Alpha-1 antitrypsin deficiency and granulomatosis with polyangiitis: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
This systematic review shows a strong association between alpha-1 antitrypsin deficiency (AATD) and granulomatosis with polyangiitis (GPA), especially in Z-allele carriers, and highlights GPA disease presentation among AATD individuals. https://bit.ly/4mgqlYD

Cite this article as: Alluhibi R, Baradwaaj S, Heyer-Chauhan N, *et al*. Alpha-1 antitrypsin deficiency and granulomatosis with polyangiitis: a systematic review and meta-analysis. *Eur Respir Rev* 2025; 34: 250088 [DOI: 10.1183/16000617.0088-2025].

Received: 22 April 2025
Accepted: 4 Aug 2025

Abstract

Introduction Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder characterised by low circulating levels of alpha-1 antitrypsin (AAT) protein, a key inhibitor of neutrophil elastase and proteinase 3 (PR3) which is also the main autoantigen in granulomatosis with polyangiitis (GPA). This systematic review examines the association between AATD and GPA.

Methods A systematic search of PubMed, Embase, Cochrane, EBSCO Medline and Scopus (December 2024) identified studies on AATD and GPA. Data extraction and quality assessment followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A random-effects meta-analysis was conducted to calculate pooled odds ratios and assess heterogeneity.

Results 23 studies (9634 individuals) met inclusion criteria. The Z-allele prevalence was 11.65% in GPA compared to 3.29% in controls and the S-allele prevalence was 10.8% in GPA compared to 5.26% in controls. Among 1755 individuals with GPA across 10 studies that provided specific genotype data, 22 (1.25%) were homozygous for the Z-allele. Meta-analysis showed that Z-allele carriers had 3.11 times higher odds of developing GPA (eight studies; 95% CI 2.43–3.9; I^2: 0%).

Conclusion This meta-analysis reinforces the link between AATD and GPA, particularly in carriers of the Z-allele, supporting the role of PR3 dysregulation in GPA pathogenesis.

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder characterised by reduced levels of alpha-1 antitrypsin (AAT) protein in the circulation [1]. Clinically important AATD is most commonly caused by homozygous Pi*Z mutation (Pi*ZZ genotype) in the *SERPINA1* gene [1]. More than 120 *SERPINA1* mutations have been reported in the literature. Normal alleles are referred to as PiM, while the most common deficiency alleles are PiZ and PiS, with PiMS, PiMZ, PiSS, PiSZ and PiZZ the most common deficiency genotypes seen [2].

AAT is mainly produced by hepatocytes and is a member of the serine protease inhibitor superfamily. The main function of these proteins is to inhibit enzymes released during inflammation, preventing tissue damage caused by protease overactivation [1]. AAT mainly inhibits serine proteases such as neutrophil elastase and proteinase 3 (PR3). Neutrophil elastase can break down lung elastin, which damages alveolar tissue. Therefore, individuals with AATD are at higher risk for developing early onset panlobular emphysema [1].

PR3, a neutrophil serine protease, is the main autoantigen in granulomatosis with polyangiitis (GPA) [3]. GPA is a rare form of vasculitis characterised by necrotising granulomatous inflammation and

small-to-medium vessel vasculitis. GPA is strongly associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCAs) in blood, in 80–90% of individuals, with specificity for neutrophil PR3 [3, 4]. GPA primarily affects the upper respiratory tract, eyes, lungs and kidneys but can also involve the skin and nervous system [5, 6].

It has been hypothesised that there is a relationship between AATD and GPA, but the underlying mechanisms are not fully understood, with several hypotheses proposed. Since AAT inhibits PR3, reduced levels of functional AAT protein in individuals with AATD may lead to increased neutrophil PR3 expression, potentially triggering an autoimmune response by circulating ANCA. Additionally, increased free PR3 could be taken up by antigen presenting cells to promote autoreactive T- and B-cell expansion and promote ANCA formation. This suggests a plausible pathophysiological link whereby AATD exacerbates immune dysregulation, resulting in a predisposition to GPA.

