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Original article

Systemic autoimmune disease as a cause of death: mortality burden and comorbidities

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Abstract

Objectives. Systemic autoimmune diseases (SAIDs) have chronic trajectories and share characteristics of self-directed inflammation, as well as aspects of clinical expression. Nonetheless, burden-of-disease studies rarely investigate them as a distinct category. This study aims to assess the mortality rate of SAIDs as a group and to evaluate co-occurring causes of death.

Methods. We used death certificate data in the Netherlands, 2013–2017 ($N = 711\ 247$), and constructed a SAIDs list at the fourth-position ICD-10 level. The mortality rate of SAIDs as underlying cause of death (CoD), non-underlying CoD, and any-mention CoD was calculated. We estimated age-sex-standardized observed/expected (O/E) ratios to assess comorbidities in deaths with SAID relative to the general deceased population.

Results. We observed 3335 deaths with SAID on their death certificate (0.47% of all deaths). The mortality rate of SAID was 14.6 per million population as underlying CoD, 28.0 as non-underlying CoD, and 39.7 as any-mention CoD. The mortality rate was higher for females and increased exponentially with age. SAID-related deaths were positively associated with all comorbidities except for solid neoplasms and mental conditions. Particularly strong was the association with diseases of the musculoskeletal system (O/E = 3.38; 95% CI: 2.98, 3.82), other diseases of the genitourinary system (O/E = 2.73; 95% CI: 2.18, 3.38), influenza (O/E = 2.71; 95% CI: 1.74, 4.03), blood diseases (O/E = 2.02; 95% CI: 1.70, 2.39), skin and subcutaneous tissue diseases (O/E = 1.95; 95% CI: 1.54, 2.45), and infectious diseases (O/E = 1.85; 95% CI: 1.70, 2.01).

Conclusion. Systemic autoimmune diseases constitute a rare group of causes of death, but contribute to mortality through multiple comorbidities. Classification systems could be adapted to better encompass these diseases as a category.

Key words: autoimmune diseases, comorbidity, mortality, epidemiology, population studies

CLINICAL SCIENCE

Rheumatology key messages

- Systemic autoimmune diseases share many characteristics, but are rarely studied as a category.
- We investigate the collective burden of systemic autoimmune diseases at the time of death.
- Classification systems could be adapted to allow all comorbidities to be considered in research and care.

Introduction

Systemic autoimmune diseases (SAIDs), affect currently 400 000 people worldwide [1]. They constitute a subgroup of autoimmune diseases, a family of complex chronic diseases characterized by dysregulation of the adaptive and the innate immune system [2, 3]. SAIDs, such as SLE or sarcoidosis, share the potential for affecting multiple organs and tissues [2], and may cause similar clinical symptoms, including skin and joint manifestations, and are often treated with immunosuppressive drugs. Furthermore, several SAIDs have a shared genetic background and their development involves to some extent several overlapping molecular pathways that are activated by environmental triggers [4–7].

In spite of similarities in their pathophysiology and clinical expression, SAIDs are not commonly treated as

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one uniform group. This may be partially because there is no clear consensus on the list of disorders that belong to SAIDs. Moreover, disease classification systems such as the International Classification of Diseases (ICD) [8] are usually organized on the basis of the affected primary organ system, resulting in SAIDs being scattered across different disease chapters. For example, SLE is classified in the chapter 'Diseases of the musculoskeletal system', whereas sarcoidosis is classified under 'Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism'. Because burden-of-disease studies often rely on standard disease categorizations, such as the ICD-10, SAIDs may be underrated in terms of their public health importance.

So far, only a limited number of studies have assessed the mortality burden of SAIDs together in one analysis. A recent study indicated an excess mortality risk for various SAIDs, but considered each SAID condition separately, reporting the highest burden for systemic sclerosis and systemic vasculitides [9]. Two other studies focussed on the mortality from autoimmune diseases as a group and found that 0.1–0.2% of all deaths had one of the included SAIDs reported as the underlying or any-mention cause of death (CoD) [10, 11]. Both studies, however, were restricted to women and did not cover the whole spectrum of SAIDs. Other previous studies report a prevalence of SAIDs ranging from 0.02% in children [12] to 0.05–0.4% in a nationwide population. However, these studies likely have underestimated the burden of SAIDs as a group, because of potential selection bias and the limited number of included SAIDs [13–16].

