Chronic Obstructive Pulmonary Disease, Asthma, and Risk of Type 2 Diabetes in Women

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OBJECTIVE — Inflammation plays a key role in chronic obstructive pulmonary disease (COPD) and asthma. Increasing evidence points toward a role of inflammation in the pathogenesis of type 2 diabetes. We wanted to determine the relation of COPD and asthma with the development of type 2 diabetes.

RESEARCH DESIGN AND METHODS — The Nurses' Health Study is a prospective cohort study. From 1988–1996, 103,614 female nurses were asked biennially about a physician diagnosis of emphysema, chronic bronchitis, asthma, and diabetes.

RESULTS — During 8 years of follow-up, we documented a total of 2,959 new cases of type 2 diabetes. The risk of type 2 diabetes was significantly higher for patients with COPD than those without (multivariate relative risk 1.8, 95% CI 1.1–2.8). By contrast, the risk of type 2 diabetes among asthmatic patients was not increased (1.0, 0.8–1.2). The asthma results remained nonsignificant even when we evaluated diabetes risk by duration of asthma exposure.

CONCLUSIONS — Our findings suggest that COPD may be a risk factor for developing type 2 diabetes. Differences in the inflammation and cytokine profile between COPD and asthma might explain why COPD, but not asthma, is associated with increased risk of type 2 diabetes.

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Chronic inflammation has emerged as a new risk factor for the development of type 2 diabetes (1–3). Increasing evidence now points toward a role of proinflammatory cytokines such as C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α in the pathogenesis of insulin resistance and type 2 diabetes (1–4). Due to the upregulation of proinflammatory cytokines in both asthma and chronic obstructive pulmonary disease (COPD) (5,6), one might hypothesize that these chronic inflammatory diseases would increase risk for type 2 diabetes.

However, the pattern of inflammation for asthma and COPD differs (7). The cellular infiltrate in asthma contains prominent numbers of eosinophils and type 2 helper (Th2) CD4 T-cells and associated cytokines (IL-4, -5, and -13) (5). By contrast, the cellular infiltrate in COPD is dominated by neutrophils, macrophages, and an increased numbers of lymphocytes thought to be type 1 helper (Th1) or CD8 T-cells (8), and the neutrophil-associated cytokines (TNF-α, IL-6, and IL-8) predominate (9). A recent report (10) from the Third National Health and Nutrition Examination Survey demonstrated that increasing severity of COPD was associated with increasing levels of CRP. Moreover, systemic inflammation in COPD is associated with increased muscle wasting and a continuous hypoxemic state due to destruction of lung tissue (11). Because of these inflammatory differences, the relationship of COPD or asthma with the development of another condition with an inflammatory component, such as type 2 diabetes, may vary.

We therefore evaluated the association between a history of physician-diagnosed COPD or asthma and incidence of type 2 diabetes among almost 100,000 participants in the Nurses' Health Study. We focused on potential differences in the diabetes risk conferred by COPD compared to that of asthma.

RESEARCH DESIGN AND METHODS

— The Nurses' Health Study cohort was established in 1976 when 121,700 female registered nurses, aged 30–55 years and residing in 11 populous states, completed a mailed questionnaire about their medical history and lifestyle. Every 2 years, follow-up questionnaires have been sent to update information on potential risk factors and to identify newly diagnosed cases of cancer, coronary heart disease, diabetes, and other medical conditions. The baseline year for this analysis was 1988, when all participants were first asked about a physician diagnosis of emphysema, chronic bronchitis, and asthma. A total of

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Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IL, interleukin; Th1, type 1 helper; Th2, type 2 helper; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

103,614 participants answered the supplementary questionnaire for asthma and COPD. For this analysis, we excluded women with type 1 diabetes, women classified as having only gestational diabetes, and those who had preexisting type 2 diabetes before 1988. We also excluded participants that lacked diabetes confirmation and were missing date of birth. Therefore, our baseline cohort for incident type 2 diabetes between 1988 and 1996 included 97,618 women.

