Patients Diagnosed With Diabetes Are at Increased Risk for Asthma, Chronic Obstructive Pulmonary Disease, Pulmonary Fibrosis, and Pneumonia but Not Lung Cancer

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OBJECTIVE — There are limited data on the risk of pulmonary disease in patients with diabetes. The aim of this study was to evaluate and compare the incidence of asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, and lung cancer in patients with and without a diagnosis of diabetes.

RESEARCH DESIGN AND METHODS — We conducted a retrospective, longitudinal cohort study using the electronic records of a large health plan in northern California. Age and sex data were available for all cohort members (n = 1,811,228). Data on confounders were available for a subcohort that responded to surveys (n = 121,886), among whom Cox proportional hazards regression models were fit.

RESULTS — Age- and sex-adjusted incidence rates and 95% CIs were calculated for members with and without diabetes in the full cohort and the subcohort. No difference was observed for lung cancer, but the incidence of asthma, COPD, fibrosis, and pneumonia was significantly higher in those members with a diagnosis of diabetes. These differences remained significant in regression models adjusted for age, sex, race/ethnicity, smoking, BMI, education, alcohol consumption, and outpatient visits (asthma hazard ratio [HR] 1.08 [95% CI 1.03–1.12], COPD HR 1.22 [1.15–1.28], pulmonary fibrosis HR 1.54 [1.31–1.81], and pneumonia HR 1.92 [1.84–1.99]). The risk of pneumonia and COPD increased significantly with increasing A1C.

CONCLUSIONS — Individuals with diabetes are at increased risk of several pulmonary conditions (asthma, COPD, fibrosis, and pneumonia) but not lung cancer. This increased risk may be a consequence of declining lung function in patients with diabetes.

Diabetes Care 33:55–60, 2010

Chronic complications of diabetes include a number of pathological changes that involve small and large blood vessels, cranial and peripheral nerves, the skin, and the retina of the eye. The lung is also a target organ for diabetic microangiopathy in patients with both type 1 and type 2 diabetes (1), and decrements in lung function have been reported among patients with diabetes over the past two decades (2–9).

Decrements in the lung function of patients with diabetes are believed to be the consequence of biochemical alterations in the connective tissue constituents of the lung, particularly collagen and elastin, as well as microangiopathy due to the nonenzymatic glycosylation of proteins induced by chronic hyperglycemia (8,10). Alterations in collagen and elastin and microangiopathy result in thickening of the alveolar epithelial basal lamina, leading to reduced pulmonary capacity for the diffusion of carbon monoxide (8,10). Previous studies investigating the potential association between diabetes and lung cancer have been inconclusive (11–13). No studies have examined the incidence of pulmonary outcomes, other than lung cancer (11), in people with diabetes compared with those without diabetes. The aim of this study was to evaluate and compare the incidence of asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, and lung cancer using the electronic medical records of 1,811,228 members of a large group practice, prepaid health plan in northern California; 77,637 members (4.3%) had been diagnosed with diabetes and 1,733,591 members (95.7%) had not.

RESEARCH DESIGN AND METHODS

— The Kaiser Permanente Medical Care Program in northern California (KPNC) is a large group-practice prepaid health plan that provides comprehensive medical services to a 14-county region. Approximately 30% of the population that resides in the area served by the KPNC are members. From the results of the 1990 and 2000 censuses, we know that the KPNC membership is representative of the population living in the 14-county geographical area with regard to demographic characteristics, race or ethnicity, and socioeconomic status, except that the very poor and the very wealthy are underrepresented (14,15).

Full cohort

A retrospective, longitudinal cohort study design was used to investigate the incidence of asthma, COPD, pulmonary fibrosis, pneumonia, and lung cancer by diabetes status among 77,637 members with a diagnosis of diabetes and 1,733,591 members without a diagnosis of diabetes who were aged ≥18 years as of 1 January 1996. Members were defined as having a diagnosis of diabetes if they were

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Received 13 May 2009 and accepted 23 September 2009. Published ahead of print at http://care.diabetesjournals.org on 6 October 2009. DOI: 10.2337/dc09-0880.

included in the KPNC diabetes registry as of 1 January 1996. Those not included in the diabetes registry were coded as not having diabetes. The diabetes registry started in 1994 and identifies members with diabetes from automated sources; the registry includes members with *1*) pharmacy prescriptions for diabetes medications or supplies, *2*) abnormal A1C values (>6.7%), *3*) primary or secondary hospital discharge diagnoses of diabetes, and *4*) emergency department visits for which a physician diagnosis of diabetes was listed. The diabetes registry has a sensitivity of ~97% (16).

