Cigarette Smoking, Alcohol Consumption, and Risk of ARDS*

A 15-Year Cohort Study in a Managed Care Setting

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Study objective: **To examine the association of cigarette smoking and alcohol consumption with hospital presentation of ARDS in a well-defined, multiethnic population.**
Design: **Retrospective cohort study.**
Setting: **Health maintenance organization in Northern California.**
Participants: **A total of 121,012 health plan subscribers (54.2% women), aged 25 to 89 years.**
Outcome measure: **Hospital presentation of ARDS (validated by medical chart review) from baseline in 1979 to 1985 through the end of 1993 (median, 9.9 years).**
Results: **There were 56 cases of ARDS (33 in men, 23 in women). The case fatality rate was 39% in both genders. ARDS was independently related to increasing age (rate ratio of 10 years, 1.38; 95% confidence interval [CI], 1.12 to 1.71), to current smoking of < 20 cigarettes/d (rate ratio vs never cigarette smokers, 2.85; 95% CI, 1.23 to 6.60), and to current cigarette smoking of ≥ 20 cigarettes/d (rate ratio vs never smokers, 4.59; 95% CI, 2.13 to 9.88). No association was observed between alcohol consumption and ARDS.**
Conclusions: **The results of this study suggest a relationship (with evidence of dose-response effect) between cigarette smoking and ARDS. Assuming a causal relationship, approximately 50% of ARDS cases were attributable to cigarette smoking.** ***(CHEST 2000; 117:163–168)***

Key words: alcohol; ARDS; epidemiology; risk factors; smoking

Abbreviations: BMI = body mass index; ICD-9 = *Ninth Revision of the International Classification of Diseases*

The ARDS is a severe clinical picture defined by the presence of dyspnea, tachypnea, hypoxemia, radiographic evidence of bilateral chest infiltrates, and decreased respiratory compliance, and is caused by inflammatory-cell-mediated endothelial lung injury.[1–3] It is a rapidly progressive syndrome, with an overall fatality rate of 40 to 60%.[1,4,5]

Since there is no specific treatment modality, the identification of patients at higher risk for the development of ARDS is paramount. Well-established clinical (or proximal) predictors of ARDS include sepsis, aspiration of gastric contents, and major trauma.[5–11] However, less is known about nonproximal factors that may increase the likelihood of eventually developing ARDS.

Cigarette smoking and alcohol consumption are potential nonproximal risk factors for ARDS. First, smoking increases the risk of many lung and systemic disorders predating ARDS,[12–16] and secondly, cigarette smoke contains highly reactive hydroxyl radicals capable of causing membrane peroxidation,[17] damage to DNA,[18] and inflammatory reactions.[12–16] In turn, chronic heavy alcohol consumption has been linked to trauma outcomes,[19,20] and to increased risk of complication during the course of hospitalization.[21]

The aim of this study was to test the hypothesis of whether cigarette smoking and alcohol consumption are independent risk factors for subsequent presentation of ARDS in a well-defined, multiethnic population.

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Materials and Methods

Cohort Description

Participants were members of the Kaiser Permanente Medical Care Program (Northern California Region), a San Francisco Bay area-based health maintenance organization. The subscribers are socioeconomically diverse, but their average education level is higher than the general population in the area served by the health plan.[22] As a result, the lowest (but also the highest) end of the socioeconomic spectrum are underrepresented.

At the multiphasic health checkup (a voluntary medical examination at the time of enrollment), members filled questionnaires about demographics, medical history, smoking and alcohol use, and a blood sample was drawn for chemistry determinations. Participants were classified into never smokers (those who reported having never used any tobacco product); former cigarette smokers (ever smokers for at least 1 year, but no longer smoking cigarettes in the current year); and current cigarette smokers (still smoking cigarettes regularly, at least five cigarettes per week, almost every week). Current cigarette smokers were subclassified into smokers of < 20 cigarettes/d and smokers of ≥ 20 cigarettes/d. Likewise, subjects were classified as never drinkers (lifelong abstainers); former drinkers (ever drinkers for at least 1 year, but no longer consuming alcohol); current drinkers of less than three drinks per day; and current drinkers of more than or equal to three drinks per day during the past year.

Weight and height were measured following standardized procedures.[23] Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Lung function tests including FVC and FEV_1 were performed using a Vertek VR5000 Lung Function computer (Electro/Med. Instruments; Houston, TX) according to methods previously described.[23] Lung function tests as a component of the multiphasic health checkup were discontinued in 1981. For participants with repeated health examinations, only data from the first available multiphasic examination were used.

