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Registry-Based Cohort Study of Alpha-1 Antitrypsin Deficiency Prevalence, Incidence and Mortality in Denmark 2000-2018

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ABSTRACT

Objective To estimate the prevalence of diagnosed alpha-1 antitrypsin deficiency (dAATD) in Denmark as of 31 December 2018, and dAATD incidence and mortality from 1 January 2000 to 31 December 2018.

Study design and setting We used the Danish National Patient Registry to identify patients with dAATD based on the International Classification of Diseases, 10th Revision (ICD-10) code E88.0A and the Danish Civil Registration System (CRS) for population counts and vital status. We estimated dAATD prevalence, incidence and mortality. We compared mortality among patients with dAATD and an age-matched and sex-matched cohort extracted from the Danish CRS. We conducted a sensitivity analysis to examine whether coding changes during 2000–2018, from a general to a more specific ICD-10 code for AATD, and left truncation affected results appreciably.

Results The prevalence of dAATD was 12.9 (95% CI 11.9 to 13.8) per 100 000 persons. The age distribution was bimodal, with peaks at ages ≤12 and ≥45 years. The incidence rate per 100 000 person-years was 0.90 (95% CI 0.85 to 0.96), again with a bimodal age distribution. Mortality was higher for patients with dAATD than for the general population (mortality rate ratio (mRR) 4.7, 95% CI 4.1 to 5.3), especially for children (mRR 33.8, 95% CI 6.8 to 167.4). The sensitivity analysis indicated that dAATD prevalence might have been as high as 19.7 per 100 000 persons due to less specific ICD-10 coding for AATD early in the study period or 21.4 per 100 000 persons correcting for left truncation.

Conclusion Diagnosed AATD was associated with increased mortality, especially for children. The finding for children was based on few deaths and had very wide 95% CIs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Alpha-1 antitrypsin deficiency (AATD) is known to be appreciably underdiagnosed and a nationwide study of diagnosed patients has never been undertaken.

⇒ This is the first national study to estimate diagnosed AATD (dAATD) prevalence and comparative mortality by age group.

WHAT THIS STUDY ADDS

⇒ We estimated prevalence in Denmark as of 31 December 2018 to be 12.9 per 100 000 persons (95% CI 11.9 to 13.8) or, in sensitivity analyses, as high as 21.4 per 100,000 (95% CI 20.3 to 22.6). Mortality was elevated compared to the general population (overall mortality ratio = 4.7, 95% CI 4.1 to 5.3), especially for children (mortality ratio 33.8, 95% CI 6.8 to 167.4).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The prevalence of dAATD was much lower than the estimated genetic prevalence of AATD (1/1600) in southern Scandinavia, confirming the appreciable underdiagnosis for this condition. The markedly elevated mortality rate ratio for children has not been estimated previously and warrants confirmation.

INTRODUCTION

Trypsin is a proteolytic enzyme produced in the gastrointestinal system.[1] Counterbalancing trypsin is its inhibitor, alpha-1 antitrypsin (AAT), predominantly produced in the liver.[2] AAT plays a role as a protector in a variety of physiological processes throughout the body.

AAT deficiency (AATD) is inherited through autosomal codominant transmission. The most severe AAT deficiency results from Z allele homozygosity. Based on a patient's genotype, the combination of alleles, and their environment, patients express different phenotypes or observable clinical characteristics.[3] AATD primarily affects the lungs and manifests as emphysema, chronic obstructive pulmonary disease (COPD) and other respiratory conditions (eg, asthma). In the liver, disease results from accumulation within the hepatocytes of unsecreted, abnormal, variant AAT protein. This accumulation causes cytotoxicity that can manifest early as neonatal liver disease or in adulthood as progressive liver disease.[2]