Observational studies have reported a higher incidence of GPA and other autoimmune conditions in individuals with AATD [4, 7, 8], indicating a potential mechanistic overlap between these two conditions. Although previous meta-analysis and a genome-wide association study, have reported associations between *SERPINA1* variants and ANCA-associated vasculitis (AAV), these focused primarily on genetic susceptibility across the broader AAV spectrum and did not examine clinical manifestations or prevalence patterns specific to AATD in GPA [9–11]. To our knowledge, no previous systematic review has evaluated the clinical and epidemiological relationship between AATD and GPA, including allele-specific risks, disease presentation and severity.

Methods

Search strategy and inclusion criteria

The search included the following terms: (lung diseases OR interstitial OR “granulomatosis with polyangiitis” OR “Wegener's granulomatosis” OR “granulomatosis with polyangiitis” OR GPA OR c-ANCA OR ASO) AND (alpha 1-antitrypsin deficiency OR A1ATD OR A1AT).

We searched PubMed, the Cochrane Central Register of Controlled Trials, EBSCO, Embase and Scopus. No specific publication date range was filtered. The search took place on 20 December 2024 and whilst the same search terms were used, the format was modified depending on the specific database. The systematic review protocol was registered with PROSPERO (CRD42021259104).

We included retrospective cohort, cross sectional, case–control, case report and case series studies. Populations included were all individuals diagnosed with GPA and AATD. AATD was defined by phenotyping or genotyping, and GPA was determined by contemporary classification criteria. Studies may have used different classification criteria for inclusion of GPA patients, as there have been numerous versions of these criteria used and endorsed by different societies. For many years covered by this review the American College of Rheumatology (1990) and the Chapel Hill Consensus Conference (1992 and 2012) classifications have predominated, which were based on clinical and histological features [12–14]. However, these early versions did not initially separate out certain ANCA associated vasculitis subtypes (such as microscopic polyangiitis) leading to potential confusion in disease classification. In addition, as was proposed in these criteria, many may have used surrogate markers for granulomatous disease (*e.g.* lung nodules defined radiologically, without histological evaluation). More recently the Diagnostic and Classification criteria in Vasculitis study led to the newer and widely adopted American College of Rheumatology/European Alliance of Associations for Rheumatology classification (2022), which are heavily weighted on the serological phenotype, but also allow classification based on surrogate features of granulomatous disease [15].

We excluded conference abstracts, editorial reports, nonresearch letters, theses and books, systematic reviews and meta-analysis, literature reviews, and studies published in any language other than English.

Quality assessment and statistical analysis

Following guidelines issued by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), the collated papers from all databases were prepared for screening. Studies were screened by their titles and abstracts using the Rayyan tool by two independent reviewers. The quality of studies was assessed by the first author using the Newcastle–Ottawa Scale (NOS) and a modified NOS for cohort, cross sectional and case–control studies. The Joanna Briggs Institute Critical Appraisal Tools were used for case reports and case series.

Data extraction was initially performed by one reviewer and then reviewed and finalised by a second reviewer.

Statistical analysis was conducted using STATA version 18. A random-effects model was employed to calculate the pooled odds ratio and corresponding 95% confidence intervals, accounting for potential heterogeneity among studies. Heterogeneity was assessed using the Cochran Q test and quantified with I^2 statistics. A p-value <0.1 was used to determine the statistical significance for heterogeneity.

Results

Study selection and characteristics

A total of 22 studies were included in this systematic review, 11 of which were case–control studies, two were cohorts, two were cross sectional studies, three were case series and four were case reports (figure 1).

The sample sizes of the studies varied, ranging from single case reports to 2361 individuals in a European cohort. A total of 9634 individuals were included across all studies [16–20]. The Z mutation was the most commonly reported allele, followed by the S mutation. 15 studies reported the prevalence of AATD in GPA, three studies reported on GPA in AATD.

