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ORIGINAL RESEARCH

The Epidemiology of Alpha-1 Antitrypsin Deficiency in Norway

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Background: Alpha-1 antitrypsin deficiency (AATD) is a genetic condition characterized by insufficient levels of alpha-1 antitrypsin and elevated risk of lung and liver disease. We aimed to estimate the prevalence and incidence of diagnosed AATD (dAATD) in Norway, and mortality after dAATD.

Methods: A nationwide cohort of individuals diagnosed with AATD between 2008 and 2019 was identified from the Norwegian Patient Registry. Prevalence and incidence rates were standardized to the Norwegian population as of December 31, 2019. Mortality rate ratios (MRRs) were calculated to compare mortality between patients with dAATD and a randomly sampled, 10:1 matched general population comparison cohort.

Results: A total of 827 patients with dAATD were identified during the study period. The prevalence of dAATD in Norway at the end of 2019 was 10.7 per 100,000 people (95% confidence interval [CI]: 9.8–11.5), and the incidence rate was 1.4 per 100,000 person-years (95% CI: 1.3–1.5). Mortality among patients with dAATD was markedly elevated, with an MRR of 6.2 (95% CI: 5.3–7.2) with respect to the general population comparison cohort. Among patients with AATD, 26.8% had an emphysema diagnosis, 12.5% had an asthma diagnosis, and 6.4% had a liver disease diagnosis.

Conclusion: This study provides the first national estimates of dAATD frequency and mortality in Norway. The mortality for patients with dAATD was found to be markedly elevated compared with their age and sex matched peers, indicating a substantial disease burden and suggesting the need for improved diagnosis and earlier therapeutic interventions.

Keywords: alpha-1 antitrypsin deficiency, prevalence, incidence, mortality

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder in which a mutation in the SERPINA1 gene leads to changes in alpha-1 antitrypsin (AAT) protein function and/or levels, and consequent organ damage.[1] AATD is inherited through autosomal codominant transmission with 95% of severe cases of AATD resulting from the homozygous substitution of a single amino acid, Glu342Lys (the Z allele), which is approximately present in 1 in 2000 persons of northern European descent.[2]

The adverse clinical manifestations differ depending on genotype, allelic combinations, and lifetime environmental exposures (eg, smoking).[3]

AATD affects primarily the lungs, as a result of uninhibited effects of neutrophil elastase on lung tissue, and can manifest as emphysema, chronic obstructive pulmonary disease (COPD), and asthma. In the liver, AATD adverse sequelae result from accumulation of an abnormally misfolded AAT in hepatocytes. Subsequently, cytotoxicity can manifest early as neonatal liver disease or in adulthood as progressive liver disease.[2]

Population-based longitudinal studies on AATD occurrence and prognosis have been conducted in only a few studies restricted to Denmark and Sweden. A recent study in Denmark during 2000 to 2018 estimated a dAATD prevalence of 12.9 per 100,000 people (95% confidence interval [CI] 11.9–13.8) using the ICD 10 code E88.0A and 19.7 per 100,000 people (95% CI 18.6–20.9) using ICD 10 code E 88.0, and a dAATD mortality rate approximately five times higher than

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that in an age- and sex-matched general population comparison cohort.[4] A similar study from Sweden in 2002–2020 indicated an AATD prevalence rate of 21 per 100,000 people (95% CI 18.6–20.9) and an AATD mortality rate 3.5 times higher than that in the general population.[5]

Data on the epidemiology, survival, and associated morbidity of AATD in Norway are lacking. Despite similarities in ethnicity and genetic background, screening policies and management differ between Scandinavian countries, which may lead to variations in the epidemiology and disease outcomes.

The primary objective of this study was to estimate the prevalence and incidence of diagnosed AATD (dAATD) in Norway, and comparative mortality versus general population peers after the diagnosis of AATD, as well as to characterize respiratory disease, hepatic disease, and related comorbidities among patients with dAATD.