There were a total of 5,986 participants with respiratory disease consistent with a diagnosis of asthma, COPD, or components of COPD, but not meeting the diagnostic criteria. Of these, 1,715 had COPD, but the date of onset was not available for 373, leaving 1,342 participants for inclusion in the study. Thus the COPD cohort included 97,245 participants: 1,342 with COPD and 95,903 free of COPD.

For the analyses of asthma, we excluded subjects with COPD ($n = 1,715$) and also those participants who had components of COPD but did not meet the diagnostic criteria ($n = 1,371$) from the baseline cohort. Date of onset of asthma was missing in 21 patients, leaving 2,879 participants with asthma for inclusion in the study. Thus the asthma cohort included 94,511 participants: 2,879 with asthma and 91,632 free of asthma.

At baseline, participants provided data on demographic, lifestyle, and biological factors, including age, race, current weight and height, smoking status, physical activity, dietary intake, and comorbid conditions. Participants also were asked if they had recently undergone a health screening examination or if they currently used any nutritional supplements. The participants contributed person-time until the end of follow-up or the time of type 2 diabetes diagnosis.

Ascertainment of respiratory disease

From 1988 to 1996, all participants were asked biennially about a physician diagnosis of emphysema, chronic bronchitis, and asthma. A supplementary questionnaire was sent in 1998 to all living nurses who reported a physician diagnosis of emphysema, chronic bronchitis, or asthma through 1996. This supplemental questionnaire requested information confirming a physician diagnosis of emphysema, chronic bronchitis, COPD, or asthma; dates of symptom onset and diagnosis; tests performed to confirm the diagnosis; and symptoms consistent with a diagnosis of chronic bronchitis (i.e., ≥2 months of productive cough for >2 years).

The supplemental questionnaires also included items on recent medication use, respiratory symptoms, health care utilization (hospital visits, emergency department visits, and urgent office visits), and results of spirometry in the preceding year. The questionnaire-based definitions of COPD and asthma have been validated in prior publications (12,13).

Cases of COPD

The contemporary clinical definition of COPD was used: a diagnosis of COPD, emphysema, or chronic bronchitis with evidence of airflow obstruction that is not fully reversible (14). Definitions were established independent of smoking status. Since COPD is rarely diagnosed before age 35 years (14), cases were excluded if the reported age at COPD diagnosis was ≤35 years. Of the participants with COPD who were included in the study, 605 (45%) had some asthmatic component.

Cases of asthma

Using information from supplementary questionnaires and the special mailing to all asthmatic (and COPD) participants in 1998, each participant reporting asthma was categorized using two case definitions. Case definition 1 required both of the following: *1*) reiterated on second questionnaire that a physician had diagnosed the subject as having asthma and *2*) reported using an asthma medication (e.g., inhaled steroids, oral or intravenous steroids, theophylline, cromolyn or nedocromil, leukotriene modifiers, and salmeterol) since diagnosis. To meet case definition 2, participants had to fulfill the criteria of case definition 1 and report use of a prescribed long-term preventive medication (e.g., inhaled steroids) in the past year.

Ascertainment of type 2 diabetes

The outcome in this analysis was newly diagnosed type 2 diabetes between 1988 and 1996. We mailed a supplementary questionnaire regarding symptoms, diagnostic tests, and hyperglycemic treatments to all women who reported a diagnosis of diabetes on any biennial follow-up questionnaire. The diagnosis of diabetes was established when at least one of the following criteria was reported on the supplementary questionnaire: *1*) one or more classic symptom (excessive thirst, polyuria, weight loss, hunger, or coma) plus a fasting plasma glucose concentration of ≥140 mg/dl (7.8 mmol/l) or a random plasma glucose concentration of ≥200 mg/dl (11.1 mmol/l), *2*) at least two elevated plasma glucose concentrations on different occasions (fasting, 140 mg/dl [7.8 mmol/l]; random, 200 mg/dl [11.1 mmol/l]; or random, 200 mg/dl [11.1 mmol/l] after at least 2 h of oral glucose tolerance testing) in the absence of symptoms, or *3*) treatment with hypoglycemic medication (insulin or oral hypoglycemic agents). The diagnostic criteria for type 2 diabetes were changed in 1997 (15). However, we used the criteria proposed by the National Diabetes Data Group (16) because all of our case subjects were diagnosed before June 1996. The questionnaire-based definition of type 2 diabetes has been validated in a sample by medical record review (17).

