α_1-Antitrypsin deficiency associated with increased risk of heart failure

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α_1-Antitrypsin deficiency is related to higher risks of hospital admission and death from heart failure in the general population https://bit.ly/3s3i2YW

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Abstract

Background Individuals with α_1-antitrypsin deficiency have increased elastase activity resulting in continuous degradation of elastin and early onset of COPD. Increased elastase activity may also affect elastic properties of the heart, which may impact risk of heart failure. We tested the hypothesis that α_1-antitrypsin deficiency is associated with increased risk of heart failure in two large populations.

Methods In a nationwide nested study of 2209 patients with α_1-antitrypsin deficiency and 21 869 controls without α_1-antitrypsin deficiency matched on age, sex and municipality, we recorded admissions and deaths due to heart failure during a median follow-up of 62 years. We also studied a population-based cohort of another 102 481 individuals from the Copenhagen General Population Study including 187 patients from the Danish α_1-Antitrypsin Deficiency Registry, all with genetically confirmed α_1-antitrypsin deficiency.

Results Individuals with *versus* without α_1-antitrypsin deficiency had increased risk of heart failure hospitalisation in the nationwide cohort (adjusted hazard ratio 2.64, 95% CI 2.25–3.10) and in the population-based cohort (1.77, 95% CI 1.14–2.74). Nationwide, these hazard ratios were highest in those without myocardial infarction (3.24, 95% CI 2.70–3.90), without aortic valve stenosis (2.80, 95% CI 2.38–3.29), without hypertension (3.44, 95% CI 2.81–4.22), without atrial fibrillation (3.33, 95% CI 2.75–4.04) and without any of these four diseases (6.00, 95% CI 4.60–7.82). Hazard ratios for heart failure-specific mortality in individuals with *versus* without α_1-antitrypsin deficiency were 2.28 (95% CI 1.57–3.32) in the nationwide cohort and 3.35 (95% CI 1.04–10.74) in the population-based cohort.

Conclusion Individuals with α_1-antitrypsin deficiency have increased risk of heart failure hospitalisation and heart failure-specific mortality in the Danish population.

Introduction

α_1-Antitrypsin deficiency is an autosomal recessive condition caused by mutations in the SERPINA1 gene, where ZZ homozygosity leads to the most severe α_1-antitrypsin deficiency and SZ compound heterozygosity to a less severe form [1, 2]. α_1-Antitrypsin deficiency results in increased degradation of elastic fibres, which is most commonly encountered within the lungs, where the increased elastase activity can cause an early onset of COPD [1, 3]. It has been speculated that increased elastase activity may also affect other tissues including the heart [4–7].

The subendocardial layer of the heart wall, located between the endocardium and the myocardium, contains loose connective tissue composed of collagen and elastin, and is in continuum with the extracellular interstitium of the myocardium surrounding the cardiomyocytes [8]. Elastic fibres are resilient

connective tissue protein bundles that are essential in maintaining elasticity and elastic recoil of the heart [9, 10]. Increased elastase activity may therefore affect elastic properties of the heart, which could impact risk of heart failure.

We tested the hypothesis that α_1-antitrypsin deficiency is associated with increased risk of heart failure in the Danish population. To do so, we followed 2209 patients with α_1-antitrypsin deficiency and 21 869 age-, sex- and municipality-matched controls without α_1-antitrypsin deficiency in a nationwide nested study and recorded admissions and deaths due to heart failure during 62 years of follow-up. We also examined a population-based cohort of 102 481 individuals from the Copenhagen General Population Study including 187 patients from the Danish α_1-Antitrypsin Deficiency Registry, all with genetically confirmed ZZ or SZ α_1-antitrypsin deficiency. There was no overlap between the two cohorts.

Materials and methods

Nationwide cohort study

The national Danish Patient Registry includes discharge diagnoses from all Danish nonpsychiatric hospitals since 1978 and additionally from outpatient clinics, emergency departments and psychiatric departments since 1995 [11]. Diagnoses are classified according to the International Classification of Diseases (ICD)-8 through 1993 and ICD-10 thereafter. We identified 2209 patients with α_1-antitrypsin deficiency using the ICD10 code E88.0 (n=1215), or genotyping/phenotyping information from the Danish α_1-Antitrypsin Deficiency Registry (ZZ, n=876; SZ, n=118). Z represents the severe deficiency allele and S represents an intermediate severity allele, while M represents the wildtype allele. Genotype and phenotype information in the nationwide cohort was not validated, as we had no access to blood samples from these individuals.

Each case patient was matched with up to 10 controls with regard to sex, age and municipality giving a total of 21 869 controls without α_1-antitrypsin deficiency. Individuals were censored at the time of outcome, emigration, death or 31 December 2018, whichever came first. The median follow-up time was 62 years. All 102 481 individuals who participated in the validation cohort mentioned in the next section were excluded from the nationwide cohort study.

