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Original Contribution

Risk Factors for Invasive Pneumococcal Disease among Navajo Adults

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Invasive pneumococcal disease (IPD) is 3–5 times more common among Navajo adults than in the general US population. The authors conducted a case-control study to identify risk factors for IPD among Navajo adults. Navajos aged ≥18 years with IPD were identified through prospective, population-based active laboratory surveillance (December 1999–February 2002). Controls matched to cases on age, gender, and neighborhood were selected. Risk factors were identified through structured interviews and medical record reviews. The authors conducted a matched analysis based on 118 cases and 353 controls. Risk factors included in the final multivariable analysis were chronic renal failure (odds ratio (OR) = 2.6, 95% confidence interval (CI): 0.9, 7.7), congestive heart failure (OR = 5.6, 95% CI: 2.2, 14.5), self-reported alcohol use or alcoholism (OR = 2.9, 95% CI: 1.5, 5.4), body mass index (weight (kg)/height (m)^2) <5th (OR = 3.2, 95% CI: 1.0, 10.6) or >95th (OR = 2.8, 95% CI: 1.0, 8.0) percentile, and unemployment (OR = 2.6, 95% CI: 1.2, 5.5). The population attributable fractions were 10% for chronic renal failure, 18% for congestive heart failure, 30% for self-reported alcohol use or alcoholism, 6% for body mass index, and 20% for unemployment. Several modifiable risk factors for IPD in Navajos were identified. The high prevalence of renal failure, alcoholism, and unemployment among Navajo adults compared with the general US population may explain some of their increased risk of IPD.

alcoholism; heart failure, congestive; Indians, North American; kidney failure, chronic; risk factors; *Streptococcus pneumoniae*; unemployment

Abbreviations: BMI, body mass index; IPD, invasive pneumococcal disease.

Streptococcus pneumoniae (pneumococcus) is a leading cause of serious community-acquired infections, including pneumonia, meningitis, and bacteremia. The risk of invasive pneumococcal disease (IPD), infections in which pneumococcus can be isolated from a normally sterile body fluid, is higher for young children and the elderly (1, 2), for African Americans (1, 2), and for persons with human immunodeficiency virus infection (3, 4). Persons with underlying medical conditions (including congestive heart failure, cancer, renal failure requiring dialysis, alcohol misuse, and human immunodeficiency virus infection) who contract IPD are more likely to die than otherwise healthy persons with IPD (1, 3, 5–7).

We have identified three controlled studies in the published literature that evaluated a range of medical and

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behavioral risk factors for IPD (8–10). In a study of immunocompetent persons aged 18–64 years, Nuorti et al. (8) found that men, African Americans, persons with one of several chronic illnesses, smokers, persons passively exposed to tobacco smoke, persons exposed to young children in day care, and persons without a college degree were at increased risk. Among male Veterans Administration patients, Lipsky et al. (9) found that institutionalized persons, smokers, and persons with congestive heart failure, cerebrovascular disease, or dementia were at increased risk. Among adults aged 18–55 years with human immunodeficiency virus infection, Breiman et al. (10) found that African Americans, current smokers, and persons who had close contact with children were at increased risk. We also identified two studies that evaluated specific risk factors for IPD (11, 12). Thomsen et al. (11) found a small increase in IPD risk among persons with diabetes after adjusting for the presence of comorbid conditions, and Talbot et al. (12) found that the odds ratio for IPD was significantly higher among adults aged 18–49 years with asthma than among those without asthma.

The Johns Hopkins Center for American Indian Health has conducted population-based, active laboratory surveillance for IPD among Navajo adults since 1989. We have shown that the incidence of IPD is 3–5 times higher in Navajo adults than in the general US population (13), but the reasons for this elevated risk are not known. Understanding the reasons for the high risk of IPD among Navajo adults is important for developing prevention strategies, particularly because pneumococcal polysaccharide vaccine has limited effectiveness in this population (14). Further, additional controlled studies of risk factors for IPD are needed to better understand the epidemiology of this disease. Therefore, we undertook a population-based case-control study to evaluate risk factors for IPD among Navajo adults. While this study was primarily exploratory and hypothesis-generating, we were specifically interested in assessing whether exposures associated with elevated risk of IPD in other populations—particularly diabetes mellitus, other chronic illnesses, tobacco smoke exposure, exposure to indoor nontobacco smoke (e.g., smoke associated with a wood stove), and exposure to young children—were associated with increased risk of IPD in Navajo adults. We also collected data on other environmental exposures common among Navajo adults to explore their possible contributions to elevated IPD risk in this population.