Statistical analysis

Person-time for each participant was calculated from the date of return of the 1988 questionnaires to the date of confirmed type 2 diabetes between 1988 and 1996. Exposure status was updated every 2 years. We calculated rates of incident type 2 diabetes for women with prior COPD or asthma by dividing the number of incident cases by the number of person-years of follow-up contributed by women with COPD or asthma, respectively. The relative risk (RR) was computed as the rate among women with prior COPD or asthma divided by the rate among women without COPD or asthma, with adjustment for 5-year age categories. Risk of type 2 diabetes also was calculated for different durations of asthma (i.e., years since first diagnosis of asthma, with categories of <10, 10–20, and >20 years). A test for trend across the categories of asthma duration was calculated by treating the categories as an ordinal variable in a proportional hazards model. Duration of COPD was not evaluated because it is a more slowly progressive disease and because, by the time of diagnosis, the patient may already have had the disease for unknown and variable amounts of time (18).

Multivariate Cox regression models were used to control for potential confounding by other risk factors for type 2

Table 1—*Baseline characteristics of the 97,245 participants of the Nurses' Health Study in 1988*

		No COPD	
	COPD	Asthma	No asthma*
n	1,342	2,879	93,024
Age (years)	58 ± 7	52 ± 7	54 ± 7
Race (%)			
White	93	92	87
Non-white	3	5	5
Missing	4	3	8
BMI (kg/m^2)	24.1 (21.6–27.3)	25.5 (22.8–29.2)	24.4 (22.1–27.5)
Family history of diabetes (%)	24	20	20
Hypertension (%)	19	20	16
Hormone replacement therapy (%)			
Premenopausal	24	29	29
Current user of estrogen only	9	12	8
Current user of estrogen and progesterone	6	7	5
Missing	20	17	20
Activity level (METs/week)	12 ± 18	14 ± 17	16 ± 22
Smoking status (%)			
Never smoker	16	48	44
Past smoker	31	41	36
Current light smoker (<25 cigarettes/day)	28	8	14
Current heavy smoker (≥25 cigarettes/day)	25	3	6
Pack-years	50 (37–67)	20 (8–35)	25 (12–43)
Daily alcohol intake (gm/day)	9 ± 14	6 ± 10	7 ± 10
Cereal fiber intake (gm/day)	4 ± 3	5 ± 3	5 ± 3
Trans fat intake (gm/day)	3 ± 1	3 ± 1	3 ± 1
Glycemic load index	10,923 ± 4,183	11,129 ± 4,118	11,044 ± 4,094
Polyunsaturated-to-saturated fat ratio	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2

Data are means ±SD or median (interquartile range), unless noted otherwise. *Includes 1,371 participants with a component of COPD not reaching diagnostic criteria and 21 subjects with asthma but without date of onset. MET, metabolic equivalent.

diabetes. The multivariate model adjusted age (in 5-year categories), time periods (in four categories), BMI (in seven categories), family history of diabetes, menopausal status, use of postmenopausal hormone therapy, weekly frequency of moderate-to-vigorous exercise (<0.5, 0.5–3.9, 4.0–6.9, or ≥7.0 h), smoking status (never smoked, former smoker, current smoker [<25 cigarettes/day] or current smoker [≥25 cigarettes/day]), daily alcohol intake, and a dietary score variable. Our choice of ≥25 cigarettes/day as a cut point was based on previously published data (19) from the Nurses' Health Study that showed that there was a 1.42-fold increased risk of diabetes associated with smoking ≥25 cigarettes per day. RR estimates were much lower and not statistically significant for lower levels of smoking, although the overall test for trend suggested a dose-response relationship.

The dietary score variable included information on dietary predictors of type 2 diabetes (20), including cereal fiber, *trans* fat, glycemic load, and the ratio of polyunsaturated to saturated fat. These data were derived from a 120-item, semiquantitative, food frequency questionnaire. Each woman was assigned a score of each nutrient on the basis of quintiles of intake (a higher score represented a lower risk), and then the four scores were summed and the total score categorized into quintiles.

