

Alpha1-Antitrypsin Deficiency Deaths in the United States From 1979-1991*

An Analysis Using Multiple-Cause Mortality Data

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Objective: To describe trends of reported α1-antitrypsin deficiency mortality in the United States from 1979-1991.

Methods: We analyzed death certificate reports in the multiple-cause mortality files compiled by the National Center for Health Statistics.

Results: Of the 26,866,600 deaths that occurred during the 13-year period, 1,930 had α1-antitrypsin deficiency listed as a cause of death. Over this period, we would have expected 5,400 to 13,400 persons with this condition to die. The age-adjusted mortality rate with reported α1-antitrypsin deficiency listed increased 86%, from 4.3 per 10 million in 1979 to 8.0 per 10 million in 1991. α1-Antitrypsin deficiency mortality rates were higher among whites than among blacks or persons of other races. α1-Antitrypsin deficiency was listed in 2.7% of all deaths with obstructive lung disease among persons aged 35-44 years old and in 1.2% of all deaths listing hepatic disease among children aged 1 to 14 years old.

Conclusions: α1-Antitrypsin deficiency is an important risk factor for obstructive lung disease and hepatic disease in the United States, and it was reported with increasing frequency through the study period, although it is still likely underreported.

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Key words: α1-antitrypsin; epidemiology; hepatic disease; mortality; obstructive lung disease

Abbreviations: ICD=International Classification of Diseases; MCMF=multiple-cause mortality file; NCHS=National Center for Health Statistics; UCD=underlying cause of death

Alpha1-antitrypsin deficiency is an autosomal co-dominant genetic disorder and serves as a model of the interaction between genetic predisposition and environmental exposures. Both adults and children with α1-antitrypsin deficiency have an increased risk of developing liver disease, and adults with this defect can develop severe lung disease in the third through fifth decades of life. People deficient in α1-antitrypsin who are exposed to tobacco smoke develop COPD earlier and more severely than people who are not deficient.

Previous studies have shown that α1-antitrypsin deficiency is present in 1 in 1,639 live births in Sweden and in an estimated 1 in 5,927 to 1 in 2,857 persons in the United States. Trends of α1-antitrypsin mortality and its contribution to overall mortality in the United States are not well documented. We analyzed national mortality data using the multiple-cause mortality files (MCMFs) to determine mortality and comorbidity of α1-antitrypsin deficiency in the United States from 1979-1991.

Materials and Methods

The National Center for Health Statistics (NCHS) annually compiles data from all death certificates filed in the United States using vital records from individual states. These data include demographic and geographic information on the decedent as well as the International Classification of Diseases (ICD) codes for the underlying cause of death and up to 20 conditions listed on the death certificate. The ICD, Ninth Revision (ICD-9), was implemented in 1979, and it was in effect during the 13-year period we studied (1979-1991). The conditions are recorded in two forms: the entity axis, which contains the conditions exactly as reported on the death certificate, and the record axis, which is edited by a computerized algorithm known as the translation of axes. The automated classification of medical entities algorithm determines the underlying cause of death (UCD) from the conditions and their positions as listed on the death certificates. Trained nosologists code the conditions at the state level, and nosologists at NCHS periodically review data from a 10% sample of the submitted death certificates. This process gives rise to the MCFM.

We searched the record axis portion of the 1979-1991 MCMFs for the records containing α1-antitrypsin deficiency (ICD-9 code 277.6), and searched these for records containing the codes for obstructive lung disease (excluding asthma, ICD-9 codes 490-492.9 and 496), pneumonia (ICD-9 codes 460-487.9), atherosclerotic
Table 1—Comparison, by Age Strata, of All Persons Who Died From 1979-1991 to Persons Who Died With α1-Antitrypsin Deficiency (α-ATD) Present, the Ratio of Male to Female Rates in Each Stratum; and, among Those Persons Who Died With α-ATD Present, Those Who Had Either a Diagnosis of Hepatic Disease or Obstructive Lung Disease*

