FVC, mL	3850 (512, 3,033–4,873)	4689 (828, 2,289–6,815)
FEV_1/FVC	82.3 (4.3, 73.0–87.0)	80.8 (5.3, 57.0–92.0)
%Ref FEV_1	101.6 (9.9, 88.6–120.6)	93.6 (11.9, 43.7–124.1)
%Ref FVC	101.9 (13.8, 82.1–121.9)	92.5 (11.1, 54.9–120.6)
%Ref FEV_1/FVC	99.5 (5.7, 88.2–106.1)	101.1 (6.7, 72.0–12.3)

*Data are presented as mean values (SD, range) unless noted otherwise.

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; %Ref, percent reference value; SD, standard deviation.

The comparisons of spirometry indices were also made within the TDI cohort, by age group, smoking status, and among four TDI exposure groups by quartiles of ml95. The difference among age groups was as expected. Smoking and TDI exposure effects were detected, but were not statistically significant. The comparisons of never versus ever smokers for mean %Ref FEV_1, FVC, and FEV_1/FVC were 94%, 93%, and 101% versus 94%, 92%, and 102% at the initial test, and 94%, 93%, and 101% versus 93, 91, and 102% at the final test. None of these differences were statistically significant. When comparing the mean %Ref of spirometry indices between the workers in the highest exposure group (''ml95'' $\geq$ 75% percentile) versus others, or among four groups by the quartiles of the TDI exposure variable ''ml95,'' the differences were in the direction of an exposure effect, but none of these were significant (data not shown).

The comparison of prevalence of spirometry abnormalities between the TDI cohort and NHANES 2007 to 2010 is summarized in Table 4. The proportion of overall abnormal spirometry for male TDI study participants was significantly higher than the U.S. general population. However, the further categorization of patterns of abnormality showed that the TDI cohort had significantly lower prevalence of obstructive pattern and higher prevalence of restrictive pattern. The prevalence of obstructive and restrictive pattern of spirometry abnormality was similar in never versus ever smokers in the TDI cohort with 0.8% and 1.4% for obstructive and 12.6% and 11.4% for restrictive at the initial test; and 0.8% and 0.0%, and 16.5% and 15.7% at the final test, respectively.

FEV_1 slope calculated by simple linear regression for 160 participants with at least three tests averaged -27.6 mL/year for males ($n = 151$) and -25.8 mL/year for females ($n = 9$). The mean follow-up years was 3.9 (range: 1 to 6 years); the mean frequency of tests was 5.9 (range: 3 to 12 observations). Comparisons of slope between never and ever smokers and among four groups of quartiles of TDI exposures were not statistically significant. Participants whose initial age was less than 30 versus at least 30 years, the slope was -21 versus -33.3 mL/year ($P = 0.0003$) (data not shown).

The parameter estimates and P values obtained from the mixed-effects model analysis for the whole cohort including 178 participants (168 males and 10 females) who had at least two test results (987 observations in total) are summarized in Table 5. The initial age, height, and weight were significantly related to the absolute value of FEV_1, as was the spirometry testing position (sitting or standing), and the time-dependent covariable of weight gain. The initial level of FEV_1 differed by race/ethnicity and gender, with black participants demonstrating significantly lower values than white and Hispanic participants. Although females values were lower than males, there was not enough power to detect statistically significant differences (female: $n = 10$ with 43 observations). The effect of smoking (never vs ever), and the time-dependent covariable of TDI cumulative exposure up to the time of spirometry testing, showed a trend toward declines in FEV_1; however, these did not reach statistical significance. The parameter estimates indicate that a 1-year increase in initial age corresponded to an average 22.6 mL decrement in FEV_1 (age effect estimated cross-sectionally), while a 1-year increase in follow-up interval corresponded to an

TABLE 2. Cross-sectional Comparison of Characteristics and Spirometry Indices Between the TDI Cohort and NHANES 2007–2010