Prevalence of AATD in AAV

A summary of studies reporting associations between AATD and AAV is provided in table 1. The largest study, with 609 GPA cases, found a significant association between the Z-allele of AATD and AAV, mainly GPA [16]. The Z-allele was associated with GPA with a hazard ratio of 2.54, CI 1.78–3.64, p<0.0001 [16]. There was no significant association between the S-allele and AAV. Mahr *et al*. [4] also reported the association between carriage of the Z-allele and increased susceptibility to GPA. MS and MZ genotypes were associated with an odds ratio of 1.47 for GPA (95% CI 0.98–2.22; p=0.06). In this study, the S-allele was observed more frequently in GPA patients (6.4%) compared to controls (3.8%) (p<0.01), suggesting that the S polymorphism of AATD is also overexpressed among patients with GPA, in contrast

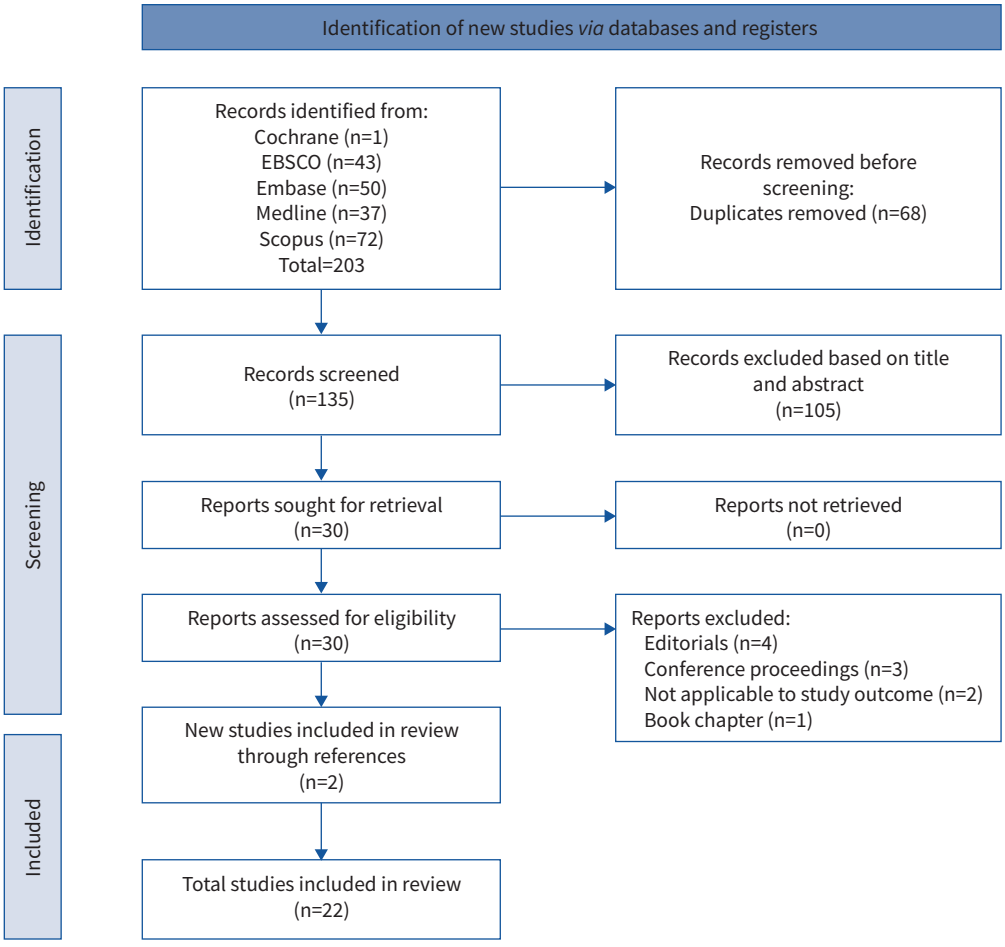

FIGURE 1 PRISMA flow diagram.