Population and Methods

Diagnosed Alpha Antitrypsin Deficiency Cohort Development

Norway is a country with approximately 5.3 million inhabitants. The Norwegian health care system is universal and provides nearly free access, although some patient fees are charged for visits to general practitioners or outpatient hospital clinics.[6] Each resident in Norway is assigned a unique personal identification number at birth or immigration, and the number follows each person for the entire lifespan.

This nationwide cohort study from Norway identified patients with AATD from the Norwegian Patient Registry (NPR) covering all patients registered between 1/1/2008 and 12/31/2019. Since the registry captures only diagnosed cases of the disease, we will use the term diagnosed AATD (dAATD) throughout the article.

NPR was founded in 1997.[6] After its establishment, the registry included inpatients in somatic hospitals. In 2009–2010, the registry was further expanded to include information from emergency departments. Importantly, before 2008, the registry did not include personal identity numbers, thus precluding linkage with other data sources.

The NPR was used to identify patients with dAATD using the International Classification of Diseases (ICD), 10th revision (ICD-10) code E88.0 (disorders of plasma-protein metabolism).[7] Prior studies have indicated that AATD comprises all diagnoses within the E88.0 ICD-10 code.[4,8]

The cohort included all patients with at least one diagnosis of AATD, encompassing both primary and secondary diagnoses from inpatient and outpatient visits. Patients with dAATD were followed-up passively, i.e based on data available in the registry only, from the AATD diagnosis date until 12/31/2019, and the year of emigration was documented through 2018 for any members of the dAATD cohort who emigrated from Norway.

Matched General Population Comparison Cohort

From the Norwegian National Population Registry, up to ten individuals from the general population were randomly sampled (with replacement) for each patient with dAATD. The matching criteria included birth date (year and month of birth) and sex.

Covariates

The NPR was used to identify baseline comorbidities among patients with dAATD. Including all inpatient and outpatient clinic visits. The diagnosis codes of these covariates were listed in Supplementary Table 1 (lung and liver diagnoses) and Supplementary Table 2 (diagnoses included in the Charlson Comorbidity Index score).[9] The length of the pre-baseline lookback period was shorter for patients diagnosed toward the beginning rather than the end of the study period (ie, left truncation), thus affecting the completeness of comorbidity identification for patients with a dAATD early in the study period.[10]

Statistical Analysis

The index date for patients with dAATD and the general population comparators was the admission date of the first hospital contact that yielded the AATD diagnosis (of note, the discharge date was not available in the data).

Demographic data for the Norwegian population by age, sex, and calendar year are publicly accessible on Statistics Norway's website (www.ssb.no). These data were used to calculate dAATD prevalence and incidence.

Prevalence

The prevalence of dAATD was calculated overall and stratified by age group and sex. Prevalence was estimated as a proportion per 10^5 people as of 12/31/2019. The 95% CIs were calculated according to the normal approximation to the binomial distribution.

Norwegian population counts are available on January 1st each year. Population counts on December 31st for each calendar year during the study period were considered equivalent to the next day's data (eg, the Norwegian population count on 12/31/2018 was assumed to be equal to the count on 1/1/2019).

Standardized prevalence was calculated overall and stratified by sex, age group, and specific timepoints during the study period (end of 2011, 2015, and 2019). The age and sex distributions from the Norwegian population as of 12/31/2019 were used as standardization weights.

Incidence Rate

We computed the incidence rates of dAATD per 10^5 person-years (PYRS). The incidence rates were standardized to the age- and sex-distribution of the general Norwegian population during the period 01/01/2008-12/31/2019. We calculated 95% CIs for the incidence rates by using the normal approximation to the Poisson distribution. The incidence rates were calculated by sex, age groups, and calendar year periods.

Mortality in Patients with dAATD and the Matched General Population Comparison Cohort

We calculated crude mortality rates for patients with dAATD and members of the age- and sex-matched comparison cohort per 10^5 PYRS overall, and by sex, age groups, and calendar time periods. We counted PYRS starting at the index dates of the patients with dAATD for individuals in the matched comparison cohort, both to mimic the counting of PYRS after diagnosis in the dAATD cohort and to avoid immortal time bias. We calculated 95% CIs for the mortality rates by using the chi-square distribution. We calculated MRRs to compare mortality between patients with dAATD and the general population comparison cohort. We applied the approximate Wald method to estimate the 95% CIs for the MRRs.