Because SAIDs can alter the risk of other diseases substantially [17], the causes of death (CoDs) reported among deaths with SAIDs may differ from those reported in the general population. In recent years, various population studies have assessed the co-occurrence of single SAIDs with other diseases at the time of death, using death certificate data. SLE has been associated with a higher reporting of coagulation and hemorrhagic disorders, and renal failure [18]. Other multiple-cause-of-death studies reported associations of giant cell arteritis with cardiovascular diseases and infections [19], of systemic sclerosis with cardiopulmonary disorders [20], and of sarcoidosis with tuberculosis, chronic respiratory diseases and infections [21]. Furthermore, SAIDs, as members of the autoimmune diseases family, have been found to be associated with a higher risk of a second autoimmune disease [14], vascular dementia [22], and mood disorders [23], as well as increased risk of death from cancer [24, 25].

The aim of this study was to investigate SAIDs as a group, joining CoDs from different chapters of the ICD-10 classification. We used this group to assess the mortality rate of SAID as underlying and non-underlying CoD. Furthermore, we assessed rates of co-occurring CoDs in deceased persons with SAID compared with the general population. For the purpose of this study, we presented a novel approach of using all information as reported on the death certificates in order to broaden our knowledge on the associations of SAIDs with serious comorbidities at the time of death.

Methods

Data collection

We obtained anonymous data from the Cause of Death database of Statistics Netherlands. In the Netherlands, for each deceased person, a death certificate is completed by the attending or the forensic physician, following the World Health Organization (WHO) model. Three lines are available to describe the causal chain of morbid events leading to death (Part I), and one line for diseases and conditions contributing to death (Part II). The ICD-coded output includes both the underlying CoD—i.e. the disease or injury initiating the chain of morbid events leading directly to death [8]—and the non-underlying—i.e. intermediate or contributory—CoD. A CoD is commonly termed as 'any-mention CoD' when reported either as the underlying or a non-underlying cause of death on the death certificate. Diseases are coded according to the 10th revision of the International Classification of Diseases (ICD-10) classification of the WHO [8]. Date of birth, date of death, sex and mention of a systemic autoimmune disease as underlying, non-underlying, and any-mention CoD were extracted from this data source for the years 2013–2017 for all deaths. Years before 2013 were omitted, because automatic coding and selection of the underlying cause of death was introduced in 2013, with the adoption of Iris 4.4.1 software [26].

SAIDs were identified based on a list of ICD-10 fourth-position codes that we constructed based on relevant studies [1, 5, 7, 12, 15, 27–29] and expert knowledge of an internist-clinical immunologist who is co-authoring this paper. We made a distinction between vasculitides and non-vasculitides (Supplementary Table S1, available at *Rheumatology* online), because of differences in their clinical presentation and complications (mainly ischaemic in vasculitides). Comorbidities of systemic autoimmune diseases as mentioned on the death certificate were classified using ICD-10 third-position or fourth-position ICD-10 codes, grouped according to the European Shortlist for Causes of Death 2012 [30]. We modified this list to include diseases of the kidney and urinary tract infections as distinct subcategories of the *Diseases of the genitourinary system* and influenza and pneumonia as distinct subcategories of *Diseases of the respiratory system*, because of their clinical significance (Supplementary Table S2, available at *Rheumatology* online). Our study population consisted of decedents in the Netherlands (2013–2017). General population data for this period were provided by Statistics Netherlands. Death certificates for persons $\leq$1 year old were excluded from the study population as they follow a different process of coding. According to the Dutch law on medical

research, no ethical approval was required for this study, as no living subjects were involved and all data were anonymized.

Statistical analysis

We calculated the number of deaths that listed each of the main SAID subclasses on the death certificate as the underlying CoD, a non-underlying CoD, and any-mention CoD. We estimated the ratio of underlying CoD to any-mention CoD by SAID subclass, to determine which diseases are relatively more important as underlying rather than contributing causes of death [31]. We calculated the absolute number of deaths and annual age-specific mortality rates (per 1 000 000 population) for the total study population, and by sex. These results are presented stratified by mention of SAID as the underlying CoD, a non-underlying CoD, and any-mention CoD on the death certificate for the total SAID group, as well as the subgroups of vasculitides and non-vasculitides.