Outcome identification

To identify cases of asthma, COPD, pulmonary fibrosis, and pneumonia, cohort members were linked to the KPNC hospital discharge database and the membership mortality files by their unique medical record number. The hospital discharge database, a complete database of all hospitalizations occurring at any KPNC hospital, codes diagnoses according to the ICD-9. Deaths among KPNC members in the mortality files are identified through an annual, automated linkage to the computerized State of California Death Certificate files, which also use ICD-9 codes (17).

To identify more severe cases of asthma, COPD, pulmonary fibrosis, and pneumonia, the case definition was restricted to include only those that required hospitalization and had the pulmonary outcome of interest listed as the primary discharge diagnosis or instances in which the outcome of interest was listed as the underlying cause of death. The first diagnosis of the pulmonary outcome of interest, as identified by either database, was used as the date of diagnosis. We used the following codes to identify cases: asthma, ICD-9 493; COPD, ICD-9 491, 492, and 494; pulmonary fibrosis, ICD-9 515 (chronic post inflammatory) and 516.3 (idiopathic), and pneumonia, ICD-9 480 through 486 and 487.0.

Cases of lung cancer were identified through the KPNC Cancer Registry, which is responsible for the identification and reporting of all new cancer diagnoses. The registry transmits these data to the California Cancer Registry and the Surveillance, Epidemiology and End Results program of the National Cancer Institute.

Cohort of survey responders

A similar study was conducted among a subsample of members who had responded to surveys sent out by the health plan (n = 121,886), thus providing data on potential confounders. These surveys included the diabetes registry survey (DRS) and the member health survey (MHS). The DRS was mailed between 1995 and 1997 to all health plan members, aged ≥18 years, who had a diabetes diagnosis, as identified by the diabetes registry.

The MHS questionnaires were mailed out in 1993, 1996, and 1999 to random samples of KPNC members, aged ≥18, stratified by age and KPNC facility. MHS responders who were also in the diabetes registry or reported having had a diagnosis of diabetes on the MHS were not included in the diabetic group. Data on potential confounding factors were taken from the earliest MHS completed. Members who responded to both surveys were included in the diabetic group, with data on potential confounders taken from the DRS. Members stating on the MHS that they had diabetes but who did not respond to the DRS were excluded, as were those who were no longer members of Kaiser Permanente at the survey date.

Covariates

In addition to the confounding variables age and sex, which were available for all members in the electronic databases, data on the following potential confounding factors were collected in the two surveys: race/ethnicity (non-Hispanic white, African American, Hispanic, Asian or Pacific Islander, other, and missing), education (some high school or high school graduate, some college, college graduate or postcollege, and missing), alcohol consumption (never, past, current, and missing), smoking, height, and weight. Health plan members were categorized according to their smoking status at the time of the survey as having never smoked, past smoker, and current smoker. BMI was calculated as weight in kilograms divided by the square of height in meters. Data on A1C (continuous), measured within 1 year (±) of the baseline date, and the number of outpatient visits occurring in the 12 months before baseline (0 as the reference, 1–2, 3–4, 5–9, 10–19, 20+ visits, and missing) were obtained from the electronic records.

Statistical analyses

For each pulmonary outcome of interest, crude incidence rates were calculated among cohort members without any inpatient or outpatient diagnoses of the outcome of interest before baseline and stratified by diabetes status at the baseline date of 1 January 1996, with 95% CIs based on the exact Poisson distribution. Age- and sex-adjusted incidence rates and 95% CIs were calculated and stratified by diabetes status at baseline, with attention to proper allocation of person-time across age categories as the cohort was followed through calendar time. The direct method of adjustment for age and sex was used, with the U.S. 2000 Census age-sex distribution among individuals aged ≥18 years as the standard population.

For incidence rate calculations in the full cohort, members began contributing person-time on 1 January 1996. In analyses that included only survey responders, DRS respondents began contributing person-time on the date of the DRS and MHS respondents began contributing person-time on the date the earliest MHS was completed. Members who completed the 1993 DRS began contributing person-time on 1 January 1996. All members contributed person-time to the denominator until one of the following occurred: *1*) the end of the study (31 December 2005); *2*) a diagnosis of asthma, pneumonia, pulmonary fibrosis, COPD, or lung cancer; *3*) death; or *4*) termination of membership in the Kaiser Permanente Medical Care Program (via electronic membership files), whichever occurred first. No complications or events, other than death, censored patients in the calculation of the incidence rates of other pulmonary outcomes. For example, a patient remained at risk and continued to contribute person-time for events other than pneumonia after an incident case of pneumonia was recorded. Members without diabetes as of 1 January 1996 stopped contributing person-time if they developed diabetes over the course of the follow-up period. The statistical significance of the difference in incidence rates between those with and without a diagnosis of diabetes was assessed via Poisson regression, controlling for age and sex.