The total sample for this study contained 121,012 health plan subscribers (55,389 men and 65,790 women) between the ages of 25 and 89 years at the time of their first multiphasic health checkup at San Francisco or Oakland between 1979 and 1985. No exclusions were performed because of prevalent disease or missing data on study variables. This study was approved by the Institutional Review Board of The Kaiser Foundation Research Institute.

Outcome Measure and Medical Record Review

Since 1971, Kaiser Permanente of Northern California has maintained an automated database of all overnight hospitalizations in the 23 medical centers affiliated with the health plan. The database contains personal information, dates of hospital admission and discharge, discharge vital status, the principal discharge diagnosis, and up to 12 possible secondary discharge diagnostic codes. For the purposes of this study, we used a computer algorithm that extracted codes 518.5 ("pulmonary insufficiency following trauma and surgery") and 518.82 ("other pulmonary insufficiency, not elsewhere classified") of the *Ninth Revision of the International Classification of Diseases* (ICD-9),[24] regardless of whether they were a principal or secondary diagnosis, for the period from 1979 to 1993. Overall, 130 hospitalizations were found that listed codes 518.5 or 518.82. Following this initial screening of inpatient records, the medical charts of these 130 patients were requested to the Kaiser facilities in the region and reviewed by a study physician (C. I.) who was unaware of the risk factor status of the participants. The hospital charts of four patients (two men and two women) were not available for review (three were sent to physician's offices, and one to a non-Kaiser Permanente medical facility). Thus, medical record abstraction was performed on 126 charts. ARDS cases were defined as hospitalizations with ICD-9 codes 518.5 or 518.82, which met the European-American ARDS consensus conference definition: acute onset of respiratory distress (*ie*, within hours); bilateral infiltrates on chest radiograph; hypoxemia (ratio of O_2 saturation to concentration of O_2 in the inspired air [PaO_2/fraction of inspired oxygen] < 200 mm Hg); and no clinical evidence of left atrial hypertension (ascertained from physician's diagnostic impressions as noted in the discharge summary report).[1] Of the 126 reviewed cases, 56 "true-positives" met all four criteria for ARDS. Thus, the positive predictive value of ICD-9 codes 518.5 or 518.82 was 44% (56/126). Because charts without ICD-9 codes 518.5 or 518.82 were not reviewed, the negative predictive value, sensitivity, and specificity of diagnosis relying on ICD-9 codes could not be established. The most common reasons for the 70 false-positive cases were lack of evidence of bilateral infiltrates and/or hypoxemia.

A secondary aim of the medical chart review was to ascertain the proximal or precipitating factors leading to ARDS. This information was obtained directly from the "Hospital Course" section of the discharge summary report.

As an attempt to characterize the number of admissions in the ICU over the follow-up period, we identified procedures typically employed in the ICU setting, including assisted ventilation (ICD-9 codes 93.90, 93.91, 96.70, 96.71 and 96.72); arterial catheterization (38.91); central venous line pressure monitoring (89.62); pulmonary artery pressure monitoring (89.63); and Swan-Ganz catheterization (89.64). In addition, we identified patients who underwent one of more of these procedures and died during the course of his or her hospitalization.

Statistical Methods

Sex- and age-specific incidence rates of hospital presentation of ARDS were calculated both per 10^5 persons and per 10^5 person-years of follow-up. Person-time was defined for each participant as the time elapsed from baseline multiphasic health checkup to the earliest of the following: hospitalization for ARDS ($n = 56$); end of health plan membership ($n = 59{,}570$); or December 31, 1993, the closing date ($n = 61{,}386$). End of membership was defined as disenrollment for > 2 consecutive years. Compared to individuals who remained in the health plan until the closing date, those who left the plan before the closing date were, on average, younger (41 ± 15 vs 45 ± 13 years) and had lower BMI (24.6 ± 4.6 vs 25.3 ± 4.7 kg/m^2), but did not differ importantly in ethnic background, education level, smoking, and alcohol consumption habits (data not shown). The median length of follow-up time was 9.9 years, with a maximum of 15 years.