Population-based cohort study

For our validation cohort we used individuals from the Copenhagen General Population Study and 187 patients from the Danish α_1-Antitrypsin Deficiency Registry [6]. Since cases in these two populations did not differ significantly for the heart failure outcomes studied (p-values for interaction $\geqslant$0.94), the two studies were combined yielding a total population of 102 481, within which 185 carried the ZZ genotype, 205 the SZ genotype, 5259 the MZ genotype, 93 the SS genotype, 5591 the MS genotype and 91 148 the MM genotype. ZZ and SZ individuals *versus* MM individuals were censored at outcome, emigration, death or 13 December 2018, whichever came first. The median follow-up time was 67 years.

The Copenhagen General Population Study is a prospective cohort study initiated in 2003 with continuous recruitment until 2015 [12, 13]. Individuals were randomly selected on the basis of the national Danish Civil Registration System to reflect the adult white population aged 20 to 100 years. Clinical characteristics were obtained through a physical examination, and a questionnaire, which was filled out on the day of the examination. We included 102 294 consecutive participants from this study, within which 48 carried the ZZ genotype, 155 the SZ genotype, 91 148 the MM genotype and 10 943 any of the other three genotypes (MS, MZ and SS). The Danish α_1-Antitrypsin Deficiency Registry was initiated in 1978 and includes patients diagnosed with α_1-antitrypsin deficiency based on protein isoelectric focusing, genotype or a doctor diagnosis. 187 patients from the registry were examined as part of the Copenhagen General Population Study, from 31 August 2009 to 6 October 2009, undergoing the exact same examinations and analyses as the other participants in this study [6].

Studies were approved by Herlev and Gentofte Hospital and Danish ethics committees (identification number H-KF-01-144/01) and were conducted according to the Declaration of Helsinki. All participants in the population-based study provided written informed consent.

End-points

Heart failure (ICD-8: 427.09–427.11, 427.19; ICD-10: I50–I50.1, I50.9) was defined as 1) hospital admissions with the ICD diagnoses as the primary or secondary discharge diagnosis, obtained from the Danish National Patient Registry, or 2) heart failure-specific deaths (ICD-8: 427.09–427.11, 427.19; ICD-10: I50–I50.1, I50.9) obtained from the national Danish Register of Causes of Death. Diagnoses of the most common causes of heart failure [14], myocardial infarction (ICD-8: 410, ICD-10: I21–I22), aortic valve stenosis (ICD-8: 395.9, 424.10–424.19; ICD-10: I35.0–I35.2), hypertension (ICD-8: 401–404;

ICD-10: I10–13, I15), atrial fibrillation (ICD-8: 427.93–427.94; ICD-10: I48.0–I48.9), as well as mitral valve insufficiency (ICD-8: 394.91, 424.01; ICD-10: I34.0) and aortic valve insufficiency (ICD-8: 395.91, 424.11; ICD-10: I35.1) were obtained through primary or secondary discharge diagnosis from the Danish National Patient Registry. COPD diagnoses (ICD-8: 491–492; ICD-10: J41–J44) were obtained through primary or secondary discharge diagnosis from the Danish National Patient Registry for sensitivity analysis.

Genotyping

All individuals in the population-based cohort study were genotyped for the S (Glu264Val) and Z (Glu342Lys) variants by using TaqMan-based PCR assays and an ABI PRISM 7900HT Sequence Detection system (Applied Biosystems, Foster City, CA, USA), as previously described [6].

Statistical analysis

We used Stata version 12.1 (StataCorp, College Station, TX, USA). Pearson's χ^2 tests were used for categorical data and t-test for continuous data. A two-tailed p-value <0.05 was considered significant. Cox regression was used to assess risk of heart failure hospitalisation in individuals with *versus* without α_1-antitrypsin deficiency. Age and sex were included as covariates in adjusted analyses in the nationwide cohort, and age, sex, smoking status and cumulative smoking were included as covariates in adjusted analyses in the population-based cohort. The cumulative incidence curves of heart failure and heart failure-specific mortality in individuals with *versus* without α_1-antitrypsin deficiency were modelled with the Aalen–Johansen estimator with age as the underlying timescale using death or death due to other causes, respectively, as competing events.