In the subcohort of survey respondents, the association between diabetes and each pulmonary outcome of interest was assessed using Cox proportional hazards regression models, providing point and interval estimates of the relative haz-

Table 1—*Characteristics of survey responders by diabetes status: KPNC, 1993–1999*

	Diagnosed diabetes	Without diabetes
n	70,645	51,241
Male sex	53.1	44.9
Age (years)		
<40	7.1	27.5
40–49	15.91	19.97
50–59	25.03	15.76
60–69	27.94	16.18
≥70	24.0	20.6
BMI (kg/m^2)	29.80 ± 6.48	26.06 ± 5.14
<25	19.74	45.93
25–26.9	12.88	16.85
27–29.9	18.61	16.60
≥30	35.34	16.70
Missing	13.43	3.91
Race/ethnicity		
White	57.88	72.04
African American	12.92	5.83
Hispanic	13.16	7.95
Asian/Pacific Islander	12.63	11.39
Other	3.22	2.58
Missing	0.17	0.22
Education		
Some high school or high school graduate	40.24	26.15
Some college	27.21	40.01
College graduate or postcollege	21.33	32.96
Missing	11.23	0.88
Alcohol consumption		
Never	18.05	10.68
Past	23.95	14.50
Current	43.37	72.18
Missing	14.63	2.64
Smoking		
Never	42.70	56.81
Past smoker	35.41	29.05
Current smoker	10.52	12.46
Missing	11.38	1.68
No. outpatient visits in the 12 months before baseline		
0	13.50	6.66
1–2	22.25	17.31
3–4	18.80	13.93
5–9	26.51	17.54
10–19	14.65	9.05
≥20	4.29	2.25
Missing	0	33.3

Data are % or means ± SD.

ard of each pulmonary outcome associated with diabetes status, with control for potential confounders. Model 1 included age, sex, and race/ethnicity; model 2 included the model 1 covariates and smoking, BMI, education, alcohol consumption, and the number of outpatient visits occurring in the 12 months before the baseline. Among those with a diagnosis of diabetes, a model that included all of the model 2 covariates and A1C at baseline, a continuous variable, was constructed. Assessment of departure from the model assumptions included diagnostic plots of weighted residuals and tests for interaction between exposure and time. All statistical analyses were conducted in SAS.

This study was approved by the human subjects committee of the Kaiser Foundation Research Institute.

RESULTS — The full cohort of KPNC members included 77,637 members with a diagnosis of diabetes (median age 60.0 years) and 1,733,591 members without diabetes (median age 43.0 years). Those with diabetes tended to be male (53.4% of those with diabetes vs. 47.3% of those without). Table 1 displays the characteristics of the subcohort of survey responders, which included 70,645 members with a diagnosis of diabetes (median age 60.0 years) and 51,241 members without diabetes (median age 51.0 years). Survey responders with diabetes tended to have higher BMI, to belong to a minority racial-ethnic group, and to be less educated than responders without diabetes.

Age- and sex-adjusted incidence rates, stratified by diabetes status at baseline, were calculated for each pulmonary outcome (Table 2). In the full cohort, a significantly higher incidence of each pulmonary condition, except for lung cancer, was observed in health plan members with a diagnosis of diabetes compared with members without diabetes. In a Poisson regression that controlled for sex and age, members with diabetes had a higher incidence of each pulmonary condition, except for lung cancer, compared with members without diabetes (likelihood ratio test, $P < 0.01$ for all pulmonary conditions except for lung cancer and $P = 0.74$ for lung cancer). In the subcohort of survey responders, the incidence of every pulmonary condition, except for lung cancer, was also significantly higher among survey responders with a diagnosis of diabetes than among survey responders without diabetes (Table 2).