	TDI Cohort ($n = 197$)		NHANES 2007–2010 ($n = 7{,}704$)*	
	Initial Test	Final Test		
	Mean (SD, range)	Mean (SD, range)	Mean (SD)	95% CI
Males	$n = 185$		$n = 3{,}829$	
Age, years	42 (9.7, 21–62)	45.3 (10.1, 24–67)	42.7 (0.4)	42.0–43.4
Height, cm	177 (7.0, 152–203)†	177.0 (6.7, 160–203)†	176.5 (0.2)	176.1–176.9
Weight, kg	81 (15.2, 43–131)‡	81.2 (15.3, 42–136)‡	89.4 (0.5)	88.3– 90.4
BMI, kg/m^2	26 (4.5, 16–41)‡	25.9 (4.6, 16–43)‡	28.6 (0.1)	28.3–28.9
%Ref FEV_1	93.7 (12.1, 43.7–124.1)‡	92.4 (11.6, 55.1–123.5)‡	96.3 (0.4)	95.5–97.1
%Ref FVC	92.5 (11.3, 54.9–120.6)	91.3 (11.5, 60.9–118.1)‡	99.0 (0.3)	98.3–99.7
%Ref FEV_1/FVC	101.1 (6.7, 72.0–112.3)†	101.2 (7.0, 79.5–126.8)†	98.1 (0.3)	97.4–98.7
Females	$n = 12$		$n = 3{,}875$	
Age, years	39.8 (6.0, 32–50)‡	41.8 (6.4, 34–53)‡	43.1 (0.4)	42.5–44.1
Height, cm	167.0 (7.0, 155–178)†	167.0 (7.0, 155–178)†	162.9 (0.1)	162.6–163.2
Weight, kg	74.3 (17.1, 46–99)‡	75.4 (17.7, 43–99)	76.2 (0.5)	75.2–77.1
BMI, kg/m^2	26.7 (6.2, 18–36)‡	27.3 (6.9, 17–38)‡	28.7 (0.2)	28.4–29.0
%Ref FEV_1	101.6 (9.9, 88.6–120.6)†	99.3 (12.0, 81.2–120.9)†	97.7 (0.3)	97.1–98.4
%Ref FVC	101.9 (13.8, 82.1–121.9)†	98.8 (14.0, 80.7–119.2)‡	100.3 (0.3)	99.8–100.9
%Ref FEV_1/FVC	99.5 (5.7, 88.2–106.1)†	100.0 (5.9, 86.3–108.5)†	97.7 (0.3)	97.2–98.2

For the comparison made between the mean obtained from TDI study cohort and the corresponding 95% CI obtained from NHANES 2007–2010: if the TDI mean falls into the NHANES 95% CI, there is no significant evidence of difference between the TDI study cohort and the U.S. general population. Otherwise, there is evidence of either significantly higher (†) or lower (‡) differences between the means of these two populations.

BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NHANES, National Health and Nutrition Examination Survey; %Ref, percent reference value; SD, standard deviation; TDI, toluene diisocyanate.

*Variance estimation using SAS PROC SURVEYMEANS for a complex survey design. For the purpose of comparing NHANES 2007–2010 with the TDI study cohort, only NHANES 2007–2010 participants aged 20–69 years were included.

†Mean of the TDI cohort is significantly higher than the mean obtained from NHANES 2007–2010.

‡Mean of the TDI cohort is significantly lower than the mean obtained from NHANES 2007–2010.

average 31.4 mL decline in FEV_1 (age effect estimated longitudinally), after controlling for initial age, height, weight, gender, race/ethnicity, plant, testing position, smoking status, change in body weight, and cumulative exposure. An additional model including only white males ($n = 118$ with 686 observations) indicated that the age effect was 24.5 and 27.7 mL/year, cross-sectionally and longitudinally, respectively, after controlling for multiple factors (Table 6).