Ethics

The project was approved by the Norwegian Ethics Committee – South-East (application number 25340), the regional ethics committee that evaluates and approves ethics applications coming from all the hospitals in south-east of Norway where Østfold hospital is located.

Results

In total, 827 patients with dAATD were identified during the study period. As of 12/31/2019, 573 were alive, whereas 249 were deceased (Table 1). Less than 1% of patients with dAATD emigrated and were lost to follow-up. The median follow-up time of patients with dAATD was 4.5 years (interquartile range (IQR): 1.6–8.0).

Table 2 summarizes the sex and age at diagnosis for the 573 patients with dAATD who were alive as of the end of the study, and the same demographic characteristics for the Norwegian population. The sex distribution for patients with dAATD was similar to that in the Norwegian population, but the patients with dAATD were generally older than the Norwegian population.

Table 1 Identification and Mortality of Patients Diagnosed with AATD in 2008–2019

Vital Status as of 12/31/2019	N	%
Alive	573	69.3
Deceased	249	30.1
Unknown/emigrated	5	0.6
Total	827	100.0

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Table 2 Characteristics of the Norwegian Population and Patients with dAATD as of 12/31/2019

	Norwegian Population		Patients with dAATD	
	N	%	N	%
Total	5,367,580	100.0	573	100.0
Sex				
Females	2,661,018	49.6	299	52.2
Males	2,706,562	50.4	274	47.8
Age (years)				
≤12	802,405	14.9	56	9.8
13–18	379,760	7.1	15	2.6
19–24	407,413	7.6	16	2.8
25–34	745,147	13.9	31	5.4
35–44	703,838	13.1	55	9.6
45–54	74,8079	13.9	86	15.0
55–64	63,9122	11.9	128	22.3
≥65	94,1816	17.5	186	32.5

The overall prevalence of dAATD at the end of 2019 was 10.7 (95% CI 9.8–11.5) per 10^5 people (Table 3). The prevalence was similar between men and women and among age groups up to 34 years of age, but it markedly increased thereafter. The prevalence increased from 5.8 per 10^5 people to 10.7 per 10^5 people from 12/31/2011 to 12/31/2019.

Table 3 Prevalence of dAATD per 10^5 People

	Population as of 12/31/2019	dAATD Cases (N)	Prevalence	95% CI
Overall (2008–2019)	5,367,580	573	10.7	9.8–11.5
By sex*				
Females	2,661,018	299	11.1	9.8–12.3
Males	2,706,562	274	10.3	9.1–11.5
By age (years)**				
≤12	802,405	56	6.9	5.1–8.8
13–18	379,760	15	4.0	2.0–6.0
19–24	407,413	16	3.9	2.0–5.8
25–34	745,147	31	4.2	2.7–5.6
35–44	703,838	55	7.9	5.8–9.9
45–54	74,8079	86	11.5	9.1–14.0
55–64	63,9122	128	20.0	16.6–23.5
≥65	94,1816	186	19.8	16.9–22.6

(*Continued*)

Table 3 (Continued).

	Population as of 12/31/2019	dAATD Cases (N)	Prevalence	95% CI
By end of year***				
2011	4,985,870	282	5.8	5.1–6.5
2015	5,213,985	421	8.2	7.4 – 9
2019	5,367,580	573	10.7	9.8–11.5

Notes: *Adjusted to the age distribution as of 12/31/2019. **Adjusted to the sex distribution as of 12/31/2019. ***Adjusted to the age and sex distribution as of 12/31/2019.

The overall incidence rate of dAATD in Norway was 1.4 per 10^5 PYRS (95% CI 1.3–1.5). Table 4 shows the incidence rates overall and stratified by sex, age, and calendar period. The incidence rates were similar for men and women, and increased with age after 35 years of age. The incidence rate was estimated to be higher earlier in the follow-up period than in later years, probably as an artifact of the left truncation, given that patients diagnosed before 2008–2011 were included as incident patients as of the date of a subsequent diagnosis during the 2008–2011 time period.

