Delay in Diagnosis of α_1-Antitrypsin Deficiency*

A Continuing Problem

James K. Stoller, MD, MS; Robert A. Sandhaus, MD, PhD; Gerard Turino, MD; Ryan Dickson, MS; Keith Rodgers, PhD; and Charlie Strange, MD

Background and study objectives: **α_1-Antitrypsin (AAT) deficiency is common but underrecognized. A 1994 mail survey showed a long delay between the onset of symptoms and the initial diagnosis of AAT deficiency. In 2003, we carried out a similar mail survey of AAT-deficient individuals to determine whether any delay in diagnosis experienced by individuals with a more recent diagnosis had become shorter. We also determined whether individuals living near medical centers with an expressed interest in AAT deficiency experienced shorter diagnostic delays than those living at a distance.**

Methods: **Results from mail surveys of two different cohorts were compared: a 1994 survey of 304 individuals with severe AAT deficiency and a 2003 survey of 1,953 AAT-deficient individuals. In the 2003 survey cohort, diagnostic delay intervals were analyzed by calendar year of initial diagnosis, rural vs urban residence, visit to a liver or lung specialist within the last year, and living within 50 miles of a medical center with particular expertise in AAT deficiency. One thousand nine hundred fifty-three individuals responded to the 2003 mail survey (37.4%).**

Results: **In the 2003 cohort, the mean ± SD diagnostic delay was 5.6 ± 8.5 years, compared with 7.2 ± 8.3 years for the 1994 cohort ($p = 0.002$). In the 2003 cohort, younger patients and male patients experienced shorter diagnostic delays than older patients and female patients ($p < 0.0001$ and $p = 0.007$, respectively). For example, the delay was 6.5 ± 8.8 years for those born in the 1940s, as compared with 0.43 ± 1.08 years for those born after 1980. Neither urban residence nor living near a center with expertise in AAT deficiency were associated with a shortened diagnostic delay interval.**

Conclusions: **Although these results show some improvement in the mean diagnostic delay in the 9-year period separating the two studies, underrecognition of AAT deficiency persists. Diagnostic delay of AAT deficiency is longer in women and in older individuals. Educational efforts are underway to enhance clinicians' diagnostic suspicion of AAT deficiency and permit earlier diagnosis and attendant benefits.** ***(CHEST 2005; 128:1989–1994)***

Key words: α_1-antitrypsin deficiency; diagnosis; survey

Abbreviations: AAT = α_1-antitrypsin; CRC = clinical resource center

Despite its affecting an estimated 100,000 Americans, α_1-antitrypsin (AAT) deficiency commonly goes unrecognized by clinicians. As a result, AAT-deficient individuals experience long delays between their first symptom and initial diagnosis, often with adverse medical and psychosocial sequelae.[1–3] For example, in a 1994 mail survey of 304 severely AAT-deficient individuals, Stoller et al[1] reported a mean interval of 7.2 years between initial symptom and first diagnosis. Furthermore, 44% of respondents reported seeing at least three physicians before the diagnosis of AAT deficiency was first made.

In the context that a mail survey was recently commissioned and completed by patient-based groups interested in the care of AAT-deficient individuals, we were able to incorporate questions regarding intervals between first symptoms of AAT

*From the Department of Pulmonary, Allergy, and Critical Care Medicine (Dr. Stoller), Cleveland Clinic Foundation, Cleveland, OH; Alpha-1 Foundation (Dr. Sandhaus), Miami, FL; St. Luke's-Roosevelt Hospital Center (Dr. Turino), New York, NY; and Division of Pulmonary and Critical Care Medicine, Asthma and Allergy (Mr. Dickson, and Drs. Rodgers and Strange), Medical University of South Carolina, Charleston, SC.

Manuscript received September 16, 2004; revision accepted March 2, 2005.