Results

We identified 2209 individuals with α_1-antitrypsin deficiency and 21 869 control subjects matched for age, sex and municipality in the nationwide nested cohort, and 390 individuals with α_1-antitrypsin deficiency

TABLE 1 Characteristics of individuals with α_1-antitrypsin deficiency, stratified by study cohort

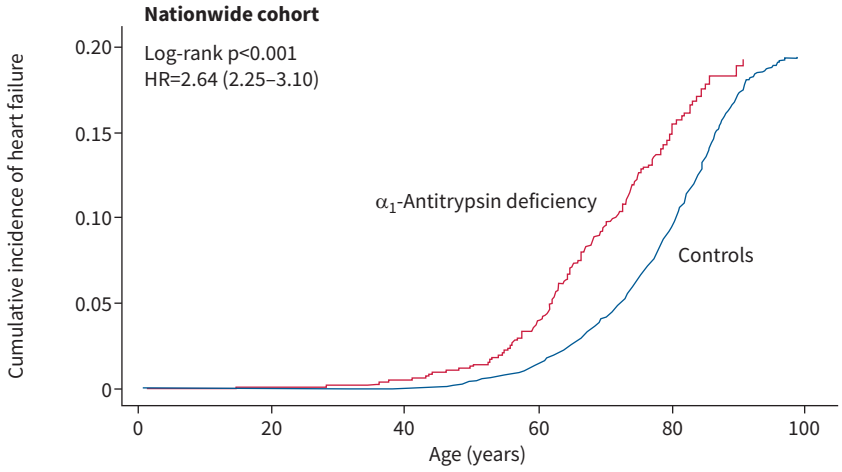
	Nationwide cohort		Population-based cohort	
	Control subjects	α_1-Antitrypsin deficiency	Control subjects	α_1-Antitrypsin deficiency
Women/men n	10 443/11 426	1055/1154	50 206/40 942	218/172
Age years	44.7±20.6	44.8±20.6	57.8±13.1	55.8±13.2**
α_1-Antitrypsin µmol·L^{-1}	-	-	24.0±4.1	7.8±4.6***
FEV_1/FVC %	-	-	77.4±15.9	68.6±17.4***
Smoking status				
Never-smoker	-	-	35 533 (40.6)	157 (42.3)
Ex-smoker	-	-	36 119 (41.3)	171 (46.1)
Current smoker	-	-	15 861 (18.1)	43 (11.6)*
Cumulative smoking				
0 pack-years	-	-	36 340 (39.8)	158 (40.3)
1–30 pack-years	-	-	36 023 (39.5)	173 (44.1)
>30 pack-years	-	-	18 863 (20.7)	61 (15.6)*
Comorbidities				
Myocardial infarction	1242 (5.7)	117 (5.3)	4179 (4.6)	9 (2.3)*
Aortic valve stenosis	337 (1.5)	27 (1.2)	1516 (1.7)	6 (1.5)
Hypertension	3900 (17.8)	408 (18.5)	18 284 (20.1)	83 (21.2)
Atrial fibrillation	1572 (7.2)	193 (8.7)	8369 (9.2)	42 (10.7)
Mitral valve insufficiency	172 (0.8)	17 (0.8)	586 (0.6)	9 (2.3)*
Aortic valve insufficiency	154 (0.7)	9 (0.4)	493 (0.5)	2 (0.5)
COPD	1500 (6.9)	1167 (52.8)***	5137 (5.7)	125 (32.1)***

Data are presented as n (%) or mean±SD unless otherwise indicated. Cumulative smoking in pack-years where 1 pack-year=20 cigarettes or equivalent per day per year was measured in ex- and current smokers only. Information for plasma α_1-antitrypsin, FEV_1/FVC, and smoking was not available for the nationwide cohort study. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease (ICD-8: 491–492; ICD-10: J41–J44). *: p<0.05, **: p<0.01, or ***: p<0.001 *versus* control subjects on t-test or Pearson's χ^2 test.

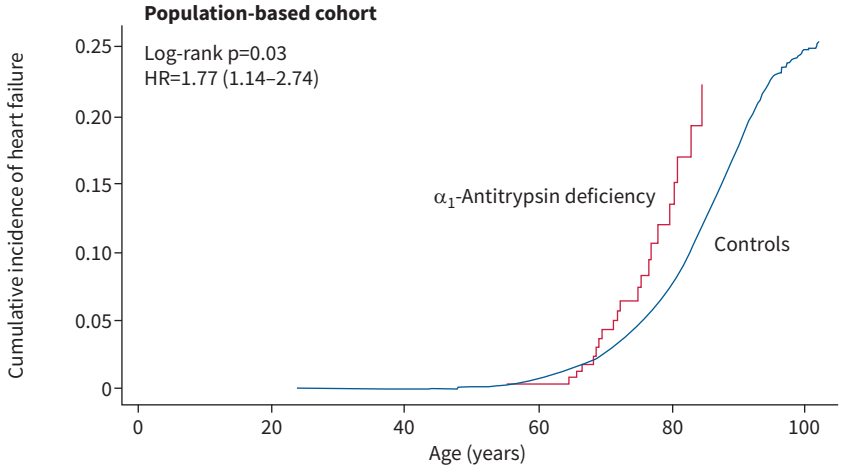
and 91 148 control subjects in the population-based cohort (table 1). Individuals with α_1-antitrypsin deficiency in the population-based cohort were younger, had lower values of plasma α_1-antitrypsin and forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC), were less likely to be current smokers and had lower cumulative tobacco consumption as compared with individuals without α_1-antitrypsin deficiency.