TABLE 1 Prevalence of alpha-1 antitrypsin deficiency alleles in individuals with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

First author [reference] year	Country	Vasculitis type	Sample size, cases/controls	Age, years	Sex, male/female	Abnormal allele carriers, n (%)				Cases with specific genotypes, n
						Z cases	S cases	Z controls	S controls	
O'Donoghue [21] 1993	UK	cANCA	40/40 14 anti-PR3 (GPA)	NR	NR	3 (7.5)	2 (5)	2 (5)	1 (2.5)	2 MZ, 1 MS, 1 SZ
Esnault [22] 1993	France	cANCA/ anti-PR3 ANCA	14	53.6 (25–76)	8/6	6 (42.8)	2 (14.2)	NR	NR	3 ZZ, 3 MZ, 2 MS
Elzouki [8] 1994	Sweden	GPA	88/NR	56.2 (22–81)	57/30	15(23)	NR	NR (5)	NR	1 ZZ
Lhotta [23] 1994	Austria	cANCA	32/868 29 GPA cases	51 (13–86)	19/13	5 (15.6)	1 (3.1)	24 (2.8)	39 (4.5)	2 ZZ, 3 MZ, 1 MS
Savige [24] 1995	Australia	Anti-PR3 ANCA	31/NR	NR	NR	3 (9.7)	4 (12.9)	NR (1.5)	NR (8.3)	1 ZZ
Baslund [25] 1996	Sweden/ Denmark	GPA	44/38	57 (14–76)	28/16	8 (18.2)	NR	NR (4.7)	NR	0
Griffith [26] 1996	UK	cANCA	99/2310	NR	NR	10 (10.1)	9 (9.1)	83 (3.6)	209 (9.0)	1 ZZ, 1 SS, 9 MZ, 9 MS
Callea [27] 1997	Italy	cANCA	38/200	61 (21–38)	36/48	2 (5.3)	2 (5.3)	3 (1.5)	NR	2 MZ, 2 MS
Borgmann [28] 2001	Germany	GPA	79/752	NR	42/37	7 (8.9)	NR	19 (2.5)	NR	1 ZZ, 6 MZ,
Mahr [4] 2010	US	GPA	433/421	53.2±15.7	229/204	32 (7.4)	50 (11.5)	18 (4.3)	32 (7.6)	4 ZZ, 2 SZ, 4 SS
Morris [16] 2011	UK/ France/ Germany/Italy	MPA and GPA	856/1505 609 GPA cases	51 (35–67)	473/383	75 (4.4)	69 (4.0)	60 (2.0)	60 (2.0)	6 ZZ, 2 SZ, 1 SS, 52 MZ, 53 MS
Chorostowska-Wynimko [29] 2013	Poland	GPA	51/658	46.2 (17–83)	23/28	3 (5.88)	2 (3.92)	18 (2.8)	10 (1.5)	1 SZ, 2 MZ, 1 MS
Mota [6] 2013	Iran	GPA	27/63	38.5 (18–58)	11/16	3 (11.1)	2 (7.4)	NR	NR	1 SS, 3 MZ, 1 MS
Pervakova [30] 2016	Russia	Anti-PR3 ANCA	38/46	18–77	16/22	5 (7.6)	NR	NR	NR	1 ZZ, 4 MZ, 2MF
Deshaye [31] 2019	France	AAV	142/NR 88 GPA cases	62 (51–71)	79/63	19 (11)	12 (7)	NR	NR	2 ZZ, 1SZ, 1 SS, 18 MZ, 12 MS

Age is reported as presented in each study: mean (range), mean±SD, median (interquartile range/range) or range only. cANCA: cytoplasmic anti-neutrophil cytoplasmic antibody; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; NR: not reported; PR3: proteinase 3.

https://doi.org/10.1183/16000617.0088-2025

to the findings of Morris *et al*. [16]. Griffith *et al*. [26] reported an increase in the frequency of the Z-allele among cytoplasmic anti-neutrophil cytoplasmic antibody-positive individuals at 0.055 compared to the control frequency 0.018 (p=0.004), the relative risk conferred by the Z-allele was 3.0.

In a smaller cohort, Pervakova *et al*. [30] observed a prevalence of AATD phenotypes in 18.4% of GPA patients (7/38). Similar trends were reported by Baslund *et al*. [25], who found an over-representation of the Z-allele among GPA patients; eight of 44 patients with GPA (18%) were positive for the Z-allele, a frequency significantly higher (p<0.001) than the 4.7% observed in the general Scandinavian population.