Correspondence to: James K. Stoller, MD, MS, Cleveland Clinic, A 90, 9500 Euclid Ave, Cleveland, OH 44195; e-mail: stollej@ccf.org

deficiency and first diagnosis similar to those posed in the aforementioned 1994 mail survey. We reasoned that growing awareness of AAT deficiency by clinicians might enhance clinical recognition and accelerate detection in affected individuals. Thus, we undertook the current analysis of mail survey results to assess whether individuals with AAT deficiency who received a more recent diagnosis had shorter delays in diagnosis than those with a diagnosis made earlier. The specific questions addressed were as follows: (1) is the interval between first symptom and initial diagnosis of AAT deficiency (the so-called "diagnostic delay interval") shorter in individuals with a more recent diagnosis than in those with an earlier diagnosis; and (2) is the diagnostic delay interval shorter in individuals living near medical centers with clinical expertise and educational activities regarding AAT deficiency than in individuals living farther away from such facilities?

Materials and Methods

A four-page mail survey was commissioned in 2003 by the three aforementioned patient-based organizations for development and distribution by an international research organization (Schulman, Ronca, and Bucuvalas, Inc.). Confidentiality agreements between Schulman, Ronca, and Bucuvalas, Inc. and the three sponsoring organizations permitted construction of a single, combined mailing list of 5,222 AAT-deficient individuals that omitted duplicates. Accompanied by a cover letter that explained the purpose of the survey and that provided a toll-free number for help, questionnaires were first sent to the 5,222 individuals on April 14, 2003, with follow-up reminder postcards to initial nonrespondents mailed on May 7, 2003. Responses were requested from the addressee or from a caregiver if the AAT-affected individual was either too young or too ill to complete the questionnaire. Responses to this survey, hereafter called the 2003 survey, were tallied and summarized for distribution to the sponsoring organizations in June 2003.

To assess trends in the time duration between first lung symptom and first diagnosis of AAT deficiency (hereafter termed the *diagnostic delay interval*), we also further analyzed the data set used in the earlier survey by Stoller et al.[1] Specifically, we reanalyzed the data in responses from 304 self-reported severely deficient individuals to assess the relationship between the diagnostic delay interval and two features of the diagnosed individuals: (1) the year of birth, and (2) the year in which the initial diagnosis of AAT deficiency was made. For the sake of clarity in distinguishing the earlier survey results from those from the "2003 survey," the earlier is dubbed the "1994 survey."

To assess whether living near a medical center with expertise in AAT deficiency affected the diagnostic delay interval, a list of 44 designated clinical resource centers (CRCs) of the Alpha-1 Foundation was used. Designation as a CRC was conferred based on review of the medical center's submitted application regarding experience in the diagnosis and management of AAT deficiency.

Statistical analysis was performed using statistical software (Stata Version 8; Stata Corporation; College Station, TX), and p values < 0.05 were deemed statistically significant. Categorical data were analyzed using χ^2 statistics, and continuous variables were analyzed with two-sided t tests. Specifically, the Mantel-Haenszel χ^2 test for trends was used to determine if the diagnostic delay interval differed by grouping of calendar years in which the diagnosis was first made. Three-way comparisons were performed using analysis of variance with Bonferroni correction for continuous variables. Geographic information systems software and zip code data were used to determine distance from a CRC and urban vs rural residence.

Results

By 2 months after the initial mailing, responses to the 2003 survey were received from 1,953 individuals (37.4% response rate). Table 1 summarizes the demographic and presenting characteristics of respondents in this recent survey and compares these individuals to respondents in the 1994 survey cohort. As shown, 49% of respondents to the 2003 survey were female, and the mean ± SD age was 53.1 ± 13.2 years. Fifty-two percent reported having emphysema, 38% reported chronic bronchitis, and 8% reported liver disease. Only 17% reported not having liver or lung disease. As previously reported, the mean age of the 304 severely AAT-deficient respondents to the original survey was 48.8 ± 11.4 years. One half were female, and all were white. Ninety-three percent reported having at least one lung symptom, 90.5% reported having dyspnea, and 9.5% reported liver disease.