Heart failure

Cumulative incidence of heart failure was higher in individuals with α_1-antitrypsin deficiency compared to control subjects in the nationwide cohort study (log-rank p<0.001) and in the population-based cohort study (p=0.03) (figure 1). In the nationwide cohort at age 80 years, 15% of those with α_1-antitrypsin deficiency at baseline had experienced heart failure *versus* 9.5% in those without α_1-antitrypsin deficiency. Corresponding values were 13% and 7.5% in the population-based study. After adjustment for age and sex, individuals with α_1-antitrypsin deficiency compared with control subjects had a hazard ratio for heart failure of 2.64 (95% CI 2.25–3.10) in the nationwide cohort (figure 1). Individuals with *versus* without



Number at risk:						
Controls	21 869	20 298	17 725	11 737	2590	10
α_1-Antitrypsin deficiency	2209	2041	1785	999	128	<5



Number at risk:						
Controls	90 934	90 933	89 265	62 637	15 015	57
α_1-Antitrypsin deficiency	390	390	372	252	42	0

FIGURE 1 Cumulative incidence of heart failure in individuals with α_1-antitrypsin deficiency. Data are presented stratified by study cohort. Modelled with the Aalen–Johansen estimator with death as competing event. If analyses were performed using Kaplan–Meier analysis, similar results were seen (log-rank: p<0.001). HR: hazard ratio.

α_1-antitrypsin deficiency had a slightly attenuated hazard ratio for heart failure of 1.77 (95% CI 1.14–2.74) after adjustment for age, sex and smoking, in the population-based cohort (figure 1). When analysing only those individuals who had ZZ α_1-antitrypsin deficiency in the population-based cohort, the adjusted hazard ratio for heart failure was similar but slightly higher at 2.24 (95% CI 1.22–4.13) (figure 2). When analysing only those individuals who had intermediate SZ α_1-antitrypsin deficiency in the population-based cohort, the adjusted hazard ratio for heart failure was attenuated at 1.46 (95% CI 0.77–2.78) (figure 2).

Stratified analyses

In the nationwide cohort study with most statistical power, we stratified for other possible risk factors of heart failure such as sex, age, myocardial infarction, aortic valve stenosis, hypertension and atrial fibrillation (figure 3). The adjusted hazard ratios for heart failure in individuals with α_1-antitrypsin deficiency compared to control subjects were similar when stratified according to sex and age (p-value for interaction $\geqslant$0.08) but differed significantly for individuals never *versus* ever diagnosed with myocardial infarction, aortic valve stenosis, hypertension and atrial fibrillation (p-values for interaction $\leqslant$0.02). Importantly, the association between α_1-antitrypsin deficiency and increased risk of heart failure was not driven by known diseases leading to heart failure, as the hazard ratios for heart failure were highest in those without myocardial infarction (hazard ratio 3.24, 95% CI 2.70–3.90), without aortic valve stenosis (2.80, 95% CI 2.38–3.29), without hypertension (3.44, 95% CI 2.81–4.22), without atrial fibrillation (3.33, 95% CI 2.75–4.04) and without any of these four diseases (6.00, 95% CI 4.60–7.82). In the statistically less powered population-based cohort study results were similar to those in the nationwide cohort study, although not all hazard ratios reached statistical significance in the stratified analyses (compare supplementary figure S1 with figure 3).

When the multiple regression model in addition adjusted for myocardial infarction, aortic valve stenosis, hypertension and atrial fibrillation, individuals with α_1-antitrypsin deficiency compared with control subjects had hazard ratios for heart failure of 2.55 (95% CI 2.14–3.03) in the nationwide cohort and 1.89 (95% CI 1.21–2.94) in the population-based cohort.

Heart failure-specific mortality

Cumulative incidence of heart failure-specific mortality was higher in individuals with α_1-antitrypsin deficiency compared to control subjects in the nationwide cohort study (log-rank p<0.001), with a similar trend in the less powered population-based cohort study (p=0.08) (figure 4). In the nationwide cohort at age 80 years, 2.5% of those with α_1-antitrypsin deficiency at baseline had died due to heart failure *versus* 2.0% in those without α_1-antitrypsin deficiency. Corresponding values were 1.5% and 0.5% in the population-based study. Individuals with α_1-antitrypsin deficiency had adjusted hazard ratios for heart failure-specific death of 2.28 (95% CI 1.57–3.32) in the nationwide cohort study and 3.35 (95% CI 1.04–10.7) in the population-based cohort study (figure 4).