AATD is largely unrecognised.[4] In fact, previous studies, including one in Denmark, estimate that less than 25% of those with this

hereditary condition are diagnosed.[5 6] Hence, in general population studies, it is important to differentiate genetic AATD from diagnosed AATD (dAATD). Diagnosed AATD includes both symptomatic cases and to a lesser extent those detected through screening, the latter showing mortality more in line with general population rates.[7] Because dAATD is rare, its frequency and sequalae are most efficiently studied with healthcare database studies, provided the databases are of acceptable quality. A recent study in Germany using a health insurance database that included approximately 87% of the country's population reported the prevalence to be 24 per 100 000 persons.[8] Prevalence estimates can vary appreciably across studies, reflecting variations in country-specific prevalence, screening activities, data sources, case definitions and analytical methods, especially the length of the disease lookback period.[9] This study focuses on the Danish national population and capitalises on the availability of lifelong, high-quality health registry data for all residents for the last several decades.[10 11]

Study objectives

The primary objective was to estimate the prevalence of dAATD in Denmark as of 31 December 2018. We defined prevalence as the number of patients with dAATD per 100 000 Danish residents, who were alive as of 31 December 2018, regardless of how long ago their AATD diagnosis was made.

Secondary objectives were to estimate dAATD incidence and all-cause mortality for patients with dAATD and to compare mortality rates for patients with dAATD to rates for a general population cohort matched on age and sex. Finally, we characterised patients with dAATD with respect to respiratory disease, hepatic disease and related comorbidities.

METHODS

Cohort development

We conducted this nationwide cohort study in Denmark covering the study period 1 January 2000–31 December 2018. The Danish National Health Service provides universal tax-supported healthcare for all Danish residents, guaranteeing free access to general practitioners and hospitals.[11 12] We linked patient data at the individual level across health and administrative registries using the unique 10-digit identifier assigned by the Danish Civil Registration System (CRS) to all residents at birth or on immigration. The CRS updates vital status and immigration status daily for the entire Danish population.[11 13 14] The study population alive at the end of the study period included 5 819 232 residents, and the cumulative study population during the study period was 7 339 133 residents.

We used the Danish National Patient Registry (DNPR) that covers all Danish hospitals to identify patients with a hospital diagnosis of AATD. The DNPR has recorded non-psychiatric inpatient hospitalisations since 1977[15 16] and outpatient specialist clinic and emergency room data since 1995. Hospitalisation records in the DNPR include one primary and one or more secondary diagnoses, coded according to the International Classification of Diseases (ICD), 8th Revision between 1977 and 1994 and and the 10th Revision thereafter. We used primary and secondary diagnoses of ICD-10 code E88.0A from inpatient and outpatient hospital visits to identify patients with dAATD. This specific ICD-10 code for AATD falls into the category E88.0 (diseases of plasma protein metabolism, not elsewhere classified), of which AATD is the predominant disease.

Information on comorbidities obtained from the DNPR included emphysema, other COPD, asthma, bronchitis, bronchiectasis, other chronic lower respiratory diseases and liver disease (see online supplemental table 1 for ICD codes). We used DNPR records from inpatient and outpatient visits before AATD diagnosis, with a maximum lookback to 1977, to calculate Charlson Comorbidity Index (CCI) scores (see online supplemental table 2 for the ICD-10 codes used in the CCI and online supplemental table 3 for the relevant ICD-8 codes). Previous research has shown high positive predictive values of ICD-10 codes in the DNPR for the 19 conditions included in the CCI.[17]

We used the CRS to construct a general population comparison cohort. For each patient diagnosed with AATD, we randomly matched up to 100 persons from the general population (with replacement) on birth year and sex.[14] During the study period, we extracted data on all-cause mortality from the CRS for patients with dAATD and for the general population comparison cohort.

Statistical analysis

We defined the index date for patients with dAATD as the discharge date of the hospital contact that yielded the AATD diagnosis. We characterised patients with dAATD by sex, age and CCI score. At the end of the study period (31 December 2018), we stratified the number of prevalent patients with dAATD and members of the general population, by age and sex for the prevalence calculation. We also summarised the number and per cent of patients with dAATD who had specific comorbidities.

We reported overall prevalence per 100 000 persons and standardised prevalence by sex, age and timepoints during the study period (end of 2004, 2009, 2014 and 2018). For standardisation purposes, we used the reference age and sex distributions from the Danish population as of 31 December 2018 or as of the end of 2004, 2009 and 2014.