MATERIALS AND METHODS

Setting and case ascertainment

This study was carried out in the Navajo Nation, a large, sparsely populated area in the southwestern United States. A case of IPD was defined as an illness in which *S. pneumoniae* was isolated from a normally sterile body fluid. Cases of IPD were identified through the Center for American Indian Health surveillance system, which is described elsewhere (13). In brief, it is an active, population-based laboratory surveillance system. Center staff members regularly visit each of the six Indian Health Service hospital microbiology laboratories that serve Navajo Nation patients to identify cases of IPD. Non-Indian Health Service hospital laboratories located near the Navajo Nation are contacted weekly for identification of any additional cases occurring among members of the Navajo tribe. Because the study area is remote and health care is provided at no cost to tribal members by the Indian Health Service, this system is likely to identify the great majority of IPD cases that have laboratory confirmation in this population.

Participants

Persons with IPD whose date of pneumococcal culture was between December 1999 and February 2002 were eligible to be included as case subjects if they were enrolled members of the Navajo tribe and were at least 18 years of age on the date of culture. When a pneumococcal isolate from an eligible person was identified by the surveillance system, the person was contacted and asked to participate in the study. If the person was too ill to consent or had died, consent was sought from a legal representative.

Age- and gender-matched control subjects were systematically selected on the basis of proximity to the case subject's household, using the following procedure. If the case subject's residence was isolated, surrounding households were approached in order of proximity to the case household. If the case subject's residence was on a street with other households, a direction from the case subject's residence was randomly selected, and study personnel visited neighboring households in the randomly selected direction in order of proximity to the case subject's household. Persons were eligible to participate if they were of the same gender and age group (18–30, 31–45, 46–64, or $\geq$65 years) as the case subject. Only one control subject was selected per household. In order to avoid misclassifying persons with a history of pneumococcal disease as control subjects, potential controls were excluded if, in the previous 10 years, they had had either IPD, an episode of radiologically confirmed pneumonia with a sputum gram-stain consistent with pneumococcus (as documented in the medical record), or hospitalization for pneumonia.

Each selected household was visited at least three times in an effort to identify an eligible control subject. We attempted to identify three controls for each case. For some cases, we were only able to identify two matched controls ($n = 7$). For other cases, we enrolled four controls ($n = 6$) because after three controls had been enrolled, an additional control was found in a selected household in which no one was home on the first or second visit.

Data collection

We collected environmental, demographic, and socioeconomic data from study participants using a structured interview form. The interview was conducted in English or Navajo by bilingual Navajo field staff. Study nurses extracted medical information from the medical records of study participants using a structured data collection tool. In addition, we reviewed the medical records of all children aged 5 years or younger who were living in study subjects'

households in order to determine their pneumococcal conjugate vaccination status. Interviewers and medical record abstractors were not blinded to the case/control status of participants.

Definitions of study variables

Alcoholism was defined as either a diagnosis of alcoholism in the medical record or documentation of conditions associated with chronic alcohol abuse (i.e., alcoholic liver disease, esophageal varices, or multiple alcohol-related injuries), with an accompanying opinion recorded in the medical record that these conditions were related to alcohol use. For data analysis, we defined ''alcohol use or alcoholism'' as either self-reported alcohol use, unknown alcohol use, or alcoholism. Current smoking was defined as having smoked at least 100 cigarettes in the past year. Former smoking was defined as having smoked at least 100 cigarettes in the past without current smoking (15). Day care was defined as a setting outside of the home where a child regularly spent 4 or more hours per week under adult supervision with at least two children from different households. Children aged 5 years or less were classified as vaccinated if they had received any doses of pneumococcal conjugate vaccine. Body mass index (BMI) was based on self-reported weight and height and was calculated as weight (kg)/height $(m)^2$.