RESULTS — Table 1 shows the general characteristics of our cohort of 97,245 women. In 1988, the mean age of the participants was 54 years. The median BMI of our participants was 25.4 kg/m^2, and 34% were overweight or obese (BMI ≥25.0 kg/m^2). Approximately 20% of the participants had a family history of diabetes, and 44% of the women were never smokers.

During 8 years of follow-up, we documented 2,959 new cases of type 2 diabetes in the COPD cohort, with 19 cases of incident type 2 diabetes among the participants who had COPD. In the asthma cohort, we documented 2,827 new cases of type 2 diabetes, with 69 cases among the participants who had asthma. We calculated the age-, BMI-, and fully adjusted RRs of type 2 diabetes for participants with COPD or asthma compared with participants who did not have COPD or asthma, respectively (Table 2).

The age-adjusted risk of type 2 diabetes was higher for patients with COPD than those without (RR 1.8). After adjusting for potential confounders, the RR of diabetes for patients with COPD did not change (RR 1.8). In order to further control for potential confounding, we also ran an expanded model adjusting for potential confounding factors including age (in 5-year categories), time periods (in four categories), BMI (in seven categories), family history of diabetes, menopausal status, use of postmenopausal hormone therapy, weekly frequency of moderate-to-vigorous exercise (<0.5,

Table 2—*Risk of type 2 diabetes from 1988 to 1996 according to COPD or asthma status*

	Person-years	Incident diabetes	Age-adjusted RR (95% CI)	Age- and BMI-adjusted RR (95% CI)	Multivariate RR (95% CI)*
COPD cohort (n = 97,245)					
No COPD	726,840	2,940	1.0 (reference)	1.0 (reference)	1.0 (reference)
COPD	2,505	19	1.8 (1.1–2.8)	1.9 (1.2–3.0)	1.8 (1.1–2.8)
Asthma cohort (n = 94,511)					
No asthma	693,066	2,758	1.0 (reference)	1.0 (reference)	1.0 (reference)
Asthma	15,389	69	1.1 (0.9–1.5)	0.9 (0.7–1.2)	1.0 (0.8–1.2)

*Adjusted for age, BMI (in four categories), sedentary (weekly frequency of moderate-to-vigorous exercise <0.5 h), smoking status (never smoked, former smoker, current smoker [<25 cigarettes/day], or current smoker [≥25 cigarettes/day]), daily alcohol intake, and a dietary score variable.

0.5–3.9, 4.0–6.9, or ≥7.0 h), smoking status (never smoked, former smoker, current smoker [<25 cigarettes/day], or current smoker [≥25 cigarettes/day]), daily alcohol intake, and a dietary score variable. The results of this expanded model were similar (RR 1.8, 95% CI 1.1–2.8) to our primary results.

By contrast, the age-adjusted risk of diabetes was not significantly higher for patients with asthma than for those without (RR 1.1). Furthermore, after adjusting for potential confounders, the RR of type 2 diabetes for asthmatic patients was null (RR 1.0, 95% CI 0.8–1.2). Additional variables, as listed above, were included in an expanded model to further adjust for potential confounding, and the asthma result did not change (1.0, 0.8–1.2). To further explore the relation of asthma to diabetes risk, we examined whether the duration of asthma exposure was associated with the risk of developing type 2 diabetes. Compared with women without asthma, those with asthma for <10, 10–20, and >20 years showed no significant association with incidence of diabetes (hazard ratios 0.6, 1.2, and 1.1, respectively).

To explore the effect of smoking on the association between COPD and asthma and risk of diabetes, we performed stratified analyses according to smoking status (Table 3). Although there was limited statistical power, there was a trend in never-smoker COPD patients for higher risk of type 2 diabetes (RR 1.4, 95% CI 0.46–4.5). There was no association between asthma (0.98, 0.69–1.38) and risk of diabetes. When we considered all smokers (past and current), the risk of diabetes remained higher in COPD patients (2.0, 1.2–3.2) when compared with asthma patients (1.01, 0.72–1.4). In a sensitivity analysis, we also controlled for physician visits, and this factor did not alter our results (data not shown).