We used the Cox proportional hazards approach to model the age-adjusted association of the predictor variables of interest (cigarette smoking and alcohol consumption) with the outcome.[25] A multivariate model was then used that included also gender, race, education level, and BMI as possible confounders. To account for possible nonlinearity, BMI was entered in the regression as three categorical levels representing quartiles. To prevent loss of data, dummy variables were created for missing observations on education level, race, cigarette smoking, alcohol consumption, and BMI, respectively; none were related to the outcome. All analyses were conducted using appropriate software (SAS Version 6.11; SAS Institute; Cary, NC).[26]

We estimated attributable risk of ARDS due to smoking as the excess cases divided by the total observed cases, in percent. We first estimated the expected (background) number of cases if everyone had been a never smoker by applying the never smoker rate to the numbers of people in the various smoker and former

smoker categories. The number of excess cases is then total observed cases minus the number of expected cases.

Results

A total of 56 confirmed cases of ARDS (33 in men, 23 in women) were ascertained during the study period (from 1979 to 1993). The in-hospital case fatality rate was 39.4% in men (13/33) and 39.1% in women (9/23). The distribution of proximal or precipitating factors leading to ARDS were as follows: diffuse pulmonary infection (n = 17; 30.3%), sepsis syndrome (n = 16; 28.6%), aspiration (n = 15; 26.8%), hypertransfusion (n = 3; 5.3%), cardiopulmonary bypass (n = 2; 3.6%), lung contusion (n = 1; 1.8%), severe nonthoracic trauma (n = 1; 1.8%), and methotrexate-induced pneumonitis (n = 1; 1.8%).

Although we are very likely underestimating the number of ARDS cases, our data suggests an incidence of 4.6 cases/100,000 persons/yr. This estimate is derived from the finding of 56 cases in 9.9 years in a population of 121,012 persons.

Over the course of the study, we identified 401 hospitalizations with an assisted-ventilation code only; 924 hospitalizations with arterial, central venous line, pulmonary, or Swan-Ganz catheterization only; and 127 hospitalizations with both an assisted-ventilation code and a code for at least one of the catheterization modalities listed above. Based on these numbers, the estimated incidence rate of assisted ventilation was 33.5/100,000 persons/yr; the incidence rate of selected catheterization procedures was 77.1/100,000 persons/yr; and the incidence rate of both assisted ventilation and selected catheterization procedures was 10.6/100,000 persons/yr. The in-hospital mortality among those receiving assisted ventilation only, selected catheterization procedures, or both was 32.4%, 33.8%, and 44.9%, respectively.

Compared to the rest of the cohort, ARDS cases were older, more likely to be men, and white (Table 1). There was a greater prevalence of current cigarette smoking (both < 20 and ≥ 20 cigarettes/d) and of current alcohol consumption of three or more drinks per day among ARDS cases compared to cohort counterparts. No difference was observed for BMI.

The false-positive cases (those with ICD-9 codes 518.5 or 518.82 but not meeting the study criteria for ARDS) were older (57 ± 11 years), more likely to be black (29%), and more likely to be current smokers of < 20 cigarettes/d (10%) and of ≥ 20 cigarettes/d (23%).

The incidence rates of hospital presentation of ARDS were higher in men than in women (Table 2). In women, the rates increased monotonically with increasing age; in men, the rates increased from ages 25 to 44 years to ages 45 to 64 years, but not from ages 45 to 64 years to ages > 65 years.

Table 1—*Baseline Characteristics of ARDS Cases vs the Rest of the Cohort. Kaiser Permanente Medical Care Program, Northern California Region (1979–1985)*

Characteristics	ARDS Cases, n = 56	Rest of the Cohort, n = 120,956	p Value*
Age, yr†	52.8 (12.6)	43.1 (14.0)	< 0.0001
Male gender, %	59	46	0.04
Race, %			
White	73	60	0.18
Black	16	25	
Asian	7	8	
Other‡ or unknown	4	7	
Smoking, %			
Never	25	49	0.001
Former	27	22	
Current, < 20 cigarettes/d	18	15	
Current, ≥ 20 cigarettes/d	28	13	
Unknown	2	1	
Alcohol, %			
Never	9	8	0.004
Former	9	3	
Current, < 3 drinks/d	57	74	
Current, ≥ 3 drinks/d	16	8	
Unknown	9	7	
BMI, kg/m^2†	25.4 (3.8)	24.4 (5.2)	0.80

*p value for *t* test comparison of continuous variables and χ^2 comparison of categorical variables.

†Presented as means (SD).

‡Hispanic or Latino nonwhite, American Indian or Alaska Native, Native Hawaiian or Pacific Islander.