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Total No. of Deaths</th>
<th>No. of Decedents With α-ATD</th>
<th>Rate per 100,000 Deaths</th>
<th>Ratio of Rates Among Male Subjects to That Among Female Subjects</th>
<th>No. (%) of Decedents With A1AT and Hepatic Disease</th>
<th>No. (%) of Decedents With α-ATD and Obstructive Lung Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>529,115</td>
<td>94</td>
<td>17.80</td>
<td>2.14</td>
<td>36 (38)</td>
<td>1 (1)</td>
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<td>1-14</td>
<td>219,537</td>
<td>92</td>
<td>41.90</td>
<td>1.79</td>
<td>45 (49)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>15-24</td>
<td>528,452</td>
<td>30</td>
<td>5.70</td>
<td>2.26</td>
<td>22 (73)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>25-34</td>
<td>702,917</td>
<td>57</td>
<td>8.11</td>
<td>1.39</td>
<td>17 (30)</td>
<td>25 (44)</td>
</tr>
<tr>
<td>35-44</td>
<td>894,617</td>
<td>310</td>
<td>34.65</td>
<td>1.32</td>
<td>35 (11)</td>
<td>222 (72)</td>
</tr>
<tr>
<td>45-54</td>
<td>1,580,587</td>
<td>561</td>
<td>35.49</td>
<td>1.55</td>
<td>55 (10)</td>
<td>421 (75)</td>
</tr>
<tr>
<td>55-64</td>
<td>3,601,879</td>
<td>415</td>
<td>11.52</td>
<td>1.50</td>
<td>69 (17)</td>
<td>316 (76)</td>
</tr>
<tr>
<td>65-74</td>
<td>6,177,936</td>
<td>261</td>
<td>4.22</td>
<td>1.00</td>
<td>95 (36)</td>
<td>160 (61)</td>
</tr>
<tr>
<td>75-84</td>
<td>7,278,052</td>
<td>93</td>
<td>1.28</td>
<td>1.13</td>
<td>36 (39)</td>
<td>52 (56)</td>
</tr>
<tr>
<td>&gt;85</td>
<td>5,348,096</td>
<td>17</td>
<td>0.32</td>
<td>1.72</td>
<td>3 (18)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>None listed</td>
<td>8,392</td>
<td>0</td>
<td>0.00</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>26,866,600</td>
<td>1,930</td>
<td>7.18</td>
<td>1.35</td>
<td>413 (21)</td>
<td>1,206 (62)</td>
</tr>
</tbody>
</table>

*From the MCMF, NCHS.

cardiovascular disease (ICD-9 codes 426-442.9 or 410-414.9), hepatic disease (ICD-9 codes 570-577.9), hepatic cancer (ICD-9 codes 155-155.9), and right ventricular failure (ICD-9 codes 415-416.9 or 428-428.9). ICD-9 code 277.6 is also the code for hereditary angioedema. We searched the database of decedents with code 277.6 for all codes that would be associated with laryngeal edema, including ICD-9 codes 478.6 (edema of larynx) and ICD-9 codes 995.0 through 995.3 (anaphylactic shock, angioneurotic edema, and unspecified adverse effect of drug, medicinal and biological substance), and excluded these from the database. In addition, we searched the MCMFs for all death records that mentioned obstructive lung disease (ICD-9 codes 490-492.9 and 496) and hepatic disease (ICD-9 codes 570-577.9) during the study period.

We analyzed the α1-antitrypsin deficiency group according to age, race, and sex. We used the 1980 and 1990 US census data (using linear interpolation to estimate population in intercensal years) to calculate rates. We also compared age-specific rates among men with those among women. For age-adjusted, state-specific rates, we used the 1980 US population as the standard.

Table 2—Comparison, by Age Strata, of All Persons Who Died With a Diagnosis of Obstructive Lung Disease From 1979-1991 to Persons Who Died With a Diagnosis of α1-Antitrypsin Deficiency (α-ATD) and Obstructive Lung Disease and All Persons Who Died With a Diagnosis of Hepatic Disease From 1979-1991 to Persons Who Died With a Diagnosis of α-ATD and Hepatic Disease*