Only one study in our review (Mahr *et al*. [4]) evaluated the risk of GPA in homozygous individuals. In this study, ZZ and SZ individuals exhibited a markedly elevated risk of GPA compared to MM carriers, with a statistically significant odds ratio of 14.6 (95% CI 1.8–∞; p=0.002) suggesting a dose-dependent relationship.

Across all studies included in this review, the overall prevalence of the Z-allele among GPA cases was 11.65% (196/1682), while the prevalence of the S-allele was 10.8% (155/1433). In comparison, the prevalence of the Z-allele in the control group was 3.29% and the prevalence of the S-allele in the control group was 5.26%. Among 1755 individuals with GPA across 10 studies that provided specific genotype data, 22 (1.25%) were homozygous for the Z-allele.

In meta-analysis (figure 2) there was a significant association between the Z-allele and GPA, with individuals carrying the Z-allele having 3.11 times higher odds of GPA compared to controls (eight studies; 95% CI 2.43–3.9; I^2=0%). In contrast, the S-allele showed no significant association, with a pooled odds ratio of 0.72 (six studies; 95% CI 0.46–1.13; I^2=19.5%).

Prevalence of AAV in AATD

Three publications reported the prevalence of GPA in AATD individuals, one exploring disease associations in AATD individuals, whilst the other two described the clinical presentation and outcome of individuals with systemic vasculitis and severe AATD (table 2). Stone *et al*. [7] reported five individuals with GPA among 651 PiZZ or PiZnull individuals (0.8%). Mohammad and Segelmark [33] further explored this association in a case series of five PiZZ individuals with primary systemic vasculitis (PSV), where three of those had GPA. Mazodier *et al*. [32] explored systemic necrotising vasculitis (SNV) in eight patients with severe AATD (PiZZ), one had GPA.

Pulmonary involvement and disease severity in AATD-associated vasculitis

Several studies included in this review explored organ-specific involvement in patients with AATD and vasculitis, particularly GPA. While some suggest a possible association with pulmonary manifestations and disease severity, the findings are not consistent across all studies. Pervakova *et al*. [30] reported that 18.4% (7/38) of GPA patients carried pathological AATD variants and all seven of these patients showed pulmonary involvement. In contrast, pulmonary manifestations were observed in 65% (20/31) of GPA patients without AATD. These findings suggest a possible association between AATD and increased risk of lung involvement in GPA. Moreover, the Birmingham Vasculitis Activity Score was significantly higher in GPA patients with abnormal AATD phenotypes (24.00±2.83) compared to those with normal phenotypes (16.42±1.50) [30]. In a

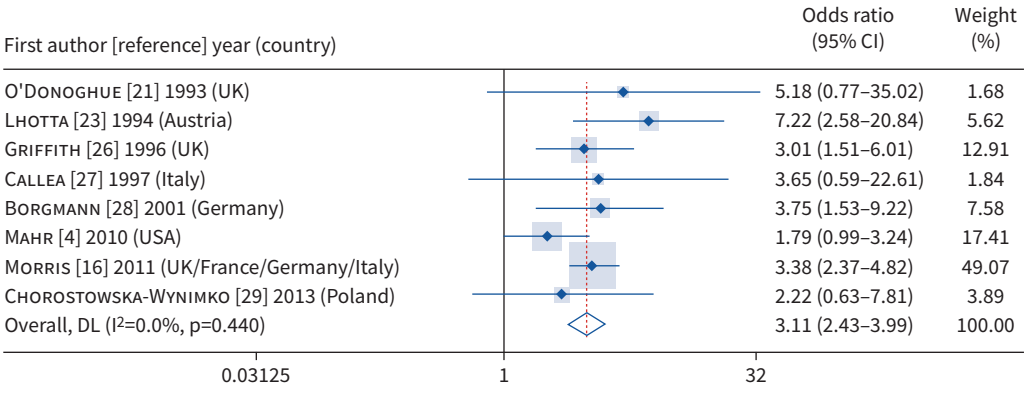

FIGURE 2 Forest plot of pooled odds ratios for the Z-allele from case–control studies of AATD and vasculitis. Weights are from the random-effects model.