To assess the association of SAIDs with other causes of death, we performed a multiple-cause-of-death analysis. We analysed the CoDs in death certificates of deceased persons with SAID as any-mention, non-underlying or underlying CoD, respectively, and present these figures as absolute numbers and percentages. A death certificate may have more than one non-underlying CoD listed, therefore the non-underlying CoDs examined were non-exclusive. In addition, we calculated the ratio of the observed (O) number of deaths to the expected (E) number of deaths, termed as the O/E ratio [32], with the expected cases adjusted for sex and age using as reference population the general Dutch deceased population between 2013 and 2017 [711 247 deaths, mean age 78 years (S.D. = 13.6), 369 255 females]. An O/E ratio over 1 means that the combination of SAID and the CoD under examination was more frequent than would be expected if these diseases were independent. The CIs of the O/E ratios were estimated using Byar's method [33].

We used R software for the statistical analyses (The R Foundation for Statistical Computing, version 3.2.3).

Results

In the 5-year period of study (2013–2017), a SAID was reported on 3335 death certificates as underlying or non-underlying CoD. This corresponds to 0.47% of all 711 247 deaths in the Netherlands.

Table 1 presents the number of deaths with SAID reported as underlying, non-underlying or any-mention CoD, according to the main subclasses of the disease group. Overall, among non-vasculitides and vasculitides, systemic sclerosis ($n = 268$) was the main SAID subclass reported as underlying CoD, while PMR ($n = 844$) was the main subclass as non-underlying CoD. Systemic vasculitis was the main subclass among vasculitides, both as underlying CoD ($n = 224$), and non-underlying CoD ($n = 178$).

Among non-vasculitides, the ratio of underlying CoD to any-mention CoD was the highest for other specified systemic involvement of connective tissue (0.89) and systemic sclerosis (0.67). Thus, these diseases were more likely to be considered as underlying CoD, when reported. PMR had the lowest ratio (0.09), excluding subclasses with very few cases. Among vasculitides, the ratio of underlying CoD to any-mention CoD was the highest for Goodpasture syndrome and Behçet's disease (0.71), and the lowest for giant cell arteritis (0.33).

Table 2 shows the age-specific mortality from SAID, according to the type of report on death certificates, by sex. About 60.2% ($n = 2007$) of the any-mention SAID deaths occurred in females. The corresponding percentages for the deaths with SAID as the underlying CoD and SAID as a non-underlying CoD were 57.2% ($n = 703$) and 62.2% ($n = 1461$), respectively. At all ages, and in each of the three CoD reporting types, females had a higher mortality rate than males. For both genders, and in each of the three CoD reporting types, there was an exponential increase of the annual mortality rate with age. Females over 80 years had the highest mortality burden, with a mortality rate of 453.9 deaths with any mention of SAID per 1 000 000 population. The median age of death of decedents with SAID as the underlying CoD was 74 years (IQR = 18), 6 years lower than the general population, with 17.3% dying younger than 60 years old. Supplementary Table S3, available at *Rheumatology* online, shows the mortality rates of vasculitides and non-vasculitides separately.

The report of different types of disorders as any-mention CoD on death certificates with any mention of a SAID is provided in Table 3. Leading any-mention CoDs were diseases of the circulatory system (55.5%), followed by diseases of the respiratory system (35.9%), endocrine and metabolic disorders (21.6%), and neoplasms (20.9%). Deaths with SAID as a cause of death had a higher report of all types of conditions as co-occurring CoDs than deaths in the general population, with the exception of solid neoplasms and mental disorders. Particularly high was the O/E ratio for diseases of the musculoskeletal system (3.38), other diseases of the genitourinary system (2.73), influenza (2.71), and diseases of the blood (2.02). Diseases of the skin and subcutaneous tissue and infectious diseases also presented high O/E ratios (1.95 and 1.85, respectively). A low O/E ratio was observed for solid neoplasms (0.48) and mental disorders (0.71).