To address the possibility that surveillance may have varied according to COPD, we performed an analysis restricted to case subjects reporting at least one symptom of diabetes at diagnosis (n = 1,554, 52% of all case subjects). Results from this subgroup were not appreciably different from those for the entire cohort (RR 1.8, 95% CI 1.0–3.4). For asthma, the results also did not change (n = 1,532, 54% of all case subjects; RR 1.1, 95% CI 0.8–1.6).

In a separate analysis, we examined the potential differences in oral steroid use among women with COPD compared with women with asthma. On a question about usual medications between 1992 and 1994, oral steroids were reported by 9% of participants with COPD and 9% of participants with asthma (P = 0.81). Similarly, use of oral steroids "in the past year" was asked on the 1998 supplementary questionnaire and yielded values of 30% among women with COPD and 32% among women with asthma (P = 0.27).

CONCLUSIONS — In this prospective cohort study involving almost 100,000 women, we found that subjects with COPD had a statistically significant, increased risk of developing type 2 diabetes that persisted after multivariate adjustment for potential confounders. By contrast, such an association was not found among women with asthma. Glucose metabolism has not been studied extensively in COPD patients, and the available studies are inconclusive, perhaps due to differences in BMI and the hypoxemic state of this patient population (21–24). Our prospective study extends these earlier physiologic observations. Some studies have suggested that a reduced lung function could be a risk factor for the development of insulin resistance or diabetes (25–27). However, these studies only focused on impaired lung function (25,26) or forced vital capacity (27) and did not look into any association between physician-diagnosed COPD or asthma and risk of developing diabetes.

Although both asthma and COPD are chronic inflammatory conditions, we found no significant association between asthma and risk of type 2 diabetes. This could be due to differences in the type of inflammation in asthma versus COPD. The cellular infiltrate in asthma contains prominent numbers of eosinophils and Th2 cells (5). By contrast, the cellular infiltrate of COPD is dominated by neutrophils, macrophages, and Th1 cells (8), with associated cytokines such as TNF-α, IL-6, and IL-8 (9), which are also believed (28) to play a major role in the development of type 2 diabetes.

There are a number of ways in which COPD might lead to the development of type 2 diabetes. Inflammatory markers that are increased in patients with type 2 diabetes have been observed to be upregulated in patients with COPD (9), suggesting that inflammation may be the common link. Elevated levels of CRP, IL-6, and TNF-α have been shown (1–4,29,30) to predict the development of the insulin resistance syndrome and type 2 diabetes, supporting a role for inflammation in the pathogenesis of diabetes.

The chronic state of inflammation in COPD patients is believed to shift the metabolism of the patients toward net protein catabolism, in turn increasing the resting energy expenditure (31). As a re-

Table 3—*Risk of type 2 diabetes associated with COPD or asthma stratified by smoking status*

	COPD		Asthma	
	n (%)	RR (95% CI)	*n* (%)	RR (95% CI)
All patients	1,342 (100)	1.8 (1.1–2.8)	2,879 (100)	1.0 (0.8–1.2)
Never smokers	215 (16)	1.4 (0.46–4.5)	1,382 (48)	0.98 (0.69–1.4)
Past smokers	416 (31)	2.2 (1.1–4.4)	1,180 (41)	1.05 (0.73–1.5)
Current smokers	711 (53)	1.7 (0.84–3.4)	317 (11)	0.79 (0.32–1.9)
All smokers	1,127 (84)	2.0 (1.2–3.2)	1,497 (52)	1.01 (0.72–1.4)

*Adjusted for age, BMI (in four categories), sedentary (weekly frequency of moderate-to-vigorous exercise <0.5 h), smoking status (never smoked, former smoker, current smoker [<25 cigarettes/day], or current smoker [≥25 cigarettes/day]), daily alcohol intake, and a dietary score variable.