Statistical analysis

The a-priori sample size for this study was 120 case subjects and 360 matched control subjects. This sample size was selected so that the analysis would have 80 percent power to detect an odds ratio of 3 or greater for risk factors present in at least 10 percent of control subjects and an odds ratio of 2 or greater for risk factors present in at least 35 percent of control subjects. Data were analyzed using SAS software (version 9.12; SAS Institute Inc., Cary, North Carolina). The dependent (outcome) variable was IPD. Univariable odds ratios and 95 percent confidence intervals for each potential risk factor were assessed using conditional logistic regression in order to account for the matched design (i.e., PROC LOGISTIC with the STRATA statement).

The objective of our analysis was to identify a set of risk factors independently associated with increased risk of IPD. Since we did not have one exposure of interest and viewed our model-building strategy as hypothesis-generating, explanatory variables that were associated with IPD (odds ratio > 1.5 or $p < 0.15$) in the univariable models were selected for inclusion in multivariable models. We hypothesized that the risk of IPD would increase with increasing severity of some diseases. For variables that may have expressed different steps along the same disease pathway, we developed disease-specific models to assess which levels of disease progression were associated with IPD. We selected the most distal or ''upstream'' level of disease progression associated with IPD for inclusion in subsequent multivariable models. Multivariable conditional logistic regression was used to determine matched, adjusted odds ratios. We utilized a manual backward modeling strategy to assess the joint effects of all covariables. The fully adjusted model contained all exposures of interest and all two-way interaction terms. We performed tests of interaction to evaluate effect measure modification using an α value of 0.15; nonsignificant interaction terms were eliminated from the model. Covariables were then eliminated from the model if their adjusted odds ratios were not statistically significant at the $p < 0.10$ level. Because age is a known risk factor for invasive pneumococcal disease and the age categories used for matching were broad, we controlled for age in the final multivariable model. We also controlled for whether cases and controls had received pneumococcal polysaccharide vaccine in the final model, because some studies have shown a protective effect of vaccination against IPD. Subjects were considered to have been vaccinated if they had ever received a dose of pneumococcal polysaccharide vaccine. We assessed collinearity in the final multivariable model.

We used the method of Bruzzi et al. (16) to estimate the fraction of disease in the population that was attributable to factors retained in the final multivariable model. Briefly, the attributable fraction was calculated as $1 - \Sigma\, p_j/R_j$, where p_j is the proportion of case subjects at each level of a given risk factor (including the referent group) and R_j is the adjusted odds ratio for that level.

Ethical considerations

The study was approved by the institutional review boards of the Johns Hopkins Bloomberg School of Public Health, the Centers for Disease Control and Prevention, the Navajo Nation, and the Indian Health Service. Approval was also given by community health boards in the study areas. Written informed consent was obtained from all participants or their legal representatives after the study protocol had been explained to them in their preferred language.

RESULTS

Characteristics of study subjects

A total of 142 IPD episodes were identified in eligible Navajo adults between December 1, 1999, and February 7, 2002. Among these 142 episodes, 118 persons (83 percent) were enrolled as case subjects, 20 refused to participate, and four were excluded (two episodes were second episodes occurring among persons already enrolled as cases, one person's medical records could not be reviewed, and one person was excluded because of an error in selecting matched control subjects). A total of 420 persons were identified as eligible control subjects. Of these, 353 (84 percent) were enrolled, 39 refused to participate, and 28 were excluded (21 had a history of possible pneumococcal disease, five had medical records that could not be located, and two were unable to give informed consent). Characteristics of case subjects are shown in table 1.

Univariable analysis

Odds ratios for selected possible IPD risk factors identified through review of medical records are shown in table 2. Immunodeficiency, asplenia, and sickle cell disease were

TABLE 1. Characteristics of case subjects* with invasive pneumococcal disease ($n = 118$), Navajo Nation, December 1999–February 2002

Characteristic	No. of cases	%
Male gender	57	48.3
Site of *Streptococcus pneumoniae* isolation		
Blood	108	91.5
Cerebrospinal fluid	4	3.4
Pleural fluid	1	0.8
Peritoneal fluid	1	0.8
Multiple sites†	4	3.4
Serotype of isolate was included in seven-valent conjugate vaccine‡	27	23.9