An overview of the comorbidities reported on the death certificate when SAID was the underlying CoD or a non-underlying CoD, respectively, is given in Table 4. For most comorbidities, the associations with SAID had the same direction—positive or negative—regardless of the type of reporting on the death certificate. For some comorbidities, there were opposite directions when SAID was the underlying CoD compared with when SAID was a non-underlying CoD. For example, a

Table 1 Deaths with SAID as cause of death, by subclass, the Netherlands 2013–2017

Systemic autoimmune disease	Underlying CoD	Non-underlying CoD	Any-mention CoD	Underlying CoD / Any-mention CoD ratio
	number	number	number	
Non-Vasculitides[a]				
SLE	100	222	251	0.40
Dermatopolymyositis	100	112	212	0.47
Sjögren syndrome	48	156	204	0.24
Systemic sclerosis	268	265	403	0.67
Mixed connective tissue disease	17	17	34	0.50
PMR	81	844	925	0.09
Antiphospholipid syndrome	24	21	45	0.53
Sarcoidosis	201	304	500	0.40
Amyloidosis	0	2	2	0.00
Still disease	2	4	6	0.33
IgG4-related disease	18	83	101	0.18
Cogan's disease	0	3	3	0.00
Other specified systemic involvement of connective tissue	17	2	19	0.89
Systemic involvement of connective tissue, unspecified	66	75	141	0.47
Vasculitides				
ANCA-associated vasculitis	205	144	349	0.59
Giant cell arteritis	52	105	157	0.33
Other systemic vasculitis	30	41	71	0.42

[a]There are no deaths with mention of relapsing polychondritis.
SAID, systemic autoimmune disease; CoD, cause of death.

Table 2 Deaths with SAID as cause of death, by age and sex

	Underlying CoD		Non-underlying CoD		Any-mention CoD	
	number	annual rate per 1 000 000 population	number	annual rate per 1 000 000 population	number	annual rate per 1 000 000 population
Females						
<40	17	0.9	25	1.3	35	1.8
40–59	99	8.2	110	9.1	179	14.7
60–79	317	36.9	493	57.4	726	84.5
≥80	270	114.9	833	354.4	1067	453.9
Total	703	16.6	1461	34.5	2007	47.4
Males						
<40	16	0.8	18	0.9	32	1.6
40–59	80	6.6	97	8.0	160	13.1
60–79	278	34.0	427	52.2	651	79.5
≥80	152	112.2	345	254.6	485	357.9
Total	526	12.7	887	21.3	1328	31.9
Females and Males						
<40	33	0.8	43	1.1	67	1.7
40–59	179	7.4	207	8.5	339	13.9
60–79	595	35.5	920	54.8	1377	82.1
≥80	422	113.9	1178	317.9	1552	418.8
Total	1229	14.6	2348	28.0	3335	39.7

SAID, systemic autoimmune disease; CoD, cause of death.

TABLE 3 Deaths with SAID as any-mention CoD, and with other condition as any-mention CoD