We computed incidence rates of dAATD per 100 000 person-years overall and standardised by sex, age and calendar timepoints during the 2000–2018 study period. We used person-years from the general Danish population during the period 1 January 2000–31 December 2018 as the reference for standardisation.

We calculated crude all-cause mortality rates for patients with dAATD and for members of the age-matched and

sex-matched comparison cohort per 100 000 person-years overall and by sex, age group and calendar time period. We counted person-years after the dAATD patients' discharge dates for individuals in the matched comparison cohort, both to mimic the counting of person-years after diagnosis in the dAATD cohort and to avoid immortal time bias. Our use of R to 1 (up to 100) matching of persons from the general population to individual patients with dAATD provides for a descriptive comparison with comparability on age and sex. However, mortality rates are not comparable for unmatched subgroups due to non-comparability on age and/or sex.

We calculated 95% CIs for the prevalence ratio and for incidence rates using the normal approximation of the binomial or Poisson distributions, respectively. When the number of events was too small to apply the normal approximation (eg, when there were few cases in a young age group), we calculated exact Poisson 95% CIs.[18] We applied the approximate Wald method to estimate the 95% CIs for mortality rate ratios (mRR) between patients with dAATD and the general population comparison cohort.[19]

In a sensitivity analysis, we examined whether dAATD cases might have been coded to E88.0, which includes E88.0A and other rarer disorders. E88.0 was used to identify patients with dAATD in the recent German study.[7] We looked for indications of possible changes in AATD coding practices during the study period. We also evaluated the use of the code E88.0 from 1994 to 1999 to assess cases possibly missed due to left truncation—diagnoses before the start of the study period for those who survive for all or part of the study period. We then recalculated prevalence at the end of 2018, incorporating our assessment of the number of patients with dAATD using the more general category code E88.0.

Patient and public involvement

This study used information from the registries cited above. No patients were involved in setting up the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation of results or writing of the manuscript.

RESULTS

Table 1 presents sex and age distributions for the Danish population and surviving patients with AATD as of 31 December 2018 end-of-study date. Females predominate slightly in the Danish population (as in most developed countries), but males were the majority among patients with dAATD. The age distribution of patients diagnosed with AATD tended to be older than the age distribution of the Danish general population.

Diagnosed AATD prevalence per 100 000 persons was 12.9 (95% CI 11.9 to 13.8) as of 31 December 2018 (table 2). Prevalence was 23% higher for males than for females. Prevalence showed a bimodal distribution by age with a slight peak for those ≤12 years of age and a more pronounced relative higher range of prevalences for those ≥35 years of age. Prevalence per 100 000 persons increased during the study period from 1.1 at the end of 2004 to 12.9 at the end of 2018.

Table 1 Age and sex of the Danish population and patients with dAATD as of 31 December 2018

	Danish population		Patients with dAATD	
	N	%	N	%
Total	5 819 388	100.0	749	100.0
Females	2 922 867	50.2	337	45.0
Males	2 896 521	49.8	412	55.0
Age (years)				
≤12	823 126	14.1	84	11.2
13–18	408 755	7.0	26	3.5
19–24	461 023	7.9	25	3.3
25–34	748 530	12.9	40	5.3
35–44	708 488	12.2	85	11.3
45–54	812 438	14.0	137	18.3
55–64	720 665	12.4	149	19.9
≥65	1 136 363	19.5	203	27.1

dAATD, diagnosed alpha-1 antitrypsin deficiency.

Diagnosed AATD incidence was 0.90 (95% CI 0.85 to 0.96) per 100 000 person-years (table 3). Incidence was 21% higher for males than for females. Incidence showed a bimodal age distribution similar to that seen for prevalence. Incidence rates increased during the study period.

Follow-up was 99.1% complete for patients with dAATD at the end of the study period. Seven hundred and forty-nine patients with dAATD were alive as of the end of 2018 and 280 died or emigrated prior to the end of the study period for a total of 1029 patients diagnosed during the 2000–2018 study period. In table 4, we detail mortality rates and mRRs for patients with dAATD compared with a matched Danish general population cohort. Overall, the mRR was 4.7 (95% CI 4.1 to 5.3). The mRR for females with dAATD was 5.3 (95% CI 4.5 to 6.3) compared with the matched female general population comparison cohort, while the mRR for males with dAATD was 4.2 (95% CI 3.5 to 4.9) compared with the matched male general population cohort.