Results of the age- and multivariate-adjusted analyses are given in Table 3. In the univariate models, the risk of ARDS increased with advancing age, male gender, current smoking, and former alcohol consumption. There was a clear dose-response association with cigarette smoking, with a 5.7-fold increased risk among heavy smokers (*ie*, ≥ 20 cigarettes/d), and a borderline association with former cigarette smoking. In the multivariate pooled analysis, ARDS continued to be related to increasing age, and to cigarette smoking in a dose-response fashion. It was also observed that, when other risk factors were considered, blacks were at lower risk than their white counterparts, and that former alcohol consumption was no longer related to the outcome. No apparent independent relationship existed with average consumption of three alcoholic drinks or more per day. There was a suggestion of a *U*-shaped association with BMI.

In a sensitivity analysis including all cases with codes 518.5 and 518.82 (n = 130), the multivariate-adjusted relative risks associated with current cigarette smoking of < 20 and ≥ 20 cigarettes/d (vs

Table 2—*Gender- and Age-Specific Incidence Rates of ARDS. Kaiser Permanente Medical Care Program, Northern California Region (1979–1993)***

Variables	Age Groups			
	25–44 yr	45–64 yr	65–89 yr	All Ages
Men				
Number of events	9	20	4	33
Number of persons	32,679	17,819	4,891	55,389
Number of person-years	270,910	197,520	48,879	517,309
Rate per 10^5 persons	27.5	112.2	81.8	59.6
Rate per 10^5 person-years	3.3	10.1	8.2	6.4
Women				
Number of events	4	14	5	23
Number of persons	39,031	20,782	5,810	65,623
Number of person-years	333,087	238,514	64,189	635,790
Rate per 10^5 persons	10.2	67.4	86.0	35.0
Rate per 10^5 person-years	1.2	5.8	7.8	3.6

*Person-years and number of events are allocated to age categories based on age at baseline.

Table 3—*Relative Risks and 95% Confidence Intervals for ARDS Associated With Selected Baseline Variables. Kaiser Permanente Medical Care Program, Northern California Region (1979–1993)***

Baseline Variables	Age Adjusted†	Multivariate Adjusted‡
Age, 10 yr	1.44 (1.19–1.74)	1.38 (1.12–1.71)
Male gender, vs female	1.81 (1.06–3.09)	1.70 (0.97–3.01)
No college education, vs some college or higher	1.67 (0.96–2.90)	1.66 (0.95–2.92)
Race		
Black, vs white	0.55 (0.26–1.13)	0.47 (0.22–0.99)
Asian, vs white	0.86 (0.31–2.42)	0.92 (0.31–2.70)
Other§ or unknown, vs white	0.51 (0.12–2.16)	0.53 (0.12–2.26)
Smoking‖		
Former, vs never	2.06 (0.99–4.28)	1.84 (0.86–3.95)
Current $<$ 20 cigarettes/d, vs never	2.74 (1.21–6.20)	2.85 (1.23–6.60)
Current $\geq$ 20 cigarettes/d, vs never	5.72 (2.78–11.79)	4.59 (2.13–9.88)
Alcohol		
Former, vs never	3.68 (1.06–12.72)	1.89 (0.52–6.87)
Current $<$ 3 drinks/d, vs never	0.93 (0.36–2.38)	0.58 (0.21–1.55)
Current $\geq$ 3 drinks/d, vs never	2.41 (0.80–7.22)	0.97 (0.30–3.16)
BMI		
21.8 to 24.2, vs $<$ 21.8 kg/m^2	0.75 (0.38–1.46)	0.73 (0.38–1.42)
24.3 to 27.2, vs $<$ 21.8 kg/m^2	0.58 (0.29–1.15)	0.52 (0.25–1.03)
$\geq$ 27.3, vs $<$ 21.8 kg/m^2	0.88 (0.67–1.15)	0.87 (0.64–1.17)

*Analysis based on 56 events in 121,012 persons.
†Separate models for each categorical or continuous predictor, adjusting for age and gender.
‡All predictors in the same model.
§Hispanic or Latino nonwhite, American Indian or Alaska Native, Native Hawaiian or Pacific Islander.
‖Number of events, by smoking status: never (14), former (15), current $<$ 20 cigarettes/d (10), current $\geq$ 20 cigarettes/d (16), unknown (1); number of events, by alcohol consumption status: never (5), former (5), current $<$ 3 drinks/d (32), current $\geq$ 3 drinks/d (9), unknown (5).

never smoking) were 1.57 (95% confidence interval, 0,86 to 2.84) and 3.82 (95% confidence interval, 2.34 to 6.27), respectively.