Table 4 Incidence Rate of dAATD per 10^5 PYRS

Incidence	Standardized Incidence Rate/10^5 PYRS	95% CI
Overall	1.4	1.3–1.5
By sex*		
Females	1.3	1.2–1.5
Males	1.4	1.3–1.5
By age (years)**		
≤12	0.8	0.6–1.0
13–18	0.4	0.2–0.6
19–24	0.3	0.1–0.4
25–34	0.6	0.4–0.8
35–44	1.1	0.9–1.3
45–54	1.7	1.4–2.0
55–64	2.5	2.1–2.9
≥65	2.7	2.4–3.1
By time period***		
2008–2011	1.9	1.7–2.0
2012–2015	1.1	1.0–1.3
2016–2019	1.2	1.0–1.3

Notes: *Standardized to the age distribution during 01/01/2008 to 12/31/2019. **Standardized to the sex distribution during 01/01/2008 to 12/31/2019. ***Standardized to the age and sex distribution during 01/01/2008 to 12/31/2019.
Abbreviations: PYRS, person-years; CI, confidence interval.

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Table 5 Comparative Mortality Among Patients with dAATD and the Age and Sex Matched Norwegian Population

	dAATD Number of Deaths	dAATD Cohort Mortality Rate per 10^5 PYRS	Matched Cohort Number of Deaths	Matched Cohort Mortality Rate per 10^5 PYRS	MRR	95% CI
Overall	249	6,025	501	978	6.2	5.3–7.2
By sex						
Females	107	5,105	256	1,022	5.0	4.0–6.3
Males	142	6,973	245	936	7.4	6.1–9.2
By age (years)						
≤18*	≤ 5	776	0	0	-	-
19–34*	≤ 5	1,351	0	0	-	-
35–44	≤ 5	900	≤ 5	65	13.8	3.1–61.9
45–54	28	3,670	20**	219	16.8	9.4–30.0
55–64	44	4,597	44	383	12.0	7.9–18.2
≥65	165	14,269	435	2,403	5.9	5.0–7.1
By time period						
2008–2011	67	9,333	80	929	10.0	7.3–13.9
2012–2015	84	5,866	164	939	6.2	4.8–8.1
2016–2019	98	4,943	257	1,021	4.8	3.8–6.1

Notes: *Age categories condensed due to be aligned with the Danish study, where were no deaths among patients with AATD 13–18 years and 25–34 years. **Rounded to the nearest 10 to avoid reporting sensitive data.
Abbreviations: dAATD, diagnosed alpha-1 antitrypsin deficiency, PYRS, person-years; MRR, mortality rate ratios; CI, confidence interval.

The overall MRR was 6.2 (95% CI 5.3–7.2) and was slightly greater for males than females. Age specific analyses for the younger age groups were hindered by few outcome events among patients with dAATD and no deaths among those in the ≤ 34-year-old segments of the matched general population comparison cohort. However, in general, we observed a noticeable trend of higher MRRs for individuals ≤ 64 years of age rather than ≥ 65 years (Table 5). The MRRs also declined by time period and were lowest in the most recent 2016–2019 period.

We characterized the 827 patients with AATD diagnosed any time during the 2008–2019 study period with respect to lung and liver conditions (Table 6). Approximately 47% had a diagnosis of chronic respiratory disease. The most frequent diagnoses were emphysema (27% of patients) and asthma (13% of patients), whereas 6.4% of patients had a liver disease diagnosis, and 1.6% of patients had diagnoses of both lung and liver disease. The frequency of various liver diseases is shown in Table 6.

Table 6 Characteristics of Patients Diagnosed with AATD During 1/1/2008 Through 12/31/2019

	N	%
Total	827	100
Females	407	49.2
Males	420	50.8

(*Continued*)

Table 6 (Continued).