* The median age of case subjects was 52 years (range, 18–96).
† Blood and cerebrospinal fluid for one case, blood and pleural fluid for one case, and blood and peritoneal fluid for two cases.
‡ Information on serotype was available for 113 cases (96%). Seven-valent conjugate vaccine serotypes were 4, 6B, 9V, 14, 18C, 19F, and 23F.

not analyzed because there were one or fewer case subjects with each of these conditions. Odds ratios for selected possible risk factors identified by interview are shown in table 3. We examined the risk of IPD according to percentile of BMI and found that the risk of IPD increased at the extremes of BMI. Therefore, we categorized BMI into three groups based on the distribution of BMI in case subjects—<5th percentile (BMI $\leq$ 19.1), 5th–95th percentile, and >95th percentile (BMI $\geq$ 38.6).

Self-reported educational and income levels were not associated with IPD in the univariable analysis (data not shown).

Multivariable analysis

We evaluated the relations between several risk factors and potentially mediating features (e.g., diabetes mellitus and chronic renal failure, alcohol use and chronic liver disease) by constructing multivariable models with two variables. Among the 115 subjects with diabetes mellitus, 23 (20.0 percent) had chronic renal failure, including 14 who were on dialysis. Among the 356 subjects without diabetes mellitus, there were nine (2.5 percent) subjects with chronic renal failure, including three on dialysis. When it was included in the same model with chronic renal failure, diabetes mellitus was no longer significantly associated with IPD (table 4). Chronic liver disease was present in 16 of 85 (18.8 percent) persons who reported any alcohol use and five of 28 (17.9 percent) persons with unknown alcohol use. Only six of 358 (1.7 percent) persons who denied alcohol use had chronic liver disease. Alcohol use and chronic liver disease were both significantly associated with IPD when included in a two-variable model (data not shown). Because alcohol

TABLE 2. Matched univariable analysis of selected medical characteristics (from medical record data) as possible risk factors for invasive pneumococcal disease among Navajo adults, December 1999–February 2002

Characteristic	Case subjects ($n = 118$)		Control subjects ($n = 353$)		Odds ratio	95% confidence interval	*p* value
	No.	%	No.	%			
Cancer	4	3.4	13	3.7	0.9	0.3, 2.9	0.88
Nephrotic syndrome	6	5.1	7	2.0	2.8	0.9, 8.6	0.08
Chronic renal failure	20	16.9	12	3.4	6.5	2.9, 15.0	<0.001
Chronic liver disease	14	11.9	13	3.7	3.6	1.6, 8.3	0.002
History of myocardial infarction	7	5.9	9	2.6	2.6	0.9, 7.5	0.09
Coronary artery disease	15	12.7	19	5.4	2.9	1.3, 6.2	0.008
Congestive heart failure	26	22.0	12	3.4	9.9	4.3, 23.0	<0.001
Diabetes mellitus	37	31.4	78	22.1	1.7	1.0, 2.9	0.04
Chronic obstructive pulmonary disease	7	5.9	6	1.7	4.6	1.3, 15.9	0.02
Asthma	8	6.8	19	5.4	1.3	0.6, 2.9	0.59
Alcoholism	36	30.5	57	16.2	3.0	1.7, 5.4	<0.001
Smoking							0.01*
Never smoker	103	87.3	337	95.5	1.0†		
Former smoker	12	10.2	11	3.1	3.7	1.5, 9.0	0.003
Current smoker	3	2.5	5	1.4	2.1	0.5, 8.8	0.33

* Overall *p* value for all levels of smoking.
† Referent.