If all participants had been never smokers, and the never smoker rate had prevailed, only 6 of 15 cases would have occurred among former smokers, only 4 of 10 cases among smokers of $<$ 20 cigarettes/d, and only 4 of 16 cases among smokers of $\geq$ 20 cigarettes/d. Thus risk of ARDS attributable to cigarette smoking is estimated to be 50%.

We also examined in the full cohort the association of ARDS with other physiologic variables, such as blood cholesterol, systolic BP, and WBC counts; these were found to be unrelated to the outcome and thus were not considered in the final analysis. In a subset of 46,138 men and women who had valid spirometry data (among whom, 21 cases of ARDS developed), no associations were found between FVC or FEV_1 and ARDS (data not shown).

Discussion

In this insured, ethnically diverse population of the San Francisco Bay area, the incidence of ARDS was low but comparable to recent estimates with similar strict criteria for ARDS.[27–29] The incidence of 4.6 cases of ARDS per 100,000 persons/yr in our population was about half the estimated incidence of hospitalizations with both assisted ventilation and selected catheterization procedures (10.6/100,000 persons/yr). Furthermore, the case fatality rate of ARDS (39%) was only slightly lower to that of inpatients who were known to have undergone assisted ventilation and selected catheterization procedures (45%).

The main finding of the study was an independent dose-response association between current cigarette smoking and the subsequent hospital presentation of ARDS. This predictive association may be explained by the fact that cigarette smokers, as shown in previous studies but not specifically examined here, are more likely to develop acute precipitating factors of ARDS such as pneumonia, sepsis syndrome, or injury, and/or to undergo digestive or cardiopulmonary surgery.[30–32] These causal pathways are also supported by evidence of impaired immunocompetence in smokers.[33,34]

In addition to the effect mediated through precipitating factors, smoking could cause alveolar damage and thus directly contribute to respiratory insufficiency and ARDS. Cigarette smoke contains high concentrations of reactive oxygen species capable of causing membrane peroxidation,[17] DNA adducts,[18] and inflammation.[12–16,35]

The risk of ARDS associated with smoking is likely to be an underestimation due to study participants who might have quit smoking during follow-up. However, this source of bias could also operate in the other direction if, for example, ex-smokers may have gone back to smoking or because some subjects could have started smoking after entry.

The relationship with increasing age is not surprising, given the reduced host defense mechanisms with advanced age,[36,37] and the age-related increased incidence of underlying illnesses, including pneumonia.

On the other hand, we found no association between alcohol consumption and ARDS incidence. One study has demonstrated that a prior history of chronic alcohol abuse increases the risk of developing ARDS in patients with an identified clinical at-risk diagnosis.[38] Moreover, some *in vitro* studies have shown that ethanol induces changes in the lung[39] and alters neutrophil function in a dose-dependent fashion.[40,41] A limitation is that the present study did not specifically address chronic alcohol abuse.

A noteworthy yet unexpected finding was a lower risk of ARDS among blacks. This result could be due to chance, and should be replicated in future studies before any interpretation can be made.

The use of ICD-9 codes 518.5 and 518.82 is likely to underestimate the true incidence of ARDS in this population. Clearly, cases coded as pneumonia, pulmonary edema, or sepsis could have also met criteria for ARDS. However, after conducting a medical chart review, we were able to identify 56 true-positive cases and rule out 70 false-positive cases. This approach is a valid one because we were interested in risk relationships, and not in determining the overall incidence of ARDS. It is our believe that, unless smoking was associated with the probability of being a true-positive case (vs being a false-negative case), then confounding should not occur.

Another limitation of the study was that the chart reviewer was not blinded to the study hypothesis. In addition, our case-ascertainment method yielded only two trauma-related ARDS cases. Thus, the current findings cannot be generalized to ARDS associated with trauma. In summary, older age and cigarette smoking were significant risk factors for the development of ARDS in our large multiethnic population. Thus, it appears that the decision to be a smoker may substantially elevate the risk of a near-fatal or fatal outcome in a critical clinical situation. These epidemiologic findings are important because they suggest that many cases of ARDS may be preventable through avoidance of smoking, probably because less smoking would lead to fewer intermediate conditions, such as pneumonia, trauma, and cardiopulmonary surgery.

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