In the subcohort of survey responders, after adjustment for age, sex, race/ethnicity, smoking, BMI, education, alcohol consumption, and number of outpatient visits occurring in the 12 months before the baseline, health plan members with a diagnosis of diabetes had a significantly higher risk of every pulmonary condition, except for lung cancer, compared with health plan members without diabetes (Table 3). Because data on medical visits only became available in the electronic medical record in 1994, data on the number of outpatient visits occurring before the baseline were not available for health plan members who responded to the 1993 MHS, representing one-third of the survey responders without diabe-

Table 2—*Age- and sex-adjusted incidence rate (per 1,000 person-years) of each pulmonary outcome in all KPNC members aged ≥18 years, by diabetes status*

	Full cohort	Survey responder
Pneumonia*		
No diabetes	2.27 (2.24–2.29)	1.96 (1.85–2.08)
Diabetes	5.88 (5.56–6.21)	5.76 (5.40–6.11)
Asthma*		
No diabetes	0.22 (0.21–0.23)	0.16 (0.12–0.21)
Diabetes	0.48 (0.36–0.61)	0.41 (0.31–0.53)
COPD*		
No diabetes	0.60 (0.59–0.62)	0.52 (0.47–0.58)
Diabetes	0.91 (0.80–1.04)	0.87 (0.75–0.98)
Fibrosis*		
No diabetes	0.09 (0.09–0.10)	0.10 (0.07–0.13)
Diabetes	0.14 (0.12–0.16)	0.13 (0.11–0.16)
Lung cancer†		
No diabetes	0.51 (0.50–0.52)	0.66 (0.60–0.73)
Diabetes	0.47 (0.44–0.50)	0.66 (0.62–0.71)

Data are age- and sex-adjusted rates (95% CI). *Listed as the primary discharge diagnosis or underlying cause of death in the Kaiser Permanente databases. †Identified through the KPNC Cancer Registry.

tes. In analyses that excluded 16,380 persons without diabetes who responded to the 1993 MHS, the associations between diabetes and the pulmonary outcomes were similar in direction and strength to the estimates presented in Table 3 (data not shown). Analyses restricted to those survey responders with a diagnosis of diabetes demonstrated a significantly increased risk of COPD and pneumonia for each unit increase in baseline A1C (hazard ratio [HR] 1.03 [95% CI 1.01–1.04] and 1.06 [1.05–1.07], respectively; both $P \leq 0.002$), but no such associations were observed for asthma and fibrosis.

CONCLUSIONS — We found that the incidence of asthma, COPD, pulmonary fibrosis, and pneumonia, but not of lung cancer, was greater in those with a diagnosis of diabetes than in those without diabetes. These findings were consistent through out all of our analyses, whether conducted among the full cohort or the subcohort of survey responders, before and after adjustment for relevant confounders. There was a significant increase in the risk of COPD and pneumonia with increasing baseline A1C among patients with diabetes. No such associations with asthma and fibrosis were observed, suggesting that these conditions might be related to factors other than glycemic control that are associated with diabetes.

Our results are consistent with those of a study by Koskinen et al. (18), in which the authors examined the rates of death among people in Finland receiving medication for diabetes compared with rates for the rest of the population. Koskinen et al. (18) found more deaths from respiratory diseases among people receiving diabetes medication than in the rest of the population. Consistent with the findings of the present study, there was no difference between the groups in deaths from lung cancer. These authors also examined COPD separately from other respiratory diseases and found no difference in mortality between those receiving diabetes medication and the rest of the population. In the study of Koskinen et al. (18), only individuals receiving medication for diabetes were classified as having the disease, so misclassification of diabetes status is likely, particularly among persons with type 2 diabetes. In addition, the authors had no information on smoking status. Smoking has been shown to be less frequent among patients with diabetes than in the general population (19,20), so the results of Koskinen et al. are difficult to interpret.

Results of previous studies investigating the potential association between diabetes and lung cancer have been inconclusive (11–13). Our findings are consistent with the results of Hall et al. (11), who also found no increased risk of lung cancer in patients with diabetes. In fact, the 95% CIs for the HRs estimated by Hall et al. (11) overlap those of the current study. In contrast to these findings, Hanbali et al. (12) reported that diabetes was associated with a lower risk of metastasis in patients with non–small-cell cancer of the lung but not lower mortality. Win et al. (13) also recently reported that diabetes was a strong predictor of poor overall survival in patients with potentially curable lung cancer.

Kornum et al. (21) conducted a case-control study to estimate the risk of pneumonia-related hospitalization in patients with diabetes. In accordance with the present study, the authors found that both type 1 and type 2 diabetes were significantly associated with an increased risk of pneumonia-related hospitalization; poor glycemic control was also found to increase the risk of pneumonia-related hospitalization (21). These findings are consistent with an in vitro study reporting an association between hyperglycemia and abnormalities in neutrophil function, such as impaired chemotaxis, phagocytes, and bacterial killing (22).