	N	%
Age (years)		
≤12	78	9.4
13–18	19	2.3
19–24	13	1.6
25–34	48	5.8
35–44	93	11.2
45–54	143	17.3
55–64	180	21.8
≥65	253	30.6
Charlson comorbidity index at diagnosis date		
0	355	42.9
1–2	336	40.6
≥3	136	16.4
Lung diseases		
No	440	53.2
Yes	387	46.8
Emphysema		
No	605	73.2
Yes	222	26.8
Asthma		
No	724	87.5
Yes	103	12.5
Other COPD		
No	559	67.6
Yes	268	32.4
Bronchitis		
No	819	99
Yes	8	1.0
Other chronic lower respiratory disease		
No	n.a.	~100
Yes	≤5	~0

(*Continued*)

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Table 6 (Continued).

	N	%
Bronchiectasis		
No	798	96.5
Yes	29	3.5
Liver disease		
No	774	93.6
Yes	53	6.4
Hepatic failure		
No	814	98.4
Yes	13	1.6
Other inflammatory liver diseases		
No	814	98.4
Yes	13	1.6
Fibrosis and cirrhosis of liver		
No	815	98.5
Yes	12	1.5
Other diseases of liver		
No	803	97.1
Yes	24	2.9
Lung and liver disease		
No	814	98.4
Yes	13	1.6

Discussion

In this first nationwide study using the ICD-10 diagnostic code E88.0, we provided data on dAATD prevalence, incidence, and mortality rates in Norway. Despite its rarity, dAATD is associated with elevated mortality compared to the general population.

AATD is largely underdiagnosed and even when diagnosed, diagnosis tends to be delayed.[11] Accordingly, AATD studies should ideally specify that disease frequency estimates relate to diagnosed AATD (dAATD) rather than AATD per se. Estimates of dAATD frequency can substantially vary across studies, thereby reflecting variations in country-specific prevalence, data sources, case definitions, screening, and analytical methods.[12]

In Norway, the prevalence of dAATD as of 12/31/2019 was 10.7 per 10^5 people (95% CI 9.8–11.5). The prevalence of dAATD in a recent study in Denmark in 2000–2018 was 12.9 per 10^5 people (95% CI 11.9–13.8) as of 12/31/2018 according to ICD 10 code E88.0A, and 19.7 per 10^5 people (95% CI 18.6–20.9) according to the more inclusive ICD-10 code E88.0, as used in the current Norwegian analysis.[4] A similar study from Sweden that included patients in 2002–2020 with ICD-10 diagnosis codes E88.0A and 88.0B and ICD-9 code 277G has also found higher prevalence rates of AATD [21.0 per 10^5 people (95% CI 18.6–20.9)] than identified in Norway.[5]

Some differences in prevalence between Norway and the two other Scandinavian countries are likely to be due to the shorter time period (2008–2019) in the present study. dAATD is a chronic illness, and some proportion of Norwegian patients diagnosed in the years shortly before the start of follow-up in 2008 would have survived through 2019 and increased the estimated prevalence for Norway. Another reason might relate to differences in ICD-10 diagnostic codes used in Scandinavia. Some patients in Norway might have received another diagnostic code, because E88.0 is not specific to AATD. However, despite the apparent difference in overall prevalence between countries, the prevalence was appreciably higher in the oldest age groups and increased during the study period, probably because of increased detection.

The estimated incidence of 1.4 per 10^5 PYRS (95% CI 1.3–1.5) in Norway was higher than that in Denmark (0.9 per 10^5 PYRS, 95% CI 0.8–1.0) but lower than that in Sweden (1.8 per 10^5 PYRS (95% CI 1.6–2.1).[4,5]

Notably, because AATD is known to be substantially underdiagnosed, screening and other medical surveillance practices, by identifying asymptomatic or mildly symptomatic cases, can affect prevalence estimates.

Studies in Germany and Italy have indicated low awareness of AATD among non-specialists and estimated AATD diagnostic delays of 7 and 6 years, respectively.[8] Of note, the prevalence results in Norway, Denmark, and Sweden are well below the predicted AATD genotype prevalence of approximately 1 per 1,600 people in Scandinavia suggested in genetic screening studies.[13,14] On this basis, only 30% of individuals with AATD appear to be identified and diagnosed in Scandinavia.[5]

A limited number of studies have reported long-term AATD mortality rates.