	SAID as any-mention cause of death		
	number	%[a]	Age-sex-standardized observed/expected (O/E) ratios [95% CI]
Condition			
Infectious and parasitic diseases	552	16.6	1.85 [1.70, 2.01]
Neoplasms	696	20.9	0.55 [0.51, 0.60]
Malignant neoplasms	643	19.3	0.53 [0.49, 0.58]
Solid malignant neoplasms	534	16.0	0.48 [0.44, 0.52]
Malignant neoplasms of lymphoid, and haematopoietin tissue	112	3.4	1.09 [0.90, 1.32]
Non-malignant neoplasms	76	2.3	1.16 [0.92, 1.46]
Diseases of the blood and blood-forming organs	137	4.1	2.02 [1.70, 2.39]
Endocrine, nutritional and metabolic diseases	721	21.6	1.27 [1.18, 1.36]
Mental and behavioural disorders	379	11.4	0.71 [0.64, 0.79]
Diseases of the nervous system and the sense organs	432	13.0	1.18 [1.07, 1.30]
Diseases of the circulatory system	1852	55.5	1.20 [1.15, 1.26]
Ischaemic heart diseases	336	10.1	1.11 [0.99, 1.23]
Acute myocardial infarction	130	3.9	0.69 [0.57, 0.82]
Other ischaemic heart diseases	227	6.8	1.08 [0.94, 1.23]
Other heart diseases	1189	35.7	1.20 [1.13, 1.27]
Cerebrovascular diseases	321	9.6	0.90 [0.80, 1.00]
Other diseases of the circulatory system	758	22.7	1.86 [1.73, 1.99]
Diseases of the respiratory system	1197	35.9	1.44 [1.36, 1.52]
Influenza	24	0.7	2.71 [1.74, 4.03]
Pneumonia	553	16.6	1.54 [1.41, 1.67]
Chronic obstructive pulmonary disease	309	9.3	0.87 [0.78, 0.98]
Other diseases of the respiratory system	600	18.0	1.67 [1.54, 1.81]
Diseases of the digestive system	326	9.8	1.28 [1.15, 1.43]
Diseases of the skin and subcutaneous tissue	75	2.2	1.95 [1.54, 2.45]
Diseases of the musculoskeletal system	255	7.6	3.38 [2.98, 3.82]
Diseases of the genitourinary system	578	17.3	1.65 [1.52, 1.79]
Diseases of the kidney	444	13.3	1.73 [1.58, 1.90]
Urinary tract infections	106	3.2	1.22 [1.00, 1.48]
Other diseases of the genitourinary system	85	2.5	2.73 [2.18, 3.38]
Symptoms, signs, ill-defined causes	873	26.2	1.12 [1.05, 1.19]
External causes of morbidity and mortality	195	5.8	0.82 [0.71, 0.95]

[a]% represents the proportion of subjects with a specific any-mention cause of death among all subjects with SAID as any-mention cause of death.
SAID, systemic autoimmune disease; CoD, cause of death.

positive association with pneumonia was observed only when SAID was the underlying CoD (O/E = 2.77 *vs* 0.81). For endocrine, nutritional and metabolic disease, a positive association was found only when SAID was a non-underlying CoD (O/E = 0.71 *vs* 1.68). Supplementary Table S4, available at *Rheumatology* online, shows the corresponding results in detail for different diseases of the circulatory system as a CoD.

Of all SAID cases, 2.4% (79 deceased) had a second type of SAID mentioned on their death certificates. Report of a SAID as non-underlying CoD was much more frequent when another SAID was the underlying or

TABLE 4 Number of deaths with SAID as the underlying CoD (or a non-underlying CoD) and with other conditions as a non-underlying CoD (or the underlying CoD), by condition, the Netherlands 2013–2017