Table 1—*Baseline Characteristics of the 2003 and 1994 Survey Populations*

Characteristics	2003 Survey (n = 1,851)	1994 Survey (n = 304)	p Value
Age, yr	53.1 ± 13.2	48.8 ± 11.4	< 0.001
Female gender	49	50	NS
Age at diagnosis, yr	43.9 ± 12.8	41.3 ± 11.0	0.002
Diagnostic delay, yr	5.6 ± 8.5	7.2 ± 8.3	0.002
At least one lung symptom	80	93	< 0.001
Liver disease present	8.0	9.5	0.40
Oxygen therapy use	45	NA	
Receiving augmentation therapy	73	NA	
Rural residence	23	NA	
Living within 50 miles of a CRC	38	NA	

*Data are presented as mean ± SD or %. NA = not assessed; NS = not achieving statistical significance ($p > 0.05$).

In the 2003 survey, respondents' mean age when AAT deficiency was first diagnosed was 43.9 ± 13.0 years, and the overall mean interval between first symptom and first diagnosis was 5.6 ± 8.5 years. In the earlier survey, the mean age at first symptom was reportedly 41.4 ± 11.0 years, and the overall mean interval between first symptom of AAT deficiency and initial diagnosis was 7.2 ± 8.3 years. The mean 1.6-year shortening of the diagnostic delay interval in the 2003 survey did achieve statistical significance ($p = 0.002$).

As shown in Figure 1, analysis of the mean interval between first symptom and initial diagnosis of AAT deficiency by birth decade in the 2003 survey showed that younger patients experienced shorter diagnostic delays than older patients ($p < 0.0001$). Specifically, the mean interval between first symptom and initial diagnosis for respondents born in the 1940s (n = 568), 1950s (n = 585), 1960s (n = 196), 1970s (n = 19), and after 1980 (n = 55) were, respectively, 6.5 ± 8.8 years, 4.6 ± 6.7 years, 4.0 ± 6.1 years, 3.8 ± 6.8 years, and 0.43 ± 1.08 years.

In the 1994 survey, a similar shortening of diagnostic delay by birth year was observed ($p < 0.0001$) [Fig 1]. Specifically, diagnostic delay intervals for those born before 1940 (n = 104), from 1940 to 1949 (n = 130), from 1950 to 1959 (n = 43), and from 1960 to 1969 (n = 3) were, respectively, 10.33 ± 11.44 years, 6.36 ± 6.64 years, 5.27 ± 5.52 years, and 3.66 ± 2.3 years.

Univariate analysis of diagnostic delay interval by other demographic characteristics of AAT-deficient individuals in the 2003 survey (Table 2) showed that men experienced a shorter diagnostic delay than women (mean, 5.0 ± 7.8 years vs 6.4 ± 9.2 years, $p = 0.0007$). Also, not having seen a lung or liver specialist and not undergoing spirometry within a year of completing the survey were associated with a shorter diagnostic delay interval and younger age at diagnosis ($p = 0.004$ and $p = 0.001$, respectively). Participants reporting no symptoms of lung or liver disease were less likely to have visited a specialist ($p < 0.0001$).

Table 2—*Demographic Features of Respondents by Diagnostic Delay Interval

Categories	Diagnostic Delay Interval	p Value
Gender		0.0007
Male (n = 944)	5.0 ± 7.8	
Female (n = 844)	6.4 ± 9.2	
Location		0.86
Rural (n = 403)	5.7 ± 7.9	
Urban (n = 1,370)	5.7 ± 8.7	
Live within 50 miles of a CRC†		0.30
Yes (n = 663)	5.4 ± 8.1	
No (n = 1,133)	5.8 ± 8.7	
Seen liver or lung specialist in last year		0.004
Yes (n = 1,640)	5.8 ± 8.5	
No (n = 156)	3.8 ± 8.1	
Spirometry in last year		0.001
Yes (n = 1,586)	5.9 ± 8.6	
No (n = 184)	3.8 ± 7.6	
Internet use		0.39
Ever (n = 924)	5.8 ± 8.4	
Never (n = 872)	5.5 ± 8.6	
Familiarity with organizations‡		0.12
Yes (n = 1,563)	5.7 ± 8.6	
No (n = 233)	4.9 ± 7.8	

*Data are presented as mean ± SD.