Comparative mortality for patients with dAATD by age group was markedly higher for younger than for older age groups compared with their age-matched and sex-matched general population peers. For example, the mRR was 33.8 (95% CI 6.8 to 167.4) for children and adolescents with dAATD, the age groups for which mortality is the lowest in the general population. The wide 95% CIs indicate that this result was based on a small number of deaths. In contrast, the mRR was 4.2 (95% CI 3.6 to 5.0) in the oldest age group (≥ 65 years), the age group for which mortality is the highest in the general population.

Table 2 Prevalence of dAATD per 100 000 persons as of 31 December 2018

	Population as of 31 December 2018	cases (N)	Prevalence	95% CI
Overall	5 819 388	749	12.9	11.9 to 13.8
By Sex*				
Females	2 922 867	337	11.4	10.2 to 12.6
Males	2 896 521	412	14.3	12.9 to 15.7
By Age (years)†				
≤12	823 126	84	10.1	8.0 to 12.3
13–18	408 755	26	6.4	3.9 to 8.8
19–24	461 023	25	5.4	3.3 to 7.5
25–34	748 530	40	5.3	3.7 to 7.0
35–44	708 488	85	12.0	9.4 to 14.5
45–54	812 438	137	16.8	14.0 to 19.6
55–64	720 665	149	20.7	17.4 to 24.0
≥65	1 136 363	203	17.9	15.4 to 20.3
By end of year†‡				
2004	5 489 869	63	1.1	0.8 to 1.4
2009	5 617 289	220	4.0	3.4 to 4.5
2014	5 728 373	468	8.2	7.5 to 8.9
2018	5 819 388	749	12.9	11.9 to 13.8

*Adjusted to the population age distribution as of 31 December 2018.
†Adjusted to the population sex distribution as of 31 December 2018.
‡Adjusted to the age and sex distribution as of 31 December 2018.
AATD, alpha-1 antitrypsin deficiency; dAATD, diagnosed alpha-1 antitrypsin deficiency.

The mRR for patients with dAATD versus the general population declined markedly over the study period, from 17.8 (95% CI 11.0 to 28.8) in 2000–2004 to 7.6 (95% CI 5.8 to 9.9) in 2005–2009, to 5.1 (95% CI 4.2 to 6.2) in 2010–2014, and ultimately to 3.2 (95% CI 2.6 to 3.9) in 2015–2018. Note that the rates during the different time intervals are based on different age and sex distributions and are not exactly comparable. Nonetheless, the general trend of declining mortality for patients with dAATD is unmistakable and likely fairly robust to differences in the age and sex distributions from the beginning to the end of the study period.

In table 5, we characterise the 1029 patients with AATD diagnosed any time during the 2000–2018 study period with respect to lung and liver conditions. Approximately 66% had a diagnosis of chronic respiratory disease. The most frequent diagnoses were emphysema in 34% of patients and asthma in 19% of patients. We found that 10.8% of patients had a liver disease diagnosis and 5.2% of patients had diagnoses of both lung and liver disease.

In the sensitivity analysis, we observed that the ICD-10 code E88.0A was infrequent early in the study period and largely replaced E88.0 by the end of our study period, indicating the predominance of AATD in the E88.0 category and a near complete shift to the more specific E88.0A ICD-10 code for AATD. Had we used ICD-10 E88.0 in addition to E88.0A during the entire study period, we would have identified 1148 patients as diagnosed with AATD and alive as of the end of the study period instead of 749 patients and prevalence would have been 19.7 (95% CI 18.6 to 20.9) per 100 000 persons instead of 12.9 (95% CI 11.9 to 13.8) per 100 000 persons. Regarding left truncation, we identified 96 patients with an E88.0 code during the 1994–1999 interval and no subsequent E88.0A or E88.0 codes who survived for all of our study period. Had they been included in the sensitivity analysis, the prevalence would have been 21.4 (95% CI 20.3 to 22.6) per 100 000 persons.