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>No. of Decedents With Obstructive Lung Disease</th>
<th>No. of Decedents With α-ATD and Obstructive Lung Disease</th>
<th>Rate (per 1,000 Obstructive Lung Disease Deaths)</th>
<th>No. of Decedents With Hepatic Disease</th>
<th>No. of Decedents With α-ATD and Hepatic Disease</th>
<th>Rate (per 1,000 Hepatic Disease Deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>529,115</td>
<td>94</td>
<td>1.43</td>
<td>5,814</td>
<td>36</td>
<td>6.19</td>
</tr>
<tr>
<td>1-14</td>
<td>219,537</td>
<td>92</td>
<td>1.19</td>
<td>3,855</td>
<td>45</td>
<td>11.67</td>
</tr>
<tr>
<td>15-24</td>
<td>528,452</td>
<td>30</td>
<td>1.24</td>
<td>6,190</td>
<td>22</td>
<td>3.55</td>
</tr>
<tr>
<td>25-34</td>
<td>702,917</td>
<td>57</td>
<td>1.24</td>
<td>37,258</td>
<td>17</td>
<td>0.46</td>
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<tr>
<td>35-44</td>
<td>894,617</td>
<td>310</td>
<td>1.14</td>
<td>157,798</td>
<td>55</td>
<td>0.35</td>
</tr>
<tr>
<td>45-54</td>
<td>1,580,587</td>
<td>561</td>
<td>7.72</td>
<td>261,096</td>
<td>69</td>
<td>0.26</td>
</tr>
<tr>
<td>55-64</td>
<td>3,601,879</td>
<td>415</td>
<td>1.14</td>
<td>295,522</td>
<td>95</td>
<td>0.32</td>
</tr>
<tr>
<td>65-74</td>
<td>6,177,936</td>
<td>261</td>
<td>0.23</td>
<td>205,365</td>
<td>36</td>
<td>0.18</td>
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<tr>
<td>75-84</td>
<td>7,278,052</td>
<td>93</td>
<td>0.02</td>
<td>89,266</td>
<td>3</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;85</td>
<td>5,348,096</td>
<td>17</td>
<td>0.02</td>
<td>308</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>None listed</td>
<td>8,392</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>26,866,600</td>
<td>1,930</td>
<td>1.35</td>
<td>1,159,303</td>
<td>413</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*From the MCMF, NCHS.

RESULTS

Among the 26,866,600 persons who died during the 13-year study period, 1,932 decedents had death records with ICD-9 code 277.6 listed. We excluded 2 death records in which codes consistent with hereditary angioedema were present for a total of 1,930 death records that we included in this analysis. α1-Antitrypsin deficiency (ICD-9 277.6) was the UCD in 1,432 (74.1%) of the 1930 deaths, whereas obstructive pulmonary disease was the UCD in 172 deaths (8.9%); atherosclerotic cardiovascular disease was the UCD in 55 (2.9%) deaths, and hepatic disease was the UCD in 51 (2.6%) deaths.

Obstructive pulmonary disease was the complication most frequently listed with α1-antitrypsin defi-
deficiency appearing in 1,206 (62.5%) of the 1,930 death records (Table 1). The highest proportion of obstructive pulmonary disease deaths occurred among persons aged 35-64 years old (Table 1). Of the 2,022,044 death records listing obstructive lung disease during the study period, $\alpha_1$-antitrypsin deficiency was listed in less than 0.1%, although it was listed in 2.7% of the deaths listing obstructive lung disease that occurred among persons 35-44 years old, and in 1.6% of these deaths among persons 25-34 years old (Table 2).

Hepatic disease was also frequently listed with $\alpha_1$-antitrypsin deficiency, appearing in 413 (21.4%) of the 1,930 death records (Table 1). The highest proportion of hepatic disease deaths occurred among children and young adults aged 1-24 years old (Table 1). Of the 1,159,303 death records in which hepatic disease was listed during the study period, $\alpha_1$-antitrypsin deficiency was listed for less than 0.1% of the deaths, although it was listed for 0.6% of hepatic disease deaths occurring among infants younger than 1 year old and for 1.2% of these deaths among children 1-14 years old (Table 2).

Fourteen of the 1,930 decedents had a code for hepatic cancer listed on their death certificate.

The median age of death increased from 46 years of age in 1979 to 52 years of age in 1991. The age-adjusted mortality rate with $\alpha_1$-antitrypsin deficiency listed increased 86.0%, from 4.3 per 10,000,000 in 1979 to 8.0 per 10 million in 1991. The age-adjusted mortality rate with $\alpha_1$-antitrypsin deficiency present increased among both men and women during the 13-year study period (Fig 1). Mortality rates were consistently higher among men than women both in every year of the study and in every age stratum except for the 65-74 years age group. $\alpha_1$-Antitrypsin deficiency mortality rates were also consistently higher among whites than among blacks or people of other races (Fig 2).