†Excludes Hawaii and Alaska.

‡Self-reported familiarity with the Alpha-1 Foundation, Alpha-1 Association, or AlphaNet.

To assess whether the diagnostic delay interval was shorter in individuals with a more recent diagnosis, we examined the mean interval between first symptom and initial diagnosis of AAT deficiency by the year in which the individual's diagnosis of AAT deficiency was first made, both in the 1994 survey cohort and in the 2003 survey cohort (Fig 2). Contrary to the idea that the diagnostic delay interval was getting shorter in more recent years, the intervals were actually longer in individuals with a more recent diagnosis in both surveys. For example, in the 1994 survey cohort, the diagnostic delay interval lengthened in more recent years (Fig 2, $p < 0.0001$, Mantel-Haenszel χ^2 test for trends), from 5.45 ± 8.52 years in those with AAT deficiency diagnosed before 1980 to 11.24 ± 12.6 years in those with a diagnosis between 1990 and 1994. Similarly, in the 2003 survey, the diagnostic delay interval was statistically significantly longer in individuals with a more recently diagnosis than in those with an earlier diagnosis ($p = 0.0002$, Mantel-Haenszel χ^2 test for trends). Specifically, the mean diagnostic delay interval for those with a diagnosis before 1980 (n = 67) was 4.72 ± 9.3 years, and the mean intervals there-

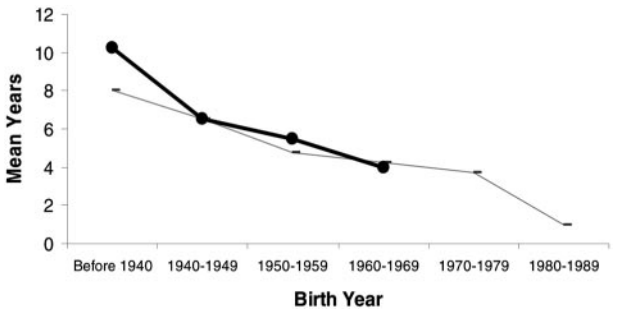

FIGURE 1. Diagnostic delay interval by birth decade in 2003 survey (narrow line) and in the 1994 survey (bold line). Because the diagnostic delay interval was available for only one subject born after 1969 in the 1994 survey, the single point is not displayed graphically.

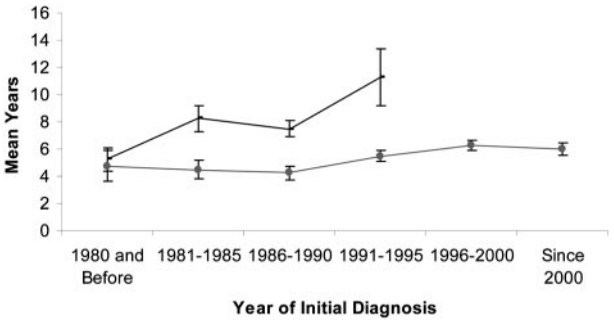

FIGURE 2. Mean interval (± SEM) between first reported symptom of AAT deficiency and initial diagnosis. In the 1994 survey by Stoller et al,[1] stratified by year of initial diagnosis (solid line), the interval is longer in individuals with a more recent diagnosis ($p < 0.001$, Mantel-Haenszel χ^2 for trends). In the 2003 survey, stratified by year of initial diagnosis (broken line), the interval length is longer in individuals with a more recent diagnosis ($p = 0.0002$ by Mantel-Haenszel χ^2 for trends).

after were 4.52 ± 6.8 years for those with a diagnosis from 1980 to 1985 (n = 106), 4.28 ± 7.9 years for those with a diagnosis from 1985 to 1990 (n = 243), 5.64 ± 8.4 years for those with a diagnosis from 1990 to 1994 (n = 434), 6.36 ± 8.6 years for those with a diagnosis from 1995 to 2000 (n = 540), and 6.0 ± 8.6 years for those with a diagnosis since 2000.