DISCUSSION

This cohort study of dAATD prevalence, incidence and mortality based on ICD-10 codes in the DNPR and population estimates from the CRS is the first to be based on an entire national population with universal medical coverage and conducted over an extended time period. The Danish data systems we used are optimum for the study of population prevalence for diagnosed conditions due to their complete coverage of the resident population and extended time period of coverage. Our estimate of Danish dAATD prevalence as of 31 December 2018 based on ICD-10 code E88.0A was 12.9 per 100 000 persons. We found that diagnosed prevalence increased during the study period presumably due to increased

Table 3 Incidence rates of dAATD per 100 000 person-years

Incidence	Standardised incidence rate/100 000 person-years	95% CI
Overall	0.90	0.85 to 0.96
By Sex*		
Females	0.81	0.74 to 0.89
Males	0.98	0.9 to 1.06
By Age (years)†		
≤12	0.64	0.53 to 0.76
13–18	0.26	0.16 to 0.36
19–24	0.19	0.10 to 0.27
25–34	0.40	0.30 to 0.50
35–44	0.91	0.76 to 1.06
45–54	1.34	1.16 to 1.53
55–64	1.74	1.52 to 1.96
≥65	1.26	1.10 to 1.43
By time period†‡		
2000–2004	0.27	0.21 to 0.33
2005–2009	0.71	0.62 to 0.81
2010–2014	1.16	1.04 to 1.28
2015–2018	1.59	1.43 to 1.75

*Adjusted to the population age distribution during 1 January 2000–31 December 2018.
†Adjusted to the population sex distribution during 1 January 2000–31 December 2018.
‡Adjusted to the population age and sex distribution during 1 January 2000–31 December 2018.
dAATD, diagnosed alpha-1 antitrypsin deficiency.

Table 4 Mortality rates per 100 000 person-years among patients with dAATD and a matched Danish general population comparison cohort and mortality rate ratios

Mortality	AATD Patients mortality rate/ 100 000 pyrs	Danish population mortality rate/100 000 pyrs	Mortality rate ratio (95% CI)
Overall	5444	1169	4.7 (4.1 to 5.3)
By sex			
Females	5774	1091	5.3 (4.5 to 6.3)
Males	5159	1239	4.2 (3.5 to 4.9)
By age (years)			
≤18*	273	8	33.8 (6.8 to 167.4)
19–34*	343	39	8.8 (1.1 to 68.4)
35–44	2628	134	19.7 (11.1 to 34.8)
45–54	3341	323	10.3 (7.2 to 14.8)
55–64	6210	806	7.7 (6.1 to 9.8)
≥65	11 775	2780	4.2 (3.6 to 5.0)
By time period			
2000–2004	16 439	923	17.8 (11.0 to 28.8)
2005–2009	8140	1076	7.6 (5.8 to 9.9)
2010–2014	5971	1176	5.1 (4.2 to 6.2)
2015–2018	3833	1201	3.2 (2.6 to 3.9)

*Age categories condensed because no deaths occurred among patients with AATD aged 13–18 years and 25–34 years.
AATD, alpha-1 antitrypsin deficiency; pop, population; pyrs, person years.

medical awareness; diagnosed prevalence was higher for men than women, presumably due to an increased likelihood of diagnosis as AATD is not sex linked and higher rates of smoking for men are likely to accelerate lung and other disease manifestations[5]; and the age distribution was bimodal—higher for those ≤12 years of age compared with adolescents and young adults and higher for those ≥45 years of age. Incidence rates followed the same general patterns.

Evaluation of mortality, compared with an age-matched and sex-matched general population cohort showed an overall mRR of 4.7 for patients diagnosed with AATD. Age-specific mortality ratios were highest in the youngest age groups, notably with very wide 95% CIs, where general population mortality is low and lowest for those ≥65 years of age. This pattern is consistent with the known clinical course of AATD. Early-onset AATD often is more severe. Liver disease dominates in early childhood along with some early cases of emphysema.[20] Chronic pulmonary disease of variable severity tends to occur after age 30.[21] The trend of decreasing mRRs for patients with dAATD over the study period likely can be explained by a combination of factors: increased recognition of less severe cases in more recent years, improvements in medical care, and short follow-up for those patients with AATD recognised late in our study period.