In a cross-sectional analysis adjusted for age, sex, education, smoking, and BMI, Methvin et al. (23) found that individuals with restricted pulmonary function, the most impaired category of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, were significantly more likely to have comorbid diabetes. In another cross-sectional analysis, Gulcan et al. (24) found that fasting and 2-h blood glucose values were significantly higher in patients with asthma bronchiale than in control subjects. However, the authors attributed this difference

Table 3—*HRs and 95% CI for the association between each pulmonary condition and diabetes status among KPNC survey responders*

	Model 1*	Model 2†
Asthma‡	2.21 (1.72–2.85)	1.08 (1.03–1.12)
COPD‡	1.57 (1.40–1.77)	1.22 (1.15–1.28)
Fibrosis‡	1.64 (1.23–2.18)	1.54 (1.31–1.81)
Pneumonia‡	2.47 (2.32–2.62)	1.92 (1.84–1.99)
Lung cancer§	1.05 (0.94–1.17)	1.10 (0.96–1.26)

*Adjusted for age, sex, and race/ethnicity. †Adjusted for age, sex, race/ethnicity, smoking, BMI, education, alcohol consumption, and number of outpatient visits. ‡Primary discharge diagnosis or underlying cause of death in the Kaiser Permanente databases. §Identified through the KPNC Cancer Registry.

to inflammation-induced insulin resistance in the asthmatic patients. No previous studies have examined the incidence of COPD and asthma in individuals with and without diabetes.

The observed association between diabetes and COPD in the present study might be explained by the increased occurrence of pneumonia in patients with diabetes, as well as decreased pulmonary function related to hyperglycemia (8,10). The Fremantle Diabetes Study (5) prospectively examined the relationship between type 2 diabetes, glycemic control, and lung function. The authors found that patients with type 2 diabetes had significantly lower spirometric values than predicted for patients of the same age, sex, and height. Glycemic exposure also emerged as a consistently strong, negative predictor of follow-up lung function after adjustment for confounding variables, leading the authors to conclude that reduced lung volume and airflow limitations might be complications of type 2 diabetes. The Rancho Bernardo Study (25) showed no association between pulmonary function and known or newly diagnosed type 2 diabetes in analyses of older men and women, adjusted for age, height, and cigarette smoking. There were significant correlations between fasting plasma glucose levels and spirometric measurements only in nondiabetic men, suggesting that the deleterious effects of glycemia may precede diabetes. Litonjua et al. (2) also found that men predisposed to develop diabetes had decreased lung function years before the diagnosis of diabetes.

Our study has several strengths. Because smoking has been shown to be less frequent among people with diabetes than in the general population (19,20) and obesity is a risk factor for developing both pulmonary disease and type 2 diabetes, it is essential that any assessment of the incidence of pulmonary conditions in people with and without diabetes accounts for these factors. We had data on smoking and BMI for the cohort of survey responders, so we were able to compare the incidences of the pulmonary outcomes among survey responders with and without a diagnosis of diabetes while controlling for these key and other confounding factors.

There are also several weaknesses to be noted. The misclassification of diabetes status is a potential issue in the present study, as we were only able to include health plan members with a diagnosis of diabetes. It is possible that members who had never been tested for diabetes did, in fact, have the disease. Such misclassification suggests that the true differences between the incidences of the pulmonary outcomes and the HRs for the association between diabetes and the pulmonary outcomes are greater than we reported. In addition, data on confounding factors were taken from surveys that were mailed to members between 1995 and 1997 for those with a diagnosis of diabetes and in 1993, 1996, or 1999 for those without a diagnosis of diabetes. Because some data were collected before the baseline date of 1 January 1996, there exists the potential for misclassification of confounding variables. It is also possible that members switched categories of confounding variables between the completion of their survey and the end of the study.

Data on physical activity, a potential confounder of the associations between diabetes and the pulmonary outcomes, were, unfortunately, unavailable. The differential diagnosis of pulmonary outcomes by diabetes status was also a potential problem, as members with a diagnosis of diabetes are likely to have more contact with the health plan than those without. We addressed this issue by restricting our outcome definition to those patients requiring hospitalization who had the pulmonary outcome of interest listed as their primary discharge diagnosis and those for whom the pulmonary outcome was listed as their underlying cause of death, thus minimizing detection bias. We also included the number of outpatient visits attended in the year before the baseline in fully adjusted models and the associations remained statistically significant.

In summary, our results suggest that patients with a diagnosis of diabetes are at increased risk for asthma, COPD, pulmonary fibrosis, and pneumonia. Future studies examining the risk of these pulmonary conditions among patients with and without diabetes could benefit from a prospective design that includes repeated measurements of smoking, alcohol consumption, BMI, and physical activity over time.

Acknowledgments— This study was funded by Eli Lilly and Company and Pfizer. A.F. has received funding from Takeda and Eli Lilly to conduct research. No other potential conflicts of interest relevant to this article were reported.

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