TABLE 3. Matched univariable analysis of selected sociodemographic characteristics (self-reported) as possible risk factors for invasive pneumococcal disease among Navajo adults, December 1999–February 2002*

Characteristic	Case subjects ($n = 118$)		Control subjects ($n = 353$)		Odds ratio	95% confidence interval	*p* value
	No.	%	No.	%			
Smoking							0.54†
Never smoker	84	71.2	267	75.6	1.0‡		
Former smoker	21	17.8	51	14.5	1.5	0.8, 2.8	0.27
Current smoker	11	9.3	34	9.6	1.1	0.5, 2.3	0.89
Passive tobacco smoke exposure	29	25.2	111	31.8	0.7	0.4, 1.1	0.14
BMI§,¶							0.008†
<5th percentile (BMI ≤ 19.1)	11	9.3	10	2.8	4.4	1.7, 11.7	0.003
5th–95th percentile	93	78.8	319	90.4	1.0‡		
>95th percentile (BMI ≥ 38.6)	9	7.6	14	4.0	2.4	0.9, 5.9	0.07
Unknown/declined to state	5	4.2	10	2.8	1.7	0.5, 5.6	0.36
Current alcohol use							0.001†
None	76	64.4	282	79.9	1.0‡		
Uses alcohol	31	26.3	54	15.3	3.0	1.6, 5.5	0.001
Unknown/declined to state	11	9.3	17	4.8	3.3	1.3, 8.4	0.01
Electricity in the home	95	81.9	307	87.2	0.5	0.26, 1.0	0.07
Indoor plumbing in the home	83	71.6	258	73.1	0.8	0.5, 1.5	0.58
Living with a child aged ≤5 years	30	25.4	108	30.6	0.9	0.7, 1.2	0.49
Living with a child aged ≤5 years who attended day care							0.50†
No children	88	74.6	244	69.3	1.0‡		
Children, no day-care attendance	26	22.0	96	27.3	0.7	0.4, 1.2	0.24
Children, day-care attendance	4	3.4	12	3.4	0.9	0.3, 3.0	0.83
Living with an unvaccinated child aged ≤5 years#							0.69†
No children	87	73.3	245	69.4	1.0‡		
All children vaccinated	5	4.2	18	5.1	0.8	0.3, 2.3	0.66
Any unvaccinated child	26	22.0	89	25.2	0.8	0.4, 1.4	0.43
Unemployed	39	33.1	58	16.4	3.7	2.0, 6.8	<0.001
Exposure to wood or coal smoke at home or at work							0.10†
No heat	21	18.3	60	17.2	1.0‡		
Heat, but not wood or coal smoke	31	27.0	70	20.1	1.6	0.6, 4.5	0.36
Heat, wood or coal smoke	63	54.8	219	62.8	0.8	0.3, 1.9	0.57

* Numbers of subjects may not add up to column totals because of missing data.
† Overall *p* value for all levels of the variable.
‡ Referent.
§ BMI, body mass index.
¶ Calculated from self-reported height and weight as weight (kg)/height $(m)^2$.
# No doses of pneumococcal conjugate vaccine.

use was felt to be a more distal factor, it was used in the development of multivariable models.

Results from the final multivariable model, along with population attributable fractions, are shown in table 5. The factors associated with the largest proportion of IPD risk were congestive heart failure, unemployment, and alcohol use or alcoholism. There was no significant collinearity in the final model.

We were unable to identify sufficiently comparable data on the prevalences of congestive heart failure or BMI in the Navajo and general US populations. However, end-stage renal disease (17, 18), alcoholism (19, 20), and unemployment (authors' unpublished analysis of US Census data (http://factfinder.census.gov/home/saff/main.html)) are more prevalent among Navajo adults than among the general US population (table 6).

DISCUSSION

We identified congestive heart failure, alcohol use or alcoholism, and unemployment as significant risk factors for

TABLE 4. Results from a multivariable model evaluating the independent effects of diabetes mellitus and chronic renal failure on the risk of invasive pneumococcal disease among Navajo adults, December 1999–February 2002

Characteristic	Odds ratio*,†	95% confidence interval*	*p* value
Neither diabetes mellitus nor chronic renal failure	1.0‡		
Diabetes mellitus alone	1.5	0.8, 2.6	0.20
Chronic renal failure alone	16.4	3.2, 84.2	<0.001
Both diabetes mellitus and chronic renal failure	5.8	2.3, 14.8	<0.001

* Odds ratios and 95 percent confidence intervals were calculated using conditional logistic regression accounting for the matched study design.

† Odds ratios were adjusted for the interaction between diabetes mellitus and chronic renal failure. The interaction term was retained in the model ($p = 0.13$).

‡ Referent.