Our estimate of dAATD prevalence in Denmark of 12.9 per 100 000 persons is appreciably lower than the estimated 23.7 per 100 000 persons in the recent report from Germany.[8] Our sensitivity analyses found that there were observable changes in ICD-10 coding during the study period from the more general category code E88.0 to the more specific code E88.0A. Had we used the ICD-10 code E88.0 as in the German study, our estimate of prevalence would have been 19.7 (95% CI 18.6 to 20.9) per 100 000 persons. Correcting for left truncation would have increased the prevalence to 21.4 (95% CI 20.3 to 22.6) per 100 000 persons. The combined impacts of the change in ICD-10 coding practices and left truncation were to underestimate prevalence, to identify some prevalent patients as incident patients for those who had the E88.0 code initially followed by the E88.0A code, and to underestimate incidence. Mortality probably was not affected because mortality rates were unlikely to be appreciably different for patients with dAATD coded using E88.0 versus those coded using E88.0A. The most marked differences in prevalence and incidence would be in analyses covering the first 10 years of the study period, when only a small fraction of patients with dAATD were

Table 5 Characteristics of patients with AATD diagnosed during the period 1 January 2000–31 December 2018

	N	%
Total	1029	100
Females	476	46.3
Males	553	53.7
Age (years)		
≤12	113	11.0
13–18	25	2.4
19–24	18	1.7
25–34	61	5.9
35–44	143	13.9
45–54	204	19.8
55–64	236	22.9
≥65	229	22.3
Charlson Comorbidity Index score at Dx date		
0	417	40.5
1–2	465	45.2
≥3	147	14.3
Lung diseases		
No	354	34.4
Yes	675	65.6
Emphysema		
No	676	65.7
Yes	353	34.3
Asthma		
No	832	80.9
Yes	197	19.1
Other COPD		
No	440	42.8
Yes	589	57.2
Bronchitis		
No	1011	98.3
Yes	18	1.7
Other chronic lower respiratory disease		
No	1021	99.2
Yes	8	0.8
Bronchiectasis		
No	972	94.5
Yes	57	5.5
Liver disease		
No	918	89.2
Yes	111	10.8
Lung and liver disease		
No	975	94.8
Yes	54	5.2

AATD, alpha-1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; Dx, diagnosis.

coded to the more specific within category ICD code E88.0A.

Our study showed that AATD sequalae manifest primarily as lung disorders and, to a lesser extent, liver disorders. This is consistent with the known predominance of pulmonary manifestations over the lifespan of patients with AATD.[22 23] A small minority of patients had disorders of both the lung and liver.

We note several important limitations with our analyses that we enumerate to allow informed interpretation. The extent of morbidity and mortality is known to depend on AATD genotype,[24] AAT serum levels, environmental exposures[5] and other risk factors (eg, smoking). That information was not available in the registries used for our analyses. Second, screening can affect prevalence by identifying asymptomatic cases. Screening is reported to be increasing in the UK and Spain.[25 26] In Denmark, according to national guidelines, first-degree relatives of patients with AATD are offered testing, but it is not known what proportion of these relatives get tested.[27] Lastly, diagnoses in the DNPR are based on ICD codes. Several classes of coding problems are known to exist including: variation among coders, errors in coding, lack of codes for certain data points, limitations in the specificity of available codes, and errors and variation in the clinical diagnoses on which the coding is based.[28–31] Evaluations in Germany and Italy found the diagnosis of AATD to be delayed significantly after initial symptoms (median 7 years and 6 years, respectively) and that there was low awareness of AATD among non-specialist general physicians.[32] This would lead to appreciable underestimation of prevalence. Indeed, our study and previous studies provide prevalence estimates well below what would be predicted by screening studies—approximately 1/1600 in southern Scandinavia.[5 6 33] Conversely, diagnoses of AATD would be expected to have very high specificity and positive predictive value.