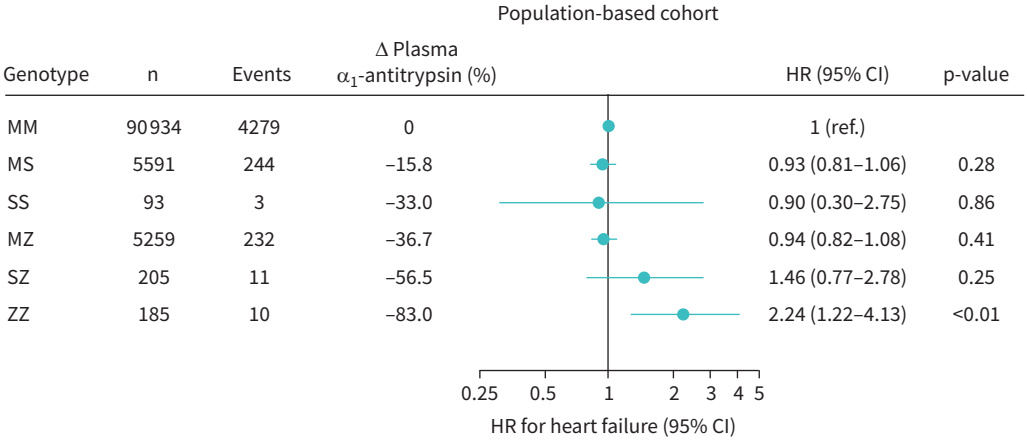


FIGURE 2 Risk of heart failure across α_1-antitrypsin deficiency genotypes. Data are presented for the population-based cohort only. Cox regression model adjusted for sex, age, smoking status and cumulative smoking. HR: hazard ratio.