IPD among Navajo adults. Chronic renal failure and extremes of BMI were also associated with increased risk of IPD, but their statistical significance was marginal ($0.05 < p < 0.10$). This study was not designed to establish a causal relation between these factors and IPD. However, several of these factors have features that suggest a causal relation—including presence before the IPD episode, large odds ratios, consistency with other studies, biologic plausibility, and coherence with the pathogenesis of IPD. Understanding the relation between these factors and IPD will be important for prevention, because all of these risk factors are potentially modifiable. Some of these risk factors are more common in the Navajo population than in the general US population. The higher prevalence of these risk factors among Navajo adults probably contributes to the increased risk of IPD in Navajos as compared with the general US adult population.

TABLE 5. Independent risk factors for invasive pneumococcal disease among Navajo adults, December 1999–February 2002*

Characteristic	Odds ratio	95% confidence interval	*p* value	Population attributable fraction (%)
Chronic renal failure	2.6	0.87, 7.7	0.087	10.4
Congestive heart failure	5.6	2.2, 14.5	<0.001	18.1
Alcohol use or alcoholism	2.9	1.5, 5.4	<0.001	30.0
BMI†,‡				6.2
<5th percentile (BMI ≤ 19.1)	3.2	0.98, 10.6	0.054	
>95th percentile (BMI ≥ 38.6)	2.8	0.97, 8.0	0.058	
Unemployed	2.6	1.2, 5.5	0.017	20.2

* Results were controlled for age and receipt of pneumococcal polysaccharide vaccine.

† BMI, body mass index.

‡ Calculated from self-reported height and weight as weight (kg)/height $(m)^2$.

The most important medical risk factors associated with IPD in this population were severe chronic organ diseases, particularly renal disease and cardiac disease. Chronic obstructive pulmonary disease was significantly associated with IPD in the univariable analysis, but we had limited power to evaluate chronic obstructive pulmonary disease in the multivariable model because the prevalence among cases and controls was low.

While diabetes mellitus was associated with IPD in the univariable analysis, it was not significant when included in multivariable models. Diabetes mellitus has been described as a risk factor for IPD, and pneumococcal polysaccharide vaccine is recommended for persons with diabetes (5). In a large Danish study, Thomsen et al. (11) found that diabetes was associated with an increased risk of IPD, but the odds ratio was relatively small (odds ratio = 1.5, 95 percent confidence interval: 1.1, 2.0) when adjusted for an aggregate measure of comorbidity. The point estimates from the present study were similar, but we had limited power to evaluate odds ratios less than 2. Lipsky et al. (9) did not identify an association between diabetes and IPD in a population that did not have chronic renal disease. Nuorti et al. (8) found that diabetes was not significantly associated with IPD when controlling for other risk factors. Our results suggest that the risk associated with diabetes may be associated with severe complications such as chronic renal failure.

Similarly, the association between IPD and heart disease was primarily seen in persons with the most severe disease (congestive heart failure). Less severe cardiac diseases, such as coronary artery disease or history of myocardial infarction, were associated with IPD in the univariable analysis but were not significantly associated with IPD when results were adjusted for congestive heart failure (data not shown). Again, our findings are consistent with those of Lipsky et al. (9), who found a significant association between IPD and congestive heart failure but not between IPD and ischemic heart disease.

Both a medical diagnosis of alcoholism and self-reported use of alcohol were strongly associated with IPD. Because self-reported drinking behavior is subject to reporting bias and was not verifiable in our study, we considered any reported alcohol use, unknown alcohol use, or a diagnosis of alcoholism to be an indication of alcohol use. Notably, among persons who reported alcohol use or did not answer the question, there was no evident difference in proportions with a diagnosis of alcoholism or levels of IPD risk for different levels of self-reported alcohol use. Reporting bias may have affected reported levels of alcohol use. The level of alcohol use may be a less important contributor to IPD risk than drinking pattern. Drinking patterns within the Navajo Nation are influenced by cultural factors and by the fact that the sale of alcoholic beverages is illegal in the Navajo Nation (21, 22). It is possible that the relation between alcohol use and IPD may be mediated by the drinking of sufficient alcohol to interfere with consciousness, thus increasing the risk for aspiration of pharyngeal pneumococci.