CONCLUSIONS

In conclusion, our estimates of incidence and prevalence show dAATD to be rare with a prevalence of approximately 12.9–21.4 per 100 000 persons using the specific versus the more general category ICD code, respectively, and correcting for left truncation. Using an estimate of the prevalence of genetic AATD variants for Scandinavia of 1/1600, our prevalence estimate of dAATD is perhaps a third or less of the true prevalence of AATD. However, it likely comprises the vast majority of patients with markedly increased morbidity and mortality. With that qualification, our analyses indicate that dAATD is associated with markedly elevated mortality, especially for children, though the mRR for children is based on few deaths and has very wide CIs.

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Patient consent for publication Not applicable.

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REFERENCES

1 Williams JA. Synthesis and activation of trypsin. *Encyclopedia of Gastroenterology* 2004.
2 Strnad P, McElvaney NG, Lomas DA. Alpha. *N Engl J Med* 2020;382:1443–55.
3 DeMeo DL, Silverman EK. Alpha1-antitrypsin deficiency. 2: genetic aspects of alpha(1)-antitrypsin deficiency: phenotypes and genetic modifiers of emphysema risk. *Thorax* 2004;59:259–64.
4 Stoller JK, Sandhaus RA, Turino G, *et al*. Delay in diagnosis of alpha1-antitrypsin deficiency: a continuing problem. *Chest* 2005;128:1989–94.
5 Seersholm N, Kok-Jensen A, Dirksen A. Survival of patients with severe alpha 1-antitrypsin deficiency with special reference to non-index cases. *Thorax* 1994;49:695–8.
6 Piitulainen E, Tanash HA. The clinical profile of subjects included in the Swedish national register on individuals with severe alpha 1-antitrypsin deficiency. *COPD* 2015;12 Suppl 1:36–41.
7 Tanash HA, Ekström M, Rönmark E, *et al*. Survival in individuals with severe alpha 1-antitrypsin deficiency (PiZZ) in comparison to a general population with known smoking habits. *Eur Respir J* 2017;50. doi:10.1183/13993003.00198-2017. [Epub ahead of print: 09 09 2017].
8 Greulich T, Nell C, Hohmann D, *et al*. The prevalence of diagnosed α1-antitrypsin deficiency and its comorbidities: results from a large population-based database. *Eur Respir J* 2017;49. doi:10.1183/13993003.00154-2016. [Epub ahead of print: 04 01 2017].
9 Rassen JA, Bartels DB, Schneeweiss S, *et al*. Measuring prevalence and incidence of chronic conditions in claims and electronic health record databases. *Clin Epidemiol* 2019;11:1–15.
10 Frank L. Epidemiology. when an entire country is a cohort. *Science* 2000;287:2398–9.
11 Schmidt M, Schmidt SAJ, Adelborg K, *et al*. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;11:563–91.
12 Laugesen K, Ludvigsson JF, Schmidt M, *et al*. Nordic health registry-based research: a review of health care systems and key registries. *Clin Epidemiol* 2021;13:533–54.
13 Pedersen CB, Gøtzsche H, Møller JO, *et al*. The Danish civil registration system. A cohort of eight million persons. *Dan Med Bull* 2006;53:441–9.
14 Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
15 Andersen TF, Madsen M, Jørgensen J, *et al*. The Danish national Hospital register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263–8.
16 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al*. The Danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90.
17 Thygesen SK, Christiansen CF, Christensen S, *et al*. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish national Registry of patients. *BMC Med Res Methodol* 2011;11:83.
18 Agresti A. *Categorical data analysis*. New York: Wiley, 1990.
19 Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd edn. Philadelphia: Lippincott, Williams, and Wilkins, 2008.
20 Green CE, Vayalapra S, Hampson JA, *et al*. PiSZ alpha-1 antitrypsin deficiency (AATD): pulmonary phenotype and prognosis relative to PiZZ AATD and PiMM COPD. *Thorax* 2015;70:939–45.
21 Stoller J, Hupertz V, Aboussouan L. Alpha-1 Antitrypsin Deficiency. In: *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle, 2006. https://www.ncbi.nlm.nih.gov/books/NBK1519/
22 Davis CP. Alpha-1 antitrypsin deficiency, chart of signs and symptoms of lung and liver disease caused by AATD26, 2021. Available: https://www.medicinenet.com/alpha_1_antitrypsin_deficiency/article.htm#alpha-1_antitrypsin_deficiency_definition_and_facts
23 Dawkins P, Wood A, Nightingale P, *et al*. Mortality in alpha-1-antitrypsin deficiency in the United Kingdom. *Respir Med* 2009;103:1540–7.
24 Nakanishi T, Forgetta V, Handa T, *et al*. The undiagnosed disease burden associated with alpha-1 antitrypsin deficiency genotypes. *Eur Respir J* 2020;56. doi:10.1183/13993003.01441-2020. [Epub ahead of print: 10 12 2020].
25 Soriano JB, Lucas SJ, Jones R. Trends of testing for and diagnosis of α. *Eur Respir J* 2018;52.
26 Belmonte I, Nuñez A, Barrecheguren M, *et al*. Trends in diagnosis of alpha-1 antitrypsin deficiency between 2015 and 2019 in a reference laboratory. *Int J Chron Obstruct Pulmon Dis* 2020;15:2421–31.
27 Alfa-1-antitrypsinmangel. Available: https://www.sundhed.dk/borger/patienthaandbogen/mave-og-tarm/sygdomme/lever/alfa-1-antitrypsinmangel/
28 Steinberg EP, Whittle J, Anderson GF. Impact of claims data research on clinical practice. *Int J Technol Assess Health Care* 1990;6:282–7.
29 Sørensen HT. Regional administrative health registries as a resource in clinical epidemiologyA study of options, strengths, limitations and data quality provided with examples of use. *Int J Risk Saf Med* 1997;10:1–22.
30 Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. *Int J Epidemiol* 1996;25:435–42.
31 Baron JA, Weiderpass E. An introduction to epidemiological research with medical databases. *Ann Epidemiol* 2000;10:200–4.
32 Greulich T, Ottaviani S, Bals R, *et al*. Alpha1-antitrypsin deficiency - diagnostic testing and disease awareness in Germany and Italy. *Respir Med* 2013;107:1400–8.
33 Aboussouan LS, Stoller JK. Detection of alpha-1 antitrypsin deficiency: a review. *Respir Med* 2009;103:335–41.