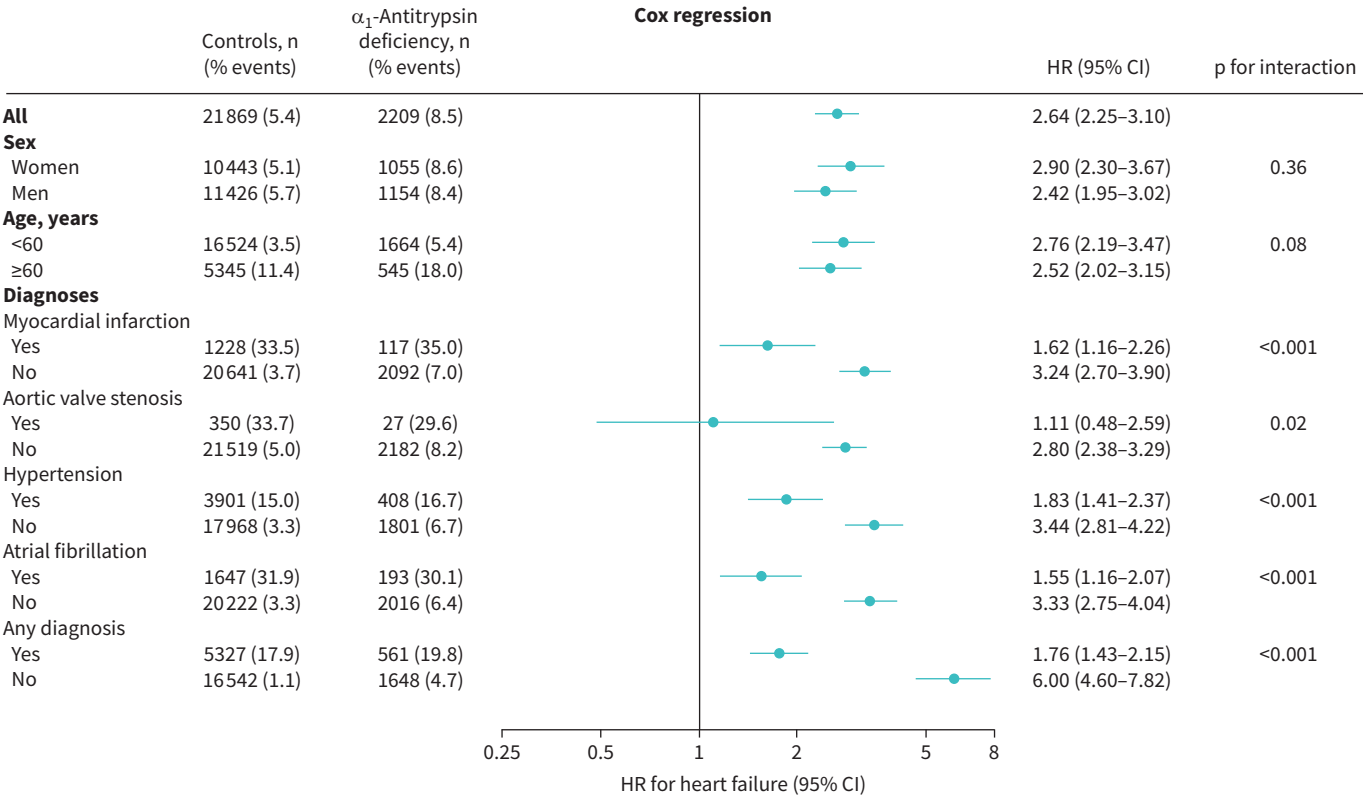


FIGURE 3 Risk of heart failure according to α_1-antitrypsin deficiency, stratified analyses. Data are presented for the nationwide cohort only. Cox regression model adjusted for sex and age. Any diagnosis: myocardial infarction, aortic valve stenosis, hypertension or atrial fibrillation; HR: hazard ratio.

When the multiple regression analysis in addition adjusted for myocardial infarction, aortic valve stenosis, hypertension and atrial fibrillation, individuals with α_1-antitrypsin deficiency compared with control subjects had hazard ratios for heart failure-specific death of 2.12 (95% CI 1.44–3.14) in the nationwide cohort and 3.42 (95% CI 1.04–11.2) in the population-based cohort.

Sensitivity analysis

When the analysis was adjusted for COPD in the nationwide cohort study, and for FEV_1/FVC or COPD in the population-based cohort study, the results were similar and remained statistically significant except for heart failure-specific death in the nationwide cohort study (compare supplementary figure S2 with figures 1 and 4). When the analysis of heart failure hospitalisation in the nationwide cohort study was stratified by heart failure type, individuals with α_1-antitrypsin deficiency had adjusted hazard ratios of 1.98 (95% CI 0.43–9.02) for right-sided heart failure and 1.67 (95% CI 1.09–2.54) for left-sided heart failure, respectively (supplementary figure S3, p=0.83 for difference between the two hazard ratios).

Discussion

In two independent and contemporary cohort studies we evaluated risk of heart failure and heart failure-specific mortality in individuals with *versus* without α_1-antitrypsin deficiency. The analyses showed that individuals with α_1-antitrypsin deficiency had an increased risk of heart failure admission in both cohorts. This increased risk was not explained by common causes of heart failure such as myocardial infarction, aortic valve stenosis, hypertension and atrial fibrillation. Further, we observed an increased risk of heart failure-specific mortality in both the nationwide cohort and the population-based study. The two independent studies demonstrate the robustness of the associations, and these findings are novel.

In support of our findings, Vizzardi *et al.* [15] conducted an echocardiography study on 33 ZZ homozygotes with α_1-antitrypsin deficiency and 33 healthy controls, and observed a higher incidence of left and right ventricular diastolic dysfunction and mitral valve prolapse in ZZ homozygotes. Furthermore, Tanash *et al.* [16] reported an increased standardised mortality ratio of heart failure in 1561 individuals