The mean BMI for the study population as a whole was significantly lower than the U.S. general population (Table 2). At the initial and final testing, the proportion of workers with a BMI less than 25 kg/m^2, 25 to 29, and at least 30 (categorized as normal, overweight, and obese) was about 44%, 35%, and 21% at initial; and 43%, 30%, and 26% at final spirometry test, respectively. The study population had a higher percentage of normal BMI and lower percentages of overweight and obese workers than the U.S. general population of 32%, 34%, and 34% (using data from NHANES 2007 to 2010 for ages 20 to 69). The study population gained an average of 0.74 kg over the 3.6 years of follow-up. For the study cohort as a whole, a 1 kg increase in weight was associated with an average 11.1 mL loss in FEV_1 (Table 5). The additional model including only white males showed similar results that a 1 kg increase in weight was associated with an 11.8 mL loss in FEV_1 (Table 6). To further explore the effect of weight gain on FEV_1, an additional mixed-effects model with the addition of a dichotomous marker variable for overweight (BMI $\geq$25 kg/m^2, yes or no) was investigated. An interaction was evaluated in white males regarding being overweight at the time of the spirometry test and the effect of weight gain on FEV_1. After controlling for the other factors in Table 6, the effect of weight gain on FEV_1 was much greater for white males who were overweight (BMI $\geq$25 kg/m^2 at the time of the test) than those who were not (-16.6 vs −8.2 mL/kg, $P = 0.0184$).

DISCUSSION

The TDI study participants showed a lower mean percentage reference value of FEV_1 and FVC at both initial and final spirometry measurements compared with the U.S. general population (2007 to 2010 NHANES) and also with a recent publication of U.S. coal miners.[24] However, the FEV_1/FVC ratio was significantly higher than the above comparison populations. The proportion of overall abnormal spirometry for male TDI study participants was significantly higher than the U.S. general population; whereas the further categorization of patterns of abnormality showed that the TDI cohort had significantly lower prevalence of obstructive pattern and higher prevalence of restrictive pattern, as defined in the Methods. While hypersensitivity pneumonitis is known to occur in response to TDI exposures, a condition that can result in a restrictive pattern on spirometry, no cases were identified in this cohort.[2–5,25] In addition, variability in measurement technique, as detailed below, seems likely to have affected the results.

In this study, 1007 valid spirometry measurements were analyzed. The correct measurement of height is very important in the calculation of the appropriate reference values and LLN. In the NHANES III survey, standing height was measured without shoes with the subject's back to a vertical backboard. Both heels were placed together, touching the base of the vertical board.[15] In this study, there was variability across plants because the standing height was measured without shoes (as recommended per ATS/ERS guidelines) for only 15% of the tests,[15] 44% with steel toe boots not removed and the shoe heels not subtracted, 41% using the computer records of heights measured at the time of hire and asking for confirmation at the time of testing. We subtracted an estimated shoe heel height of 2 cm from the "height" for those measured with shoes/boots in the database and recalculated the reference value and the LLN to further evaluate the means of spirometry indices and the

TABLE 3. Cross-sectional Comparison of Spirometry Indices Between the TDI Cohort and NHANES 2007–2010 by Smoking Status and Age Group for White Males