	SAID as underlying cause of death			SAID as non-underlying cause of death		
	number	%[a]	Age-sex-standardized observed/expected (O/E) ratios [95% CI]	number	%[b]	Age-sex-standardized observed/expected (O/E) ratios [95% CI]
Condition						
Infectious and parasitic diseases	215	17.5	2.69 [2.34, 3.08]	102	4.3	2.12 [1.72, 2.57]
Neoplasms	69	5.6	0.26 [0.20, 0.33]	504	21.5	0.72 [0.66, 0.79]
Malignant neoplasms	56	4.6	0.23 [0.17, 0.29]	478	20.4	0.71 [0.65, 0.78]
Solid malignant neoplasms	42	3.4	0.17 [0.12, 0.23]	395	16.8	0.64 [0.58, 0.70]
Malignant neoplasms of lymphoid, and haematopoietic tissue	14	1.1	1.91 [1.04, 3.21]	83	3.5	1.58 [1.26, 1.96]
Non-malignant neoplasms	16	1.3	1.81 [1.03, 2.93]	26	1.1	0.99 [0.65, 1.46]
Diseases of the blood and blood-forming organs	42	3.4	2.24 [1.61, 3.02]	10	0.4	1.51 [0.72, 2.78]
Endocrine, nutritional and metabolic diseases	114	9.3	0.71 [0.59, 0.86]	93	4.0	1.68 [1.35, 2.05]
Mental and behavioural disorders	48	3.9	0.49 [0.36, 0.66]	150	6.4	0.87 [0.73, 1.02]
Diseases of the nervous system and the sense organs	99	8.1	1.45 [1.18, 1.76]	127	5.4	1.09 [0.91, 1.30]
Diseases of the circulatory system	558	45.4	1.52 [1.39, 1.65]	627	26.7	1.09 [1.00, 1.18]
Ischaemic heart diseases	56	4.6	1.25 [0.95, 1.62]	142	6.0	1.06 [0.89, 1.24]
Acute myocardial infarction	20	1.6	1.69 [1.03, 2.60]	80	3.4	1.02 [0.81, 1.27]
Other ischaemic heart diseases	36	2.9	1.06 [0.74, 1.47]	62	2.6	1.23 [0.94, 1.58]
Other heart diseases	372	30.3	1.50 [1.35, 1.66]	217	9.2	0.96 [0.84, 1.10]
Cerebrovascular diseases	68	5.5	1.30 [1.01, 1.65]	125	5.3	0.86 [0.72, 1.02]
Other diseases of the circulatory system	215	17.5	1.96 [1.71, 2.24]	143	6.1	1.86 [1.57, 2.20]
Diseases of the respiratory system	506	41.2	2.22 [2.03, 2.43]	208	8.9	1.16 [1.01, 1.33]
Influenza	3	0.2	3.80 [0.76, 11.12]	19	0.8	4.08 [2.45, 6.36]
Pneumonia	264	21.5	2.77 [2.44, 3.12]	38	1.6	0.81 [0.57, 1.11]
Chronic obstructive pulmonary disease	70	5.7	1.13 [0.88, 1.43]	90	3.8	0.91 [0.73, 1.12]
Other diseases of the respiratory system	291	23.7	2.57 [2.29, 2.89]	61	2.6	2.14 [1.64, 2.75]
Diseases of the digestive system	77	6.3	1.18 [0.93, 1.47]	101	4.3	1.47 [1.20, 1.79]
Diseases of the skin and subcutaneous tissue	21	1.7	2.16 [1.34, 3.30]	7	0.3	1.61 [0.64, 3.31]
Diseases of the musculoskeletal system	55	4.5	3.20 [2.41, 4.17]	41	1.7	2.86 [2.06, 3.89]
Diseases of the genitourinary system	210	17.1	2.32 [2.02, 2.66]	70	3.0	1.49 [1.16, 1.88]
Diseases of the kidney	183	14.9	2.69 [2.31, 3.10]	29	1.2	1.07 [0.72, 1.54]
Urinary tract infections	22	1.8	1.16 [0.73, 1.76]	27	1.1	1.73 [1.14, 2.52]
Other diseases of the genitourinary system	22	1.8	2.58 [1.61, 3.90]	14	0.6	3.19 [1.74, 5.36]
Symptoms, signs, ill-defined causes	275	22.4	1.21 [1.07, 1.36]	12	0.5	0.23 [0.12, 0.41]
External causes of morbidity and mortality	54	4.4	0.63 [0.48, 0.83]	48	2.0	0.47 [0.35, 0.63]
SAID	43	3.5	10.45 [7.56, 14.07]	43	1.8	10.81 [7.82, 14.56]

[a]% represents the proportion of subjects with a specific non-underlying cause of death among the subjects with SAID as the underlying cause of death.
[b]% represents the proportion of subjects with the specific underlying cause of death among the subjects with SAID as a non-underlying cause of death.
SAID, systemic autoimmune disease; CoD, cause of death.

non-underlying CoD, and vice versa (O/E = 10.45 *vs* 10.81). The most common SAID pairs in our study were giant cell arteritis with PMR (9 deaths); SLE with antiphospholipid syndrome (6); systemic vasculitis with IgG4-related disease (4); SLE with Sjögren syndrome (4); systemic sclerosis with mixed connective tissue disease (5)/Sjögren syndrome (5)/SLE (3).