Reasoning that proximity to a CRC and that living in an urban area would offer access to clinical expertise in AAT deficiency that would translate into earlier diagnosis, we assessed age at first diagnosis and diagnostic delay interval among the 38% of respondents living within 50 miles from a CRC vs those living outside a 50-mile geographic radius and in those 77% living in urban areas vs rural dwellers. As shown in Table 2, neither living within 50 miles of a CRC nor urban dwelling were associated with a shortened diagnostic delay interval.

DISCUSSION

The main findings in this study regarding the interval between first symptom of AAT and first diagnosis of AAT deficiency are as follows: (1) the diagnostic delay interval remains long without evidence of significant shortening over 2 decades (*ie*, from before 1980 to after 2000); in fact, the diagnostic delay interval increased over time in both surveys; (2) while the diagnostic delay interval increased over 2 decades for both cohorts, the overall diagnostic delay interval was significantly shorter in the larger 2003 cohort (Table 1); (3) in both surveys, younger individuals had shorter diagnostic delays than older individuals; and (4) neither urban dwelling nor living near a center with expertise in AAT deficiency was associated with a shortened diagnostic delay interval.

Our finding that the diagnostic delay interval for individuals with AAT remains long (mean, 5.6 years in the 2003 survey cohort) is consistent with previous observations that AAT deficiency is clinically underrecognized.[1–4] For example, based on prevalence estimates derived from blood bank specimens, Silverman et al[4] estimated in 1989 that only 4% of the expected 700 PI*ZZ individuals in St. Louis were medically recognized. In 1994, Stoller et al[1] described a mean diagnostic delay of 7.2 years in a cohort of 304 severely deficient individuals surveyed through a mailing of the Alpha-1 Association. Furthermore, in that 1994 survey,[1] while 25% of respondents reported having the diagnosis of AAT deficiency rendered on the first physician encounter, 44% of respondents reported seeing at least three physicians before the diagnosis was made initially. Although the small decrement in the overall diagnostic delay interval from the overall 1994 survey to the 2003 survey (mean, 1.6 years) may offer some optimism about enhanced detection, our observation of lengthening diagnostic delays over time within each survey cohort suggests that underrecognition of individuals with AAT deficiency persists. In this regard, underrecognition of AAT deficiency is part of a larger phenomenon of underrecognition of individuals with COPD.[5,6] For example, Mannino et al[5] reported that of the 24 million Americans with evidence of impaired lung function from the third National Health and Nutrition Examination Survey, only 10 million reported having physician-diagnosed COPD.

The observation of persisting diagnostic delay in recognizing individuals with AAT deficiency invites discussion of benefits conferred by prompt diagnosis. Beyond averting the adverse psychosocial effects of delayed diagnosis,[1] earlier diagnosis would offer several benefits: (1) closer observation and management of affected individuals, especially regarding pulmonary and hepatic health; (2) consideration of testing family members, at least some of whom may be liver or lung affected; (3) more aggressive smoking cessation efforts, which have been associated with lower rates of smoking among AAT-deficient individuals screened at birth[7,8]; (4) reconsideration of occupational environment in the context that exposures to some occupational dusts and vapors appear associated with accelerated and worsened pulmonary symptoms[9,10]; and (5) possible initiation of augmentation therapy, which has been recommended to slow the rate of FEV_1 decline in some AAT-deficient individuals with established emphysema.[2]

Underrecognition of AAT deficiency has recently prompted educational campaigns by national professional societies (*eg*, the American Thoracic Society,

the American College of Chest Physicians, the American Association for Respiratory Care) and patient-led organizations (*eg*, the Alpha-1 Foundation, the α_1 Association) to disseminate information about AAT deficiency to clinicians and the interested lay community. A major goal of such educational programs has been to enhance clinicians' knowledge about AAT deficiency, with the hope that AAT-deficient individuals will receive an earlier diagnosis and receive optimal care.