TABLE 2 Granulomatosis with polyangiitis (GPA) in individuals with alpha-1 antitrypsin deficiency (AATD)

First author [reference] year	Country	Sample size	Age, years median (range)	Sex, male/ female	AATD types	Patients with GPA	GPA manifestations
Mazodier [32] 1996	Sweden	Eight AATD	48 (44–84)	4/4	5 ZZ 2 SZ	1 (ZZ)	Skin involvement: leg ulcers Kidneys: glomerulonephritis Upper respiratory tract: otitis and sinusitis
Stone [7] 2013	UK	615 AATD	NR	NR	All ZZ/ Z/Null	5 (0.8%)	NR
Mohammad and Segelmark [33] 2014	Sweden	Five AATD and primary systemic vasculitis	49 (17–67)	2/3	All ZZ	3	General symptoms, renal and lungs involvement, skin lesions

NR: not reported.

cohort of 40 ANCA-positive patients, O'Donoghue *et al*. [21] demonstrated that Z- and S-alleles were significantly overrepresented ($p<0.05$) in ANCA-associated vasculitis patients with pulmonary haemorrhage. Deshayes *et al*. [31] found that carriers of Z- and/or S-alleles had a significantly higher frequency of intra-alveolar haemorrhage compared to those with vasculitis without AAT-deficiency alleles (43% (15/35) *versus* 21% (22/107), $p<0.01$). In a case series by Mohammad and Segelmark [33], five patients with PSV and AATD were described, three of whom had GPA. All three GPA cases had pulmonary involvement, whereas the two non-GPA cases did not. Kidney, ear, nose, and throat involvement were also present in all GPA patients. In contrast, Morris *et al*. [16] found no significant association between Z-allele carriage and disease severity, survival and relapse. Beyond pulmonary complications, Baslund *et al*. [25] observed that Z carrier individuals had a higher prevalence of eye involvement than noncarriers (5/8 *versus* 8/36, respectively).

A summary of case reports is presented in table 3. These cases highlight the diverse presentations of GPA in individuals with AATD, demonstrating a spectrum of pulmonary, renal and systemic manifestations.

Discussion

This meta-analysis estimated the overall prevalence of Z- and S-allele carriers among individuals with GPA and the pooled odds ratio of Z- and S-allele carriers among GPA individuals. The findings demonstrate a significant overrepresentation of the Z-allele in individuals with GPA, with an overall prevalence of 11.65% compared to 3.29% in the control group. The odds of carrying the Z-allele were three times higher in GPA cases compared to controls, supporting the hypothesis that AATD may predisposes individuals to vasculitic disease, particularly GPA. The prevalence of the S-allele among GPA patients was 9.22%, while it was 5.26% in the control group. The S-allele was not significantly associated with GPA with an overall odds ratio of 0.72. These findings highlight the strong association of the Z-allele with GPA while suggesting no relationship with the S-allele.

There is much less data on the prevalence of GPA in individuals with AATD compared to the general population, in which the prevalence of GPA is 20–160 cases per million [35]. The largest AATD-focused study included in the review by Stone *et al*. [7] reported five GPA cases among 651 PiZZ or PiZnull individuals, suggesting a significantly higher risk. Mohammad and Segelmark [33] described five individuals with AATD and primary systemic vasculitis, three of whom had GPA, and Mazodier *et al*. [32] found one GPA case in eight PiZZ individuals with SNV. These findings suggest a significantly increased risk of GPA in individuals with AATD.