Age-specific mortality rates of $\alpha_1$-antitrypsin deficiency were highest among infants younger than 1 year old and lowest among people aged 1-34 years (Fig 3). Rates among persons 35-64 years old and 65 years and older were similar and increased over the study period (Fig 3). When we compared the number of deaths of persons with $\alpha_1$-antitrypsin deficiency to the total number of deaths, we detected 2 peaks, the first among the 1-14 year olds (41.90 per 100,000 deaths) and another among 45-54 year olds (35.49 per 100,000 deaths).

The age-adjusted death rates with $\alpha_1$-antitrypsin varied among states from the lowest rate, 2.5 per 10 million in New Jersey, to the highest, 22.5 per 10 million in Maine.

**DISCUSSION**

The main role of $\alpha_1$-antitrypsin, which is produced primarily in the liver, is to defend the lower respiratory tract against neutrophil elastase. The $\alpha_1$ allele, which is coded for by the polymorphic $\alpha_1$ gene, determines the serum level of $\alpha_1$-antitrypsin. More than 75 versions of these alleles exist, and they are categorized on the basis of the status of $\alpha_1$-antitrypsin in the serum. Mutations in the coding exons of the $\alpha_1$ gene result in low serum and lung levels of $\alpha_1$-antitrypsin. Combinations of deficient alleles (S or Z family) and null alleles result in decreased protection against neutrophil elastase, thereby predisposing affected individuals to developing lung disease. The phenotype, which is determined on the basis of serum $\alpha_1$-antitrypsin level, designates the magnitude of risk and the kind of disease for which the individual is at risk. Serum $\alpha_1$-antitrypsin levels (referred to functional antielastase activity) range from deficient (<11 nmol/L), to low (11 to 20 nmol/L), to normal (>20 nmol/L).

People who inherit the PiZ or PiMnull alleles are
at an increased risk of developing liver disease. Although the progression of liver disease occurs differently among children than among adults, the pathogenesis for both involves the intracellular accumulation of α₁-antitrypsin within the rough endoplasmic reticulum of the hepatocytes. We found α₁-antitrypsin-associated hepatic disease listed most frequently among younger decedents (Tables 1 and 2). Hepatic disease, which occurs in about 10% of all Pi ZZ newborns, initially occurs as hepatitis with cholestasis, but sometimes progresses to cirrhosis and liver failure in late childhood and early adolescence. We determined that α₁-antitrypsin was listed in 1.2% of all hepatic disease deaths that occurred among children from age 1-14 years old. Adults with α₁-antitrypsin deficiency are reported to be at risk of developing chronic liver disease and hepatocellular carcinoma, and we found hepatic cancer present in 14 of the 1,930 decedents (72 per 100,000). This rate can be contrasted with the rate of hepatic cancer among all decedents in the United States in 1987 of 40 per 100,000. Chronic liver disease, which progresses slowly in persons with α₁-antitrypsin deficiency, is unlikely to be detected before the age of 50 years. In our study, the highest percentage of deaths of persons with α₁-antitrypsin-associated liver disease in adults occurred among 65 to 84 year olds, although this deficiency was reported in less than 0.1% of persons who died with hepatic disease listed in this age group.

Persons with α₁-antitrypsin deficiency are at an increased risk of developing obstructive lung disease, and we found that 63% of the decedents who had this deficiency listed on their death certificates also had a code listed for obstructive lung disease. Some researchers have estimated that up to 2% of obstructive lung disease might be related to α₁-antitrypsin deficiency. We found that this deficiency was listed in less than 0.1% of all records listing obstructive lung disease, but was listed in 2.7% of records listing obstructive lung disease among 35-44 year olds and in 1.6% of these records among 25-34 year olds. Results of recent studies have shown that many persons of type Pi Z (those with Pi ZZ or Pi Z null types) have normal lung function well into middle age. Thus, an explanation for our finding of a lower-than-expected rate of α₁-antitrypsin deficiency among persons older than age 55 years who died with an obstructive lung disease might be related to clinicians not testing for and diagnosing this deficiency in older individuals.

We found that the reporting of α₁-antitrypsin deficiency occurs at a much higher rate among whites than it does among blacks or people of other races, most likely because the mutated α₁ gene occurs more frequently among whites than among people of other races.