		TDI Cohort ($n = 129$)		NHANES 2007–2010 ($n = 1,714$)	
		Initial Test	Final Test		
Smoking Status and Spirometry Indices	Age Group*	Mean	Mean	Mean	95% CI
Current smoker					
%Ref FEV_1	20–39	92.4‡	90.8‡	94.8	93.2–96.4
	40–59	91.7†	90.2	88.5	85.8–91.2
	60–69	—	—	80.4	75.6–85.3
%Ref FVC	20–39	93.5‡	90.3‡	99.5	98.2–100.7
	40–59	91.1‡	87.8‡	96.5	94.1–98.9
	60–69	—	—	92.9	88.7–97.1
%Ref FEV_1/FVC	20–39	98.7†	100.2†	95.2	93.9–96.6
	40–59	101.1†	103.1†	91.4	89.5–93.2
	60–69	—	—	86.6	82.6–90.6
Ex-smoker					
%Ref FEV_1	20–39	98.4	97.1	98.3	95.5–101.0
	40–59	91.5‡	93.0	95.2	92.9–97.6
	60–69	—	100.2†	92.9	90.3–95.5
%Ref FVC	20–39	94.4‡	94.6‡	100.4	97.8–103.0
	40–59	89.1‡	91.6‡	97.8	95.7–100.0
	60–69	—	94.8‡	97.5	95.4–99.7
%Ref FEV_1/FVC	20–39	104.1†	103.0†	97.5	95.9–99.1
	40–59	102.7†	101.3†	97.3	95.6–98.9
	60–69	—	105.2†	95.2	93.3–97.1
Never smoker					
%Ref FEV_1	20–39	97.2	93.9‡	98.0	96.5–99.4
	40–59	92.5‡	93.9‡	97.7	96.4–99.0
	60–69	97.5‡	91.6‡	100.0	98.1–101.9
%Ref FVC	20–39	95.6‡	95.2‡	99.6	98.5–100.8
	40–59	91.6‡	92.4‡	98.8	97.2–100.3
	60–69	91.7‡	86.3‡	101.9	99.6–104.3
%Ref FEV_1/FVC	20–39	101.3†	98.5	98.2	97.2–99.1
	40–59	100.8†	101.5†	98.9	97.6–100.2
	60–69	106.4†	105.8†	98.4	97.1–99.6

For the comparison made between the mean obtained from TDI study cohort and the corresponding 95% CI obtained from NHANES 2007–2010: if the TDI mean falls into the NHANES 95% CI, there is no significant evidence of difference between the TDI study cohort and the U.S. general population. Otherwise, there is evidence of either significantly higher (†) or lower (‡) differences between the means of these two populations.

CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NHANES, National Health and Nutrition Examination Survey; %Ref, percent reference value; TDI, toluene diisocyanate.

*The number of subjects in the age groups of 20–39, 40–59, and 60–69 was 10, 9, and 0 in Current smokers; 7, 15, and 0 in Ex-smokers; and 35, 50, and 3 in Never smokers at the initial test; and 10, 17, 0; 10, 30, 3; and 37, 82, 8 in the final test; and 260, 195, 54; 126, 198, 148; and 304, 313, 116 in the NHANES 2007–2010 survey, respectively.

†Mean of the TDI cohort is significantly higher than the mean obtained from NHANES 2007–2010.

‡Mean of the TDI cohort is significantly lower than the mean obtained from NHANES 2007–2010.

TABLE 4. Comparison of Prevalence of Spirometry Abnormalities Between the TDI Cohort and NHANES 2007–2010

	TDI Cohort ($n = 197$)		NHANES 2007–2010 ($n = 7,683$)*	
	Initial Test	Final Test		
	N (%)	*N* (%)	*N* (%)	95% CI
Males	$n = 185$		$n = 3,819$	
Normal	170 (86.3)‡	162 (82.2)‡	3,376 (89.5)	88.0–91.0
Abnormal	27 (13.7)†	35 (17.8)†	443 (10.5)	9.0–12.0
Mixed	1 (0.5)	2 (1.0)	45 (1.0)	0.5–1.4
Obstructive	2 (1.0)‡	1 (0.5)‡	143 (3.8)	3.0–4.6
Restrictive	24 (12.2)†	32 (16.2)†	255 (5.8)	4.8–6.8
Total	197 (100.0)	197 (100.0)	3,819 (100.0)	
Females	$n = 12$		$n = 3,864$	
Normal	12 (100.0)†	11 (91.7)	3,516 (91.3)	90.4–92.1
Abnormal	0 (0.0)‡	1 (8.3)	348 (8.7)	7.9–9.6
Mixed	0 (0.0)‡	0 (0.0)‡	49 (1.2)	0.8–1.7
Obstructive	0 (0.0)‡	0 (0.0)‡	99 (2.9)	2.3–3.5
Restrictive	0 (0.0)‡	1 (8.3)†	200 (4.6)	3.7–5.6
Total	12 (100.0)	197 (100.0)	3,864 (100.0)	

For the comparison made between the prevalence obtained from the TDI study cohort and the corresponding 95% CI obtained from NHANES 2007–2010: if the TDI prevalence falls into the NHANES 95% CI, there is no significant evidence of difference between the TDI study cohort and the U.S. general population. Otherwise, there is evidence of either significantly higher (†) or lower (‡) differences between these two populations.

CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; TDI, toluene diisocyanate.

*Variance estimation using SAS PROC SURVEYFREQ for a complex survey design. For the purpose of comparing NHANES 2007–2010 with the TDI study cohort, only NHANES participants aged 20–69 years were included; 21 with a missing "height" were excluded.

†Prevalence of the TDI cohort is significantly higher than the prevalence obtained from NHANES 2007–2010.

‡Prevalence of the TDI cohort is significantly lower than the prevalence obtained from NHANES 2007–2010.

TABLE 5. Parameter Estimates (mL) from Fitting a Mixed-effects Model to All FEV_1 Results, 178 Participants and 987 Spirometry Observations*

	Gender	Race/Ethnicity	Plant	Testing Position	Smoking Status	Estimate, mL	SE	*P*
Intercept, mL						−4249.3	900.5	<0.0001
Initial age, years						−22.6	3.5	<0.0001
Initial height, cm						55.0	5.4	<0.0001
Initial weight, kg						−8.8	2.3	0.0001
Gender	Female					−245.8	149.5	0.1005
Gender	Male					0.00	—	—
Race/ethnicity		Black				−653.7	119.3	<0.0001
Race/ethnicity		White				68.0	101.5	0.5030
Race/ethnicity		Hispanic				0.0	—	—
Plant			A			110.8	78.6	0.1588
Plant			B			−5.9	90.2	0.9478
Plant			C			0.0	—	—
Testing position				Sitting		−59.2	21.0	0.0050
Testing position				Standing		0.00	—	—
Smoking status					Never	20.1	69.7	0.7729
Smoking status					Ever	0.00	—	—
Weight gain, kg						−11.1	1.6	<0.0001
Cumulative exp, ppb.year						−3.8	5.6	0.5022
Time (Interval, year)						−31.4	4.8	<0.0001

SE, standard error; TDI, toluene diisocyanate.

*Model variables included initial test age, height, weight, gender, race/ethnicity, plant, testing position, and smoking status, as well as the time-dependent covariables (values recorded at the time of each test) including change in body weight from the baseline weight, cumulative TDI exposure during study period, and interval since initial test in years.

prevalence of spirometry abnormality. It did not change the main findings, but resulted in 2% reduction in prevalence of overall restrictive abnormality. The testing position also varied; about half of the tests were performed in a sitting position. The prevalence of restrictive pattern abnormality was higher in testing performed in sitting position (16.1% vs 12.1%, $P = 0.06$).

The prevalence of restrictive abnormality within the study cohort increased about 4% in males from the initial (12.2%) to the final test (16.2%) (Table 4). Despite the technical limitations described above, a possible effect of TDI exposure should not be ignored considering the increase in prevalence of a restrictive impairment within the study cohort in the population of participants tested using the same position. The lower prevalence of obstructive and mixed abnormalities may partly be due to measurement variability and resulting misclassification. The high proportion of never smokers (64%) in the study population may also play an important role.

The FEV_1 measurements in the study participants were significantly affected by the initial age, height, weight, as well as change in body weight and testing positions. FEV_1 results obtained from different testing positions differed on average by as much as 59 mL, or two times the mean annual longitudinal decline. In the mixed-model analysis, the weight gain parameter is derived from the measured changes (in both FEV_1 and weight) for individual participants over the time interval between the date of the initial spirometry and the date of each follow-up test. The parameter estimate for weight gain can be interpreted to reflect the reduction in FEV_1 associated with a 1 kg weight gain, with both changes

TABLE 6. Parameter Estimates (mL) from Fitting a Mixed-effects Model to All FEV1 Results for White Males, 118 Participants and 686 Spirometry Observations*