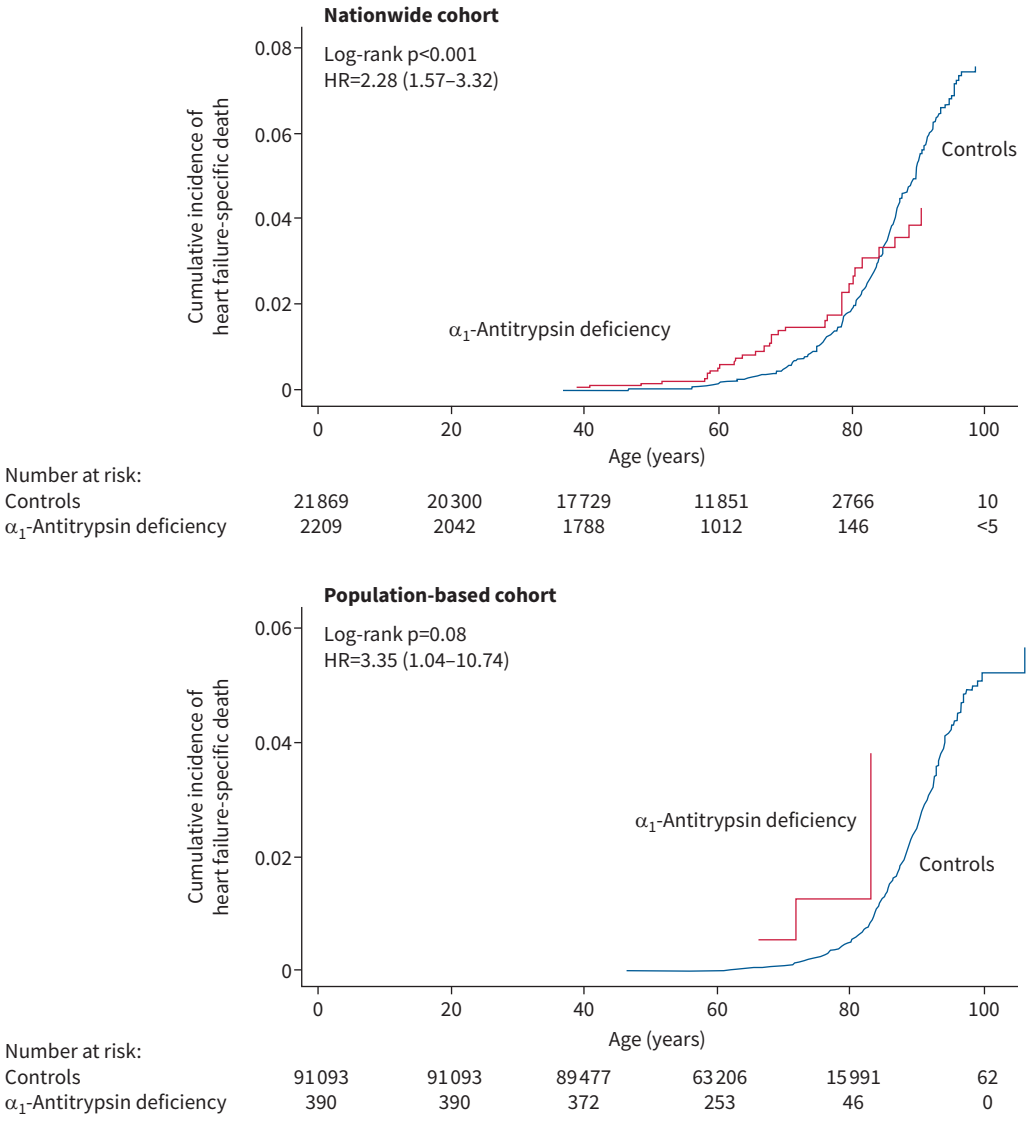


FIGURE 4 Cumulative incidence of heart failure-specific death in individuals with α_1-antitrypsin deficiency. Data are presented stratified by study cohort. Modelled with the Aalen–Johansen estimator with death by other causes as competing event. If analyses were performed using Kaplan–Meier analysis, similar results were seen (log-rank: p<0.001). HR: hazard ratio.

with α_1-antitrypsin deficiency, irrespective of lung function, compared to controls with known smoking habits in the Swedish general population, while Fähndrich *et al.* [17] found a trend towards lower risk of cardiac insufficiency in 139 individuals with α_1-antitrypsin deficiency in the German population.

It is well known that persons with COPD have an increased risk of right-sided heart failure [18, 19]. Since reduced lung function and COPD is part of the phenotype in α_1-antitrypsin deficiency, some of the association seen could be driven by the phenotype itself. However, when our analysis is adjusted for COPD in the nationwide study, and for lung function or COPD in the population-based study, similar results to those presented were seen (supplementary figure S2). This suggests that reduced lung function and COPD did not drive the association between α_1-antitrypsin deficiency and heart failure in the present study. These results are also in accordance with Tanash *et al*. [16] who found that the association between α_1-antitrypsin deficiency and increased risk of heart failure-specific mortality is independent of lung function. Further the sensitivity analysis did not suggest substantially higher risk for right-sided heart failure *versus* left-sided heart failure in individuals with α_1-antitrypsin deficiency in the present study (supplementary figure S3).

A possible mechanism explaining the increased risk of heart failure in persons with α_1-antitrypsin deficiency could be that the cardiac tissue undergoes remodelling in persons with α_1-antitrypsin deficiency [20], which is also suggested by Vizzardi *et al* [15]. It seems plausible that the increased elastase activity in α_1-antitrypsin deficiency affects the elastic properties of the heart wall resulting in an attenuated elastic recoil, increasing the influences by haemodynamic forces of the circulation which over time may lead to impaired cardiac contraction and susceptibility to heart failure. Heart valves are also known to contain large amounts of elastic fibres [21], and we speculated whether a loss of elastic fibres here could lead to an increased risk of heart valve insufficiencies and contribute to the development of heart failure. This hypothesis would be in line with the finding by Vizzardi *et al*. [15] that saw an increased risk of mitral valve prolapse. Since both heart valve insufficiencies and α_1-antitrypsin deficiency are rare diseases, we could not obtain enough power to test that hypothesis in the current study (data not shown).