A Registry-based Cohort Study of Alpha-1 Antitrypsin Deficiency Prevalence, Incidence, and Mortality in Denmark 2000-2018

Appendix

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APPENDIX – SUPPLEMENTARY TABLES 1 - 3 AVAILABLE ONLINE ONLY

Supplementary Table 1. Characteristics of patients with AATD diagnosed during the period 1/1/2000 through 12/31/2018, classified by ICD-10 diagnosis codes

ICD-10 Diagnosis Description	ICD-10 Code
Lung diseases	**J40-J47**
Bronchitis	J41
Emphysema	J43
Other chronic obstructive pulmonary disease	J 44
Asthma	J45
Bronchiectasis	J47
All other chronic lower respiratory diseases	J46
Liver disease	K70 – K76

Abbreviation: ICD= *International Classification of Diseases*

Supplementary Table 2. Conditions included in the Charlson Comorbidity Index, according to ICD-8 and ICD-10 Codes

Charlson Condition	ICD-8 Code	ICD-10 Code
Myocardial infarction	410	I21, I22, I23
Congestive heart failure	427.09–427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440-445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09–290.19, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490–493, 515–518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	135.99, 446, 712, 716, 734	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531–534	K22.1, K25-K28
Mild liver disease	571, 573.01, 573.04	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Diabetes mellitus	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1, E10.9, E11.0; E11.1; E11.9
Diabetes mellitus with chronic complications	249.01-249.06, 249.08, 250.01-250.05, 250.08	E10.2-E10.8, E11.2-E11.8
Hemiplegia	344	G81, G82
Moderate/severe renal disease	403, 404, 580–584, 590.09, 593.19, 753.10–753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85, C88, C90, C96
Moderate/severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00–456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic solid tumor	195-199	C76-C80
AIDS	079.83	B21-B24