	Plant	Testing Position	Smoking Status	Estimate, mL	SE	*P*
Intercept, mL				−4690.3	1221.9	0.0002
Initial age, years				−24.5	4.5	<0.0001
Initial height, cm				60.2	7.3	<0.0001
Initial weight, kg				−12.7	2.8	<0.0001
Plant	A			68.0	102.6	0.5080
Plant	B			−78.8	116.6	0.4985
Plant	C			0.00	—	—
Testing position		Sitting		−86.0	26.4	0.0012
Testing position		standing		0.00	—	—
Smoking status			Never	32.9	90.3	0.7156
Smoking status			Ever	0.00	—	—
Weight gain, kg				−11.8	1.9	<0.0001
Cumulative exp, ppb.year				−10.6	7.4	0.1523
Time (Interval, year)				−27.4	5.7	<0.0001

SE, standard error; TDI, toluene diisocyanate.

*Model variables included initial test age, height, weight, gender, race/ethnicity, plant, testing position, and smoking status, as well as the time-dependent covariables (values recorded at the time of each test) including change in body weight from the baseline weight, cumulative TDI exposure during study period, and interval since initial test in years.

occurring over the same time interval. After adjustment in the model for other significant factors, the FEV_1 effect attributed to a 1 kg weight gain in this study for white males (Table 6) was on average of -11.8 mL/kg, very similar to a previous study of 1884 chemical workers (−2.3 mL/kg).[26] An interaction was evaluated in white males regarding being overweight and the effect of weight gain on FEV_1 after controlling for the other factors in Table 6. It was found that the effect of weight gain on FEV_1 was much greater for white males who were overweight (BMI $\geq$25 kg/m^2) at the time of the test than those whose BMI was in the normal range (−16.6 vs −8.2 mL/kg, $P = 0.0184$).

The current study has several limitations. First, the spirometry reference values and measurements were affected by variations in height measurements and testing posture. Second, no detailed information on smoking history was available to estimate the number of pack-years. A third limitation relates to the wide range of interval between tests, from less than 1 month to 2.8 years; thus, the mixed-model approach was limited to a pure random model and the repeated statement could not be computed appropriately. The American Thoracic Society outlines approaches to evaluating lung function decline.[27] They report a typical loss of FEV_1 in adult nonsmokers to be 29 mL/year. A loss of 15% or more after accounting for age-associated loss is considered excessive.[13,27] Prolonged follow-up is recommended for reliable estimates of the rate of longitudinal change in spirometry measurements in individuals, and only relatively large changes over 1- to 2-year monitoring intervals are confidently identified as abnormal.[28–30] It has also been reported that a year-to-year decline in FEV_1 greater than 8% or 330 mL should be considered abnormal in working populations.[30] To effectively interpret serial spirometry results for the purpose of identifying individuals likely to have excessive long-term declines in FEV_1, a previous study investigated the relationship between FEV_1 changes observed during routine spirometry monitoring and subsequent long-term declines using data from a large occupational spirometry monitoring program spanning 30 years.[31] Their findings indicated that changes in FEV_1 between two tests over 1 to 5 years are significantly associated with long-term lung function declines. In our study, the follow-up duration ranged from 1 to 6 years, with approximately 44% of slopes calculated using repeated measures of FEV_1 in 5 to 6-year intervals. Although the FEV_1 annual decline rate was not excessive for the study population at large, a subset of 19 participants were identified who had at least one annual decline of FEV_1 greater than 350 mL/year or 10%. These are discussed in a companion paper.[32] Monitoring change in FEV_1 is useful for assessing adverse respiratory effects in an individual, a yearly decline in FEV_1 greater than 10% might be an early indicator for triggering further evaluation for TDI-induced asthma in the workplace medical monitoring and surveillance program. The prevalence of restrictive pattern on spirometry was not anticipated in this study population based upon TDI asthma pathophysiologic considerations. The prevalence of a restrictive pattern may be partially accounted for by methodologic/testing issues, but it increased over time and constitutes an important focus for further research to evaluate this observation.

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