The mortality among patients with dAATD in Norway [6.0 per 10^5 PYRS (95% CI 5.0–7.1)] was similar to that in Denmark [5.4 per 10^5 PYRS (95% CI 4.8–6.1)] but higher than in Sweden [2.6 per 10^5 PYRS (95% CI 2.4–2.9)].[5] The MRR was 6-fold higher in patients with dAATD than the age and sex matched general population. The MRR increased substantially after the age of 35 years. The MRRs tended to be slightly higher in Norway than in Denmark, but both countries showed lower MRRs in the oldest age groups, in which total mortality is highest. These findings are also consistent with the known clinical course of dAATD, wherein earlier-onset disease is more severe. In Sweden, a 3.5 times higher in AATD with respect to the matched general population.[5]

The present study in Norway, and prior studies in Denmark and Sweden, indicated that the primary manifestations among patients with dAATD are lung disorders and, to a lesser extent, liver disorders. The proportion of patients with these sequelae was estimated to be lower in Norway than Denmark, a finding likely to have been influenced by the much longer lookback period for identifying comorbidities in the Denmark study.

A recent systematic review including 38 studies on disease burden has indicated that pulmonary morbidity is frequently reported, including COPD (36.3–75.8% prevalence), emphysema (14.4–53.8% prevalence), and bronchiectasis (3.8–73.1% prevalence). Our findings of 32%, 27%, and 3% affected by COPD, emphysema, and bronchiectasis, respectively, are near or within those ranges.[15] In our study, liver disease was reported in 6.4% of the patients, whereas 1.6% of the patients had both lung and liver disorder. The prevalence of liver disease reported among studies in the systematic review ranged widely, from 1% to 88%. Reported liver diseases included hepatic fibrosis, cirrhosis, hepatitis, and hepatocellular carcinoma.[15]

Several limitations must be considered to properly interpret the dAATD results from Norway. First, diagnoses based on ICD codes are subject to error associated with variation among coders, coding errors, limitations in the specificity of available codes, and errors and variation in the clinical diagnoses on which the coding is based.

Of note, the ICD-10 code for AATD has not been formally validated. In Norway, no specific ICD-10 code sublevel exists for AATD, and the diagnosis is covered by E88.0. Consequently, other diagnoses involving protein deficiency conditions might have been included, but this has been found to be rare by other authors.[8] Second, we cannot exclude that some patients may have been diagnosed in the primary care only without being referred to the hospital and consequently not being captured by the NPR. However, we believe that this practice is very limited and the extent of which would unlikely have any significant effect on our results.

Third, the extent of morbidity and mortality associated with AATD depends on genotype, AAT serum levels, and environmental exposures (eg, smoking). Although we lacked access to that information in the registries used in this study, such information would have been informative in analyses of mortality and chronic sequelae. The lack of information on smoking status, among both the dAATD group and the controls, could have had an impact on the

mortality rate ratio. The prevalence of smoking is low in Norway, but conceivably the MRR could have been overestimated slightly if smoking was more common among peers of patients with dAATD.

Fourth, diagnostic information before the start of follow-up in 2008 was unavailable in the registries used in this study. This left truncation of study information resulted in an underestimation of Norwegian dAATD prevalence and less comprehensiveness of comorbidity diagnoses for patients with dAATD. Nonetheless, diagnoses of AATD, which are usually based on evaluation of serum AAT levels, should have very high specificity and positive predictive value. Therefore, studies in patients with dAATD identified by ICD codes should be informative regarding the sequelae and medical needs for patients who receive AATD diagnoses.

In conclusion, we provided the first national estimates of dAATD prevalence, incidence, and mortality in Norway, along with the frequency of diagnosed lung and liver disorders for these patients. Although the prevalence appears lower than those in neighboring countries, probably because of underdiagnosis and registry limitations, the disease burden remains substantial, thus underscoring the need for improved detection and earlier targeted therapeutic interventions.

Disclosure

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