TABLE 6. Prevalence of risk factors for invasive pneumococcal disease among Navajo adults as compared with the general US population, according to specified medical and sociodemographic characteristics, December 1999–February 2002

Characteristic	Navajo adults		US adults		Prevalence ratio
	Prevalence (%)	Source (ref. no.)	Prevalence (%)	Source (ref. no.)	
Chronic renal failure with dialysis	0.34	Hochman et al. (18)*	0.14	United States Renal Data System (17)	2.4
Alcoholism	22	Kunitz et al. (20)†	8.5	Grant et al. (19)	2.6
Unemployed	15.8	US Census Bureau‡	4.8	US Census Bureau‡	3.3

* The authors' analysis of data from the United States Renal Data System (http://www.usrds.org/).

† Population data on self-reported alcohol use are not available for Navajo adults. Because of possible differences in drinking patterns, alcoholism may be a more comparable variable between populations than self-reported alcohol use.

‡ Unpublished US Census data (http://factfinder.census.gov/home/saff/main.html).

Alternatively, alcohol may reduce the immune response to some strains of pneumococcus (23). Alcohol abuse has been a common finding among patients with IPD (1, 3, 6). Further research into the relation between alcohol use and IPD would be useful for targeting prevention strategies.

We found that extremes of BMI were associated with IPD. It is possible that low BMI could be a marker for malnutrition or unidentified chronic disease. Very high BMI was also associated with IPD. The possible mechanism by which obesity might cause IPD is unclear, but it could be related to changes in lung volume, respiratory muscle strength, and the work of breathing or to an increased risk of aspiration (24).

Finally, we found that more than 20 percent of IPD was associated with unemployment in this population. The relation between unemployment and IPD is unclear. It is possible that unemployment is a marker for some other characteristic that could increase IPD risk, such as poor nutrition or reduced access to health care. Further research into the relation between unemployment and IPD is needed.

This study was subject to several limitations. We had limited power to identify risk factors with low prevalence. This may explain why exposure to cigarette smoke and exposure to children in day care, which have been associated with IPD in previous studies, were not significantly associated with IPD in this study (8, 10). Of note, among Navajo smokers, the number of cigarettes smoked daily was low. There are at least two possible reasons for the lower smoking prevalences and higher IPD odds ratios associated with smoking when data are taken from medical records as opposed to self-reports. First, medical documentation of smoking may be more likely in heavier smokers. Second, documentation of smoking may be more likely in persons with IPD or other medical conditions associated with IPD. Because the proportion of IPD cases caused by serotypes included in the seven-valent conjugate vaccine and the proportion of subjects living with vaccinated children were low, we could not assess the potential for childhood vaccination with pneumococcal conjugate vaccine to reduce IPD in adults. We evaluated a wide variety of potential risk factors for IPD. Therefore, some of the observed associations may have been a chance occurrence related to multiple comparisons. We have shown precise p values and confidence intervals in this paper to enable readers to reach conclusions about the precision and strength of the associations. Several of the risk factors we identified, particularly BMI, alcohol use, and unemployment, were based on self-reported data and may have been subject to reporting bias. However, it is unlikely that misreporting of these variables would have resulted in differential misclassification. We believe that nondifferential misclassification due to reporting bias in the direction of more normal BMI, lower alcohol use, and positive employment would be more likely, and this would have resulted in underestimation of the associations of these factors with IPD. Finally, this study was carried out in a specific population with a high incidence of IPD. Our findings regarding the importance of various risk factors may not be generalizable to other populations.

In conclusion, we found that chronic renal failure, congestive heart failure, alcohol use or alcoholism, extremely high or low BMI, and unemployment were associated with increased risk of IPD among these Navajo adults. Some of these risk factors are more prevalent among Navajo adults than in the general US population and therefore could contribute to the increased risk of IPD seen among Navajo adults. The risk factors for IPD identified in this study are potentially modifiable, and if there is a causal relation, efforts to reduce the prevalence of chronic renal failure, prevent alcohol abuse, prevent congestive heart failure, reduce extreme under- and overweight, and reduce unemployment could have the additional benefit of reducing the incidence of IPD in this population.

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