As described in our previous study [6], augmentation therapy was not available in Denmark at the time of data collection as opposed to the Fähndrich study, which suggested lower risk of cardiac insufficiency and likely reflects a population many of whom are/were on augmentation therapy [17]. Augmentation therapy is a replacement therapy with human-derived α_1-antitrypsin that the patients receive as intravenous infusions weekly [22]. It has been shown to reduce emphysema progression by 36% in patients with α_1-antitrypsin deficiency [23] and to diminish the symptoms from other α_1-antitrypsin deficiency-related comorbidities such as fibromyalgia, panniculitis, systemic vasculitis and bronchial asthma [24]. We speculate that the reduced tissue remodelling seen in the lungs, and possibly also in the skin and vasculature, may also be seen within the heart, so that the loss of elastic fibres is reduced and cardiac contraction maintained; however, this needs to be tested directly in a randomised controlled trial.

Strengths and limitations

Strengths of our study include: 1) a high number of α_1-antitrypsin deficiency cases (n=2209) in our nationwide study and the possibility to match based on sex, age and municipality, in order to diminish the influence from possible confounders; 2) complete Danish health registries essentially without loss to follow-up; and 3) genetic evidence of association between α_1-antitrypsin deficiency and increased risk of heart failure in an independent population-based cohort that comprises a randomly chosen sample from an ethnically homogeneous population even allowing additional confounders to be taken into account.

Limitations of our study include that we do not have access to the α_1-antitrypsin deficiency genotype for all the persons included in our nationwide cohort: we know the genotype or protein isotype for 45%. However, the Danish guideline for diagnosing α_1-antitrypsin deficiency uses a plasma α_1-antitrypsin cut-off value of 11 µM combined with confirmation by genotyping or phenotyping, and results obtained in the population-based cohort, where individuals were genotyped, showed similar results to those from the nationwide cohort design. If the analysis of the nationwide cohort was restricted to only those individuals who had information available for ZZ or SZ genotype/phenotypes (n=994), individuals with α_1-antitrypsin deficiency *versus* control subjects had adjusted hazard ratios of 2.72 (95% CI 2.20–3.39) for heart failure hospitalisation and 2.71 (95% CI 1.65–4.46) for heart failure-specific mortality.

A major risk and limitation is selection bias, as people may be more likely to get diagnosed with α_1-antitrypsin deficiency if they have symptoms or conditions such as airflow limitation and other comorbidities, which could create spurious associations between α_1-antitrypsin deficiency and conditions such as heart failure. Residual confounding by concurrent lung function impairment, emphysema or COPD is a concern. However, if the analysis of the population-based cohort was restricted to only those individuals who had α_1-antitrypsin deficiency without knowledge of the condition (n=203), the results were similar to those presented, although the hazard ratios did not reach statistical significance due to lower statistical power for the analysis (adjusted hazard ratio for heart failure hospitalisation 1.76, 95% CI 0.98–3.17; adjusted hazard ratio for heart failure-specific mortality 3.11, 95% CI 0.74–13.0).

Another potential limitation is the relatively small sample size of people with α_1-antitrypsin deficiency and heart failure, which could limit comparisons in some subgroup analyses due to insufficient statistical power; however, results were consistent throughout, supporting the conclusion that risk of heart failure is increased in people with α_1-antitrypsin deficiency. Because the power is likely low in the interaction analyses, the risk of chance findings is increased and the data on interactions should be interpreted with care.

Generalisability of our results could potentially be constrained as we studied a Danish Caucasian population; however, this also makes the results less dependent on potential influences caused by ethnic differences. That said, we are not aware of results which would suggest that our findings are not relevant to individuals of all races.

Conclusions

α_1-Antitrypsin deficiency is associated with an increased risk of heart failure, and this relationship is not explained by other common causes of heart failure like myocardial infarction, aortic valve stenosis, hypertension and atrial fibrillation. Further, we found that α_1-antitrypsin deficiency is associated with an increased risk of dying from heart failure.

Provenance: Submitted article, peer reviewed.

Studies were approved by Herlev and Gentofte Hospital and Danish ethics committees (identification number H-KF-01-144/01) and were conducted according to the Declaration of Helsinki. All participants in the population-based study provided written informed consent.

Author contributions: S.V. Winther, E.M. Landt and M. Dahl had full access to all data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the study concept and design, and collection, analysis and interpretation of the data. S.V. Winther wrote the draft manuscript and did the statistical analyses. E.M. Landt, B.G. Nordestgaard, N. Seersholm and M. Dahl revised the manuscript for important intellectual content. M. Dahl obtained funding and provided administrative, technical or material support. E.M. Landt and M. Dahl supervised the study.

Conflict of interest: B.G. Nordestgaard has consultancies with Amarin, Akcea, Amgen, AstraZeneca, Denka Seiken, Kowa, Novartis, Novo Nordisk and Silence Therap. No conflicts of interest exist for S.V. Winther, E.M. Landt, N. Seersholm and M. Dahl.

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