We determined that the age-adjusted mortality rate was consistently higher among men than among women in every age group except the 65-74 year olds. Because this deficiency is not a sex-linked genetic disorder, the most likely explanation for this finding is a diagnostic bias by clinicians. The higher occurrence of obstructive lung disease related to α₁-antitrypsin deficiency among male subjects could be attributed to cigarette smoking, as smoking has been more common among male subjects. Results of a study of α₁-antitrypsin-deficient patients showed that the patients who had smoked were dying an average of 10 years earlier than the nonsmokers. Another explanation for higher rates of α₁-antitrypsin deficiency mortality among men is that men are more likely to be employed in dusty occupations, such as mining and construction, which are linked to obstructive lung disease. We also found a higher rate of α₁-antitrypsin disease mortality among men than women among persons younger than age 35 years, when liver disease is the major cause of mortality. The reasons for this finding are unclear but would not be related to smoking or other exposure factors.

We also observed geographic variability of reported α₁-antitrypsin mortality rates in the United States, with age-adjusted mortality rates ranging from 2.5 per 10 million in New Jersey to 22.5 per 10 million in Maine. The reasons for this finding are unclear but may be related to differences in regional gene pools, differing racial composition of different states, or an ascertainment and reporting bias by physicians. Previous surveys of large populations in the United States have estimated that the prevalence of α₁-antitrypsin deficiency varies geographically, from a low of 1 in 5,097 among infants in Oregon to a high of 1 in 2,857 among adults in St. Louis.

Despite its apparent ease of diagnosis, α₁-antitrypsin deficiency is underreported; it may affect as many as 90,000 people in the United States. If the prevalence...
of this deficiency is similar in decedents to its prevalence in the population, one would have expected from 5,400-13,400 decedents to have this diagnosis, figures that are higher than the 1,930 decedents included in our study. One explanation for this finding may come from the process of diagnosing this deficiency. There is no international standard for detecting normal levels of α₁-antitrypsin, and medical laboratories use commercially available diagnostic kits that may differ in their standards for normal serum levels. These different standards may result in misdiagnosis, as normal ranges may vary among clinical laboratories, and may also result in an overestimation of α₁-antitrypsin levels for some patients. Another possible explanation for the underreporting of this disease is that physicians are not looking for it unless they believe its presence is a clinical possibility, such as may be the case when a young person develops severe emphysema. In 1 study, 42% of the α₁-antitrypsin-deficient patients participating in the study saw 5 physicians before their conditions were diagnosed correctly. Our findings are consistent with this type of underreporting bias, in that α₁-antitrypsin deficiency was noted to be present among 2 to 3% of some younger groups of decedents with obstructive lung disease, but in much lower proportions among older age groups with obstructive lung disease.

Our study has several limitations. The code we searched for, ICD-9 277.6, is used to indicate both α₁-antitrypsin deficiency and hereditary angioedema, which may be present in as many as 1 in 10,000 people. Hereditary angioedema is not linked to either obstructive lung disease or hepatic disease, as α₁-antitrypsin deficiency is. We searched for laryngeal edema, which is linked to mortality from hereditary angioedema, and eliminated subjects with this diagnosis from the study. It is possible, however, that some of the subjects we included may had the diagnosis of hereditary angioedema. Another limitation of the database is that we are dependent on both physicians recognizing that disease is present and listing this disease on death certificates. Many persons with α₁-antitrypsin deficiency are nonsmokers who have normal lung function. It is doubtful that such persons would be recognized as having a deficiency and having it noted on their death certificates. Conversely, most persons with obstructive lung disease do not have α₁-antitrypsin deficiency. Thus, the upward trend we detected is most likely related to improved recognition of the deficiency among both younger and older persons with obstructive lung disease rather than to an increasing prevalence. Because death certificates are dependent on a physician’s judgment in recording the causes of death, it is also possible that some persons without a deficiency, such as MZ heterozygotes, may have been included in the database.

New therapies for α₁-antitrypsin deficiency include augmentation therapy, pharmacologic therapy, gene therapy, and transplantation. The best treatment, especially for prevention of severe obstructive lung disease, might be early recognition and encouragement not to smoke.

CONCLUSION

We determined that the mortality rate of reported α₁-antitrypsin deficiency increased over the study period, and the mortality rates reported for this disease were higher among men than women and among whites than people of other races. We detected 2 mortality peaks, 1 among children and 1 among persons aged 45-54 years old, a finding that reflects that this deficiency manifests itself in two ways: as hepatic failure among children and as obstructive lung disease among adults. The increase in mortality rates we detected is probably due to improved diagnosis and increased recognition, although this deficiency is still likely underreported, especially among older persons with obstructive lung disease.

REFERENCES