The available data on whether AATD modulates disease severity and organ involvement in GPA are mixed. Some studies suggest that pulmonary involvement and intra-alveolar haemorrhage may be more prevalent in individuals with AATD-associated GPA [23, 30, 31, 33], pointing to a potential pathogenic link in the respiratory system. However, other large-scale studies, such as that by Morris *et al*. [16], did not find significant associations between Z-allele carriage and clinical severity, relapse or survival. These discrepancies suggest that while certain patterns of organ involvement particularly pulmonary have been observed in Z-allele carriers, the overall evidence remains inconsistent. Beyond pulmonary features, limited reports have noted renal, ocular and ENT involvement in individuals with AATD and GPA, although these associations also lack consistent replication across studies [21, 31].

The mechanistic association between AATD and GPA likely involves protease–antiprotease imbalance and immune dysregulation. Failure to adequately inhibit PR3, a major autoantigen in GPA, in AATD likely

TABLE 3 Case reports of individuals with alpha-1 antitrypsin deficiency (AATD) and granulomatosis with polyangiitis (GPA)

First author [reference] year	Age/sex	AATD type	Primary symptoms	Diagnosis	Systemic involvement	Treatment	Outcome
Louboutin [20] 1993	28/F	PiZZ	Headaches, fatigue, fever, anorexia, weight loss, polyarthralgia and myalgia	Fulfilled the ACR criteria for GPA, and ANCA test was significantly positive	Right-sided hemiparesis and hypoesthesia, impaired vision of the left eye and hepatomegaly	Prednisone and cyclophosphamide	The patient recovered in 3 weeks and had only residual mild right hemiparesis The right peroneal nerve monoparesis disappeared within 2 months
Barnett [19] 1999	38/F presented at age 27	PiZZ	Arthralgias, sinusitis and episcleritis After several months she had dyspnoea and wheezing	Open lung biopsy which showed necrotising granulomatous inflammation vasculitis and focal alveolar haemorrhage	Vasculitis resolved; she developed emphysema over the next few years	Prednisone and cyclophosphamide	Symptom resolution, she died of sepsis and respiratory failure 17 months after transplantation
Lonardo [17] 2002	63/M	PiZ and rare $PiM_{Procida}$	Myalgia and fatigue On radiography lung coin lesion and basal bullae of emphysema on both sides	Fulfilled the ACR clinical criteria and on ANCA positivity	Pulmonary (infiltrates, cavitation), renal (crescentic GN), ENT (nasal crusting)	Methylprednisolone plus cyclophosphamide	Improvement in symptoms Maintained remission with azathioprine
Inaty [18] 2013	25/F	PiZZ	Cough, haemoptysis, sinusitis and renal symptoms	cANCA were positive at 1:80	Pulmonary (cavitary lesions), renal (proteinuria, haematuria), ENT (sinusitis)	Corticosteroids, cyclophosphamide, AAT augmentation	Significant improvement Remission maintained with augmentation therapy
Hernández Pérez [34] 2013	84/F	PiZZ	A 4-week illness characterised by malaise, arthralgia and anorexia	ANCA-PR3 >100 $U \cdot mL^{-1}$ Biopsy of the skin lesions revealed cutaneous and subcutaneous haemorrhage with necrosis and acute inflammation and vascular thrombus suggesting vasculitis	Air flow limitation and a predicted forced expiratory volume in 1 s of 63% Renal function impairment	Methylprednisolone for 3 consecutive days Cyclophosphamide was avoided in favour of therapy with glucocorticoids and replacement therapy with AAT at 60 $mg \cdot kg^{-1}$ body weight	Notable improvement of the skin lesions and normalisation of renal function

AAT: alpha-1 antitrypsin; ACR: American College of Rheumatology; ANCA: anti-neutrophil cytoplasmic antibody; cANCA: cytoplasmic anti-neutrophil cytoplasmic antibody; ENT: ear, nose, throat; GN: glomerulonephritis; PR3: proteinase 3.