sult, the fat-free mass of such patients is depleted (32–34), which is accompanied by an increase in systemic markers of inflammation (35,36). Other studies have also shown a link between systemic inflammation and skeletal muscle loss in COPD, even when weight loss is not apparent (37,38). Circulating TNF-α levels have been found to be elevated in cachectic COPD patients with chronic hypoxemia, a potential stimulus for activation of the proinflammatory cytokine system (39) in such patients. TNF-α, a central inflammatory mediator in the process of muscle wasting, promotes cachexia by reducing peripheral insulin action (30,40). Muscle loss and decreased fat oxidative capacity, along with low physical activity, lead to further muscle loss and fat gain. Fat gain in turn elevates circulating TNF-α, escalating insulin resistance and muscle loss.

Oxidative stress as seen in patients with COPD results in injury to the airspace epithelium, increased influx of neutrophils into the lungs, and activation of transcription factors, including nuclear factor-κB, which switches on the genes for TNF-α, IL-8, and other inflammatory mediators (6,41,42). Such oxidative stress has been implicated in insulin resistance (43). Reactive oxygen species interfere with insulin signaling at various levels and are able to inhibit the translocation of GLUT4 in the plasma membrane, leading to insulin resistance (43). Moreover, an increase in insulin or glucose levels further increases reactive oxygen species production and oxidative stress, impairing both insulin action and secretion and accelerating the progression to overt type 2 diabetes.

The current study has some potential limitations. Our subjects included only women, the vast majority of whom were Caucasian and had a similar socioeconomic status. Although the homogeneity in the sample would reduce confounding, it may also reduce the generalizability of our findings. Currently, we have no reason to suspect that men or non-Caucasians would differ in terms of the effects of COPD on diabetes. Future studies to evaluate this association in other populations would be informative. Women in our cohort who did not report diabetes were not uniformly screened for glucose intolerance. This may have misclassified some participants with unrecognized diabetes. Our epidemiologic definition of asthma and COPD also may have resulted in some misclassification of participants. There also might have been some misclassification of other covariates, and we cannot exclude a component of uncontrolled or residual confounding. We did, however, adjust for the major risk factors for diabetes (20).

We cannot rule out the possibility of that some or all of the effects of COPD on the risk of diabetes incidence that we observed was a result of residual confounding by cigarette smoking. In our analyses, we attempted to control for smoking in the multivariate models and through stratified analyses, dividing the population into four categories. Interestingly, we observed a 40% higher risk among subjects with COPD who reported being lifelong nonsmokers, although this finding did not reach statistical significance.

Our observation that 16% of the COPD patients reported being lifelong nonsmokers is consistent with prior epidemiological studies (44) that have reported that 5–12% of patients with prevalent COPD report having never smoked. Whether this reflects reporting bias, the effects of second-hand smoke, or other exposures is unknown.

Another potential limitation is that the higher risk of type 2 diabetes among individuals with COPD may have been mediated, at least in part, by the use of systemic corticosteroids (45). We did not have data on the dosage or frequency of steroid use, so we were unable to control for it. The risk of developing corticosteroid-induced diabetes has only been seen with the use of systemic steroids (46,47), whereas there is no evidence for an association with the use of inhaled corticosteroids (47). In our cohort, at two different time points, there was no significant difference in the use of oral steroids between participants with asthma and COPD. If corticosteroid use was responsible for the development of type 2 diabetes, we would have expected to see a similar increased risk of type 2 diabetes among subjects with asthma. There remains a potential for detection bias as an explanation for these findings (e.g., adults with the diagnosis of COPD or asthma were more likely to be screened for diabetes). If that were the case, however, we would have expected to see similar increases in the diagnosis of diabetes for both the COPD and asthma groups.

In summary, our findings suggest that COPD but not asthma may be associated with a higher risk of developing type 2 diabetes. Further prospective studies are needed to test this hypothesis and to examine cytokine profiles (both Th1 and Th2) in COPD or asthmatic patients who go on to develop type 2 diabetes. Moreover, future prospective studies might examine whether COPD or asthma are associated with increased risk of other diseases with an inflammatory component, such as atherosclerosis.

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