Examples of important recent educational activities have included the following: (1) development, publication, and widespread distribution of an international evidence-based standards[2] for the management of AAT-deficient individuals that was first published in October 2003; (2) inclusion of presentations and publications about AAT deficiency in recent symposia regarding COPD (including the American Association for Respiratory Care in 2003 and the American Thoracic Society in 2004)[3]; (3) an expansion of lectures about AAT deficiency sponsored both by patient advocacy organizations (such as the Alpha-1 Foundation and Alpha-1 Association) and by pharmaceutical companies producing pooled human plasma antitrypsin augmentation therapy medications over the last several years; (4) organization of "patient education days" by the Alpha-1 Foundation and Alpha-1 Association to enhance patient knowledge and to enable patients to better partner with their clinicians in "collaborative self-management" since 2002[11,12]; and (5) development in 2004 of a systematic disease management program regarding AAT deficiency intended for delivery to clinicians of affected individuals by their patients.

While our observation that the diagnostic delay interval has not clearly decreased could be construed as challenging the effectiveness of these educational activities, in fact these activities postdate the 1994 survey and are likely too new to be reflected in data from the 2003 survey. For example, the American Thoracic Society/European Respiratory Society standards for the diagnosis and management of individuals with AAT deficiency[2] were published in October 2003, postdating both surveys. The Alpha-1 Foundation/Alpha-1 Association patient education day series has been formally underway only since 2002, likely too soon before the 2003 mail survey to have fully exerted the desired impact. We believe that educational efforts will enhance clinicians' diagnostic suspicion of AAT deficiency to the extent that they reach and are made relevant to the broad community of physicians to whom AAT-deficient patients may present, including family practice physicians, internists, pulmonologists, allergists, and hepatologists.

However, it bears mentioning that one of the early results of an effective educational program might be to paradoxically raise the reported interval between first symptom and initial diagnosis of AAT deficiency. Specifically, to the extent that clinicians' enhanced awareness causes them to suspect AAT deficiency in patients under their care for a long time, the first wave of newly detected patients may report longer diagnostic delay intervals than patients newly presenting with symptoms. Also, much effort is currently underway to promote testing of individuals whose clinical picture is consistent with typical COPD, a generally older population. Indeed, our finding that the diagnostic delay interval in patients with a diagnosis since 2000 is actually longer than in patients with a diagnosis made before 1990 is consistent with this paradoxical early effect of education. However, this same model would predict that as the pool of patients with a "latent" diagnosis of AAT deficiency is exhausted through effective detection, those with a diagnosis thereafter would be expected to show a shortened diagnostic interval. While our data do not show this second mode of a later shortening after an initial lengthening of the diagnostic delay interval, we suspect that the educational campaign is too new to have depleted the "latent diagnosis" pool of individuals.

Results from both surveys show that the diagnostic delay interval is shorter in younger individuals. We speculate that this reflects clinicians' appropriate awareness that AAT deficiency can present as fixed airflow obstruction in young individuals and their higher suspicion of AAT deficiency in this setting. At the same time, the long diagnostic delay interval in general suggests either that affected individuals delay seeking medical attention or that clinicians are less prompt in suspecting AAT deficiency when it presents in other ways (*eg*, as liver disease, as airflow obstruction in older individuals). Against patients' delay in presenting is the finding from the 1994 survey that 44% of respondents saw at least three physicians before the diagnosis of AAT deficiency was first made.

Why the diagnostic delay interval was shorter in men than in women in the 2003 survey is unclear. Lack of information about smoking status by gender precludes specific analysis, but if the rate of smoking was higher among female than male respondents, it is possible that clinicians' suspicion of AAT deficiency was lowered by women having an alternate risk factor for fixed airflow obstruction (*ie*, smoking). Of course, to the extent that these explanations underlie the longer diagnostic delay in women, they emphasize the pitfalls in diagnosing AAT deficiency and underscore the importance of testing all symptomatic adults with fixed airflow obstruction (as has

been recommended in the recent American Thoracic Society/European Respiratory Society standards document.[2]

Similarly, reasons that the diagnostic delay was shorter in respondents who did not see lung or liver specialists in the last year or who did not undergo spirometry in the year before are unclear. We can speculate that individuals referred to such specialists had been followed up by primary care physicians for a sustained time period without establishing a diagnosis, and when the referral was ultimately made a correct diagnosis was established. Also, many of these individuals with short diagnostic delays may be siblings of symptomatic individuals who received a diagnosis by family testing in the absence of any symptoms. Participants without symptoms would be less likely to visit a specialist.