amplifies neutrophil activation and the inflammatory cascade, perpetuating vasculitic damage [10]. Genetic analyses, such as those by Esnault *et al.* [22] and Borgmann *et al.* [28], underscore the link between AAT-deficient alleles and PR3-ANCA positivity, implicating AATD as a driver of autoimmune mechanisms. Moreover, a meta-analysis by Rahmattulla *et al.* [11] and a genome-wide association study by Lyons *et al.* [10] reported genetic associations between *SERPINA1* variants particularly the Z-allele and AAV. These findings support the role of *SERPINA1* polymorphisms as a genetic risk factor, especially in PR3-ANCA-positive vasculitis, reinforcing the link between AATD and disease susceptibility [10, 11]. Additional indirect evidence supporting the critical role of AAT in individuals with GPA comes from a case report describing successful treatment of an 84-year-old woman with AATD and GPA using AAT replacement therapy [34]. This intervention, combined with corticosteroids, resulted in resolution of skin lesions and normalisation of renal function. The positive outcome in this case highlights the potential importance of addressing the protease–antiprotease imbalance in AATD-associated GPA. However, augmentation therapy may not be an effective solution if disease pathogenesis is primarily driven by the pro-inflammatory effects of Z-allele polymers. This possibility was raised in the study by Morris *et al.* [16], which reported the presence of AAT polymers in a kidney biopsy from a Z-allele carrier individual with active GPA. These findings suggest that AAT polymers might contribute directly to local inflammation and immune activation, potentially limiting the effectiveness of standard AAT replacement therapy. The role of unregulated protease activity in enhancing tissue damage is reinforced by studies reporting the ability of polymers of the Z variant of AAT to potentiate neutrophil chemotaxis [36]. Moreover, a recent study also demonstrated that in addition to circulating AAT levels the functional state of AAT is critical as oxidative modification of methionine residues within AAT can impair its ability to clear PR3 from the neutrophil surface, diminishing its anti-inflammatory effects [35]. To date, there are no clinical trials that have assessed the efficacy of augmentation therapy specifically in AATD patients with GPA, leaving its therapeutic role unproven in this context. This adds further complexity to the therapeutic equation and becomes more relevant with recent developments in AATD therapies including investigational drugs that aim to block polymer formation and emerging gene therapies designed to restore functional circulating AAT [37]. These newer therapeutic strategies are still in early stages and it remains uncertain whether they will prove effective in reducing the incidence of GPA in individuals with AATD.

This is the first systematic review and meta-analysis to examine both the epidemiological and clinical relationship between AATD and GPA, including Z- and S-allele prevalence, disease severity, and organ-specific involvement. However, it is not without limitations. Most studies included in this review were retrospective or small-scale, introducing potential biases. The lack of longitudinal data precludes definitive conclusions about the relationship between AATD and the development of GPA. Another challenge lies in disease classification, the criteria used to define GPA have evolved significantly over time. As such, variations in diagnostic definitions across studies may affect case ascertainment and introduce heterogeneity. While we recognise this as a limitation, we relied on the individual studies adequately classifying their GPA cases, based on the criteria that were available and used at the time.

Nevertheless, our systematic review highlights a potential association between AATD and GPA, particularly in relation to genetic predisposition, pulmonary involvement and proposed pathogenic mechanisms. While these findings suggest that AATD contribute to the pathogenesis of GPA, the evidence remains limited and inconsistent, especially in relation to disease severity and patterns of organ involvement. There is a clear need for well-designed, prospective, genotype-stratified studies with standardised definitions and long-term follow-up to better understand the true nature of this association and its potential therapeutic implications.

Points for clinical practice

- Individuals with AATD, particularly Z-allele carriers, are at increased risk of developing GPA.
- The identification of AATD in GPA patients may hold relevance for understanding variability in pulmonary involvement.
- While augmentation therapy remains unproven in this setting, its theoretical benefits suggest a rationale for further exploration in selected AATD-associated GPA cases.

Questions for future research

- Could novel therapies for AATD have an impact on GPA incidence in affected individuals?
- What are the potential mechanistic links through which AATD may contribute to intra-alveolar haemorrhage in individuals with GPA?

Provenance: Submitted article, peer reviewed.

The systematic review protocol was registered with PROSPERO (https://www.crd.york.ac.uk/prospero/) with identifier: CRD42021259104.

Conflict of interest: All authors have nothing to disclose.

Support statement: D.A. Lomas is supported by the Medical Research Council (UK) MR/V034243/ and UCLH NIHR BRC.

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