Several limitations of this study warrant discussion. First, unlike the 1994 survey, because the 2003 survey did not ask how many physicians were seen before the initial diagnosis of AAT deficiency, we cannot establish that the diagnostic delay was due to underrecognition of AAT deficiency by clinicians. For example, although unlikely, it is possible that the diagnostic delay reported by respondents was due to their delay in bringing symptoms to the attention of their health-care providers rather than to underrecognition of the cause of these symptoms by the providers.

Second, because the response rate to the 2003 survey was 37.4%, we cannot discount the possibility of sample bias in our results. For example, if nonrespondents had experienced long diagnostic delay intervals, results based on the subset of respondents would underestimate the true diagnostic delay interval. Furthermore, because our survey addressed only individuals with known AAT deficiency, AAT-deficient individuals without a diagnosis (who are especially likely to have long diagnostic delays intervals by virtue of not yet having received a diagnosis) would not be included. In this regard, the value of the diagnostic delay interval derived from the subset of AAT-deficient respondents is again likely to be an underestimate.

Finally, we cannot discount the possibility that some respondents to the earlier survey also participated in the 2003 study, thereby potentially confounding the comparison of diagnostic delays in the two studies. However, ascertainment of prospective participants in the two surveys was by completely independent methods, and the unlikely inclusion of even the majority of the 300 respondents to the 1994 survey would be unlikely to dominate the results from the much larger 2003 survey group.

In summary, these results suggest that underrecognition of AAT deficiency persists. Because establishing a diagnosis of AAT deficiency can confer benefits of specific therapy[2] and of identifying at-risk family members, enhanced diagnostic suspicion and increased testing have been recommended.

References

1 Stoller JK, Smith P, Yang P, et al. Physical and social impact of α_1-antitrypsin deficiency: results of a mail survey of the readership of a national newsletter. Cleve Clin J Med 1994; 61:461–467

2 American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of patients with α_1-antitrypsin deficiency. Am J Respir Crit Care Med 2003; 168:816–900

3 Stoller JK. Key current clinical issues in α-1 antitrypsin deficiency. Respir Care 2003; 48:1216–1224

4 Silverman E, Miletich SP, Pierce JH, et al. Alpha-1 antitrypsin deficiency: high prevalence in the St. Louis area determined by direct population screening. Am Rev Respir Dis 1989; 140:961–966

5 Mannino DM, Homa DM, Abikami LJ, et al. Chronic obstructive pulmonary disease surveillance–United States, 1971–2000. MMWR Morb Mortal Wkly Rep 2002; 51(SS06): 1–16

6 Zaas D, Wise R, Wiener C, for the Longcope Spirometry Investigation Team. Airway obstruction is common but unsuspected in patients admitted to a general medical service. Chest 2004; 125:106–111

7 Wall M, Moe E, Eisenberg J, et al. Long-term follow-up of a cohort of children with α-1 antitrypsin deficiency. J Pediatr 1990; 116:248–251

8 Sveger T. Liver disease in α-1 antitrypsin deficiency detected by screening 200,000 infants. N Engl J Med 1976; 294:1316–1321

9 Piitluainen E, Torning G, Eriksson S. Environmental correlates of impaired lung function in non-smokers with severe α-1 antitrypsin deficiency (PI*ZZ). Thorax 1998; 53:939–943

10 Mayer A, Stoller JK, Bucher Bartelson B, et al. Occupational exposure risks in individuals with PI*Z α-1 antitrypsin deficiency. Am J Respir Crit Care Med 2000; 162:553–558

11 Make B. Chronic obstructive pulmonary disease: developing comprehensive management. Respir Care 2003; 48:1225–1237

12 Make B. Collaborative self-management strategies for patients with respiratory disease. Respir Care 1994; 39:566–579