Discussion

In this study, we analysed >3000 Dutch death certificates with mention of a systemic autoimmune disease. Our findings suggest that SAID is a rare group of causes of death, with a mortality rate of about 15 and about 40 per million population measured as an underlying CoD and any-mention CoD, respectively. The mortality rate is higher for female decedents and is rising exponentially with age. We identified a pattern of comorbidities predominant in decedents dying with SAID that involved musculoskeletal, genitourinary and blood disorders, as well as infections—including influenza and pneumonia—and skin disorders.

This is one of the first studies to construct an exhaustive list of SAIDs and investigate SAIDs as a group of causes of death. We used multiple-cause-of-death data, covering the total Dutch population. The use of national data, which are universal and cover all sociodemographic backgrounds, avoids the potential selection bias of cohort studies. We conducted a multiple-cause-of-death analysis that allows quantification of the association between each comorbidity at the time of death and SAID, taking into consideration the role of diseases in the dying causal chain.

The limitations of this study include properties of the data used. First, multiple-cause-of-death data come with the known risk of occasional arbitrary classification of a condition as non-underlying instead of underlying CoD or generally its omission from the death certificates. Diseases may be omitted due to restricted relevance to death, either because of low severity, or being in remission. The way that certificates are filled in depends on the subjective judgement of the physician, who is supposed to decide between reporting every possible condition or only the conditions that evidently contributed to death. In the absence of clinical records to verify each individual diagnosis and to capture all comorbidities, our findings may be conservative and underestimate the contribution of SAID to mortality in the Netherlands. A recent study on SLE found substantial underreporting on death certificates of cases, especially for older people [34]. However, the extent of the potential underreporting for SAID as a group has not been studied explicitly in the literature.

Second, we cannot make causal inferences about the relationship of SAID with another disease at the time of death, as we examine cross-sectional associations. However, when a disease tends to occur with SAID as underlying CoD, but not with SAID as non-underlying CoD, this would indicate that this disease acts more likely as a complication of SAID rather than a concurrent independent condition contributing to death. Although, observer–certifier variation in the reporting of associations affects the accuracy of information for individual patients or groups of patients, for large-scale population-based estimates a cancelling-out of inaccuracies might be expected. Third, unfortunately, there were not enough cases to perform a separate analysis of comorbidities for patients dying from either vasculitides or non-vasculitides, nor patients by sex and age class.

Our finding of ~15 persons per million population dying annually from a SAID as the underlying CoD (0.2% of all deaths) is in relative agreement with previous evidence of 10–17 persons per million in western countries, based on numbers for selected SAIDs analysed among the much larger group of autoimmune diseases in nationwide data [10, 11] or as part of registries [9]. When investigating SAID as any-mention COD, we found that ~40 persons per million had mention of a SAID on their death certificates (0.5% of all deaths). This estimate was much higher than a study reporting 17 persons per million population, but missed common SAIDs such as PMR, sarcoidosis and giant cell arteritis [10].

The predominance of systemic sclerosis and systemic vasculitis, particularly ANCA-associated vasculitis, as leading underlying CoD among SAIDs in our population is consistent with a recent Norwegian study [9].

The considerably higher mortality rate of SAID for females in our study (50% higher in any-mention CoD analysis) may reflect the worldwide prevalence estimates of three times more women suffering from a SAID [1]. Contrary to our expectations, a recent registry study reported higher mortality for males [9]. Given the fact that we have no information on the clinical course of SAIDs in those who died from or with the disease, we cannot make claims on the ways in which sex is associated with mortality of SAID patients or what caused this excess female mortality. For some diseases, like SLE, studies are inconclusive about the role of sex in mortality, reporting higher incidence in females, but inconsistent evidence on the clinical course and mortality [35].

Our finding that the mortality risk from SAID in the population is increasing with age may be explained by lifetime accumulation of damage involving several vital systems and more rarely by occurrence of elderly-onset cases [36].

Deaths with report of one type of SAID were proportionally more frequent in cases with another SAID as CoD compared with the general population. This finding implies that patients with a SAID are more likely to suffer from a concomitant type of SAID at the time of death. Other studies have found a higher risk for a second autoimmune disease for people who suffer from one autoimmune disease [14]. Shared determinants, such as genes, environment and lifestyle have been proposed as underlying mechanisms [4–7].

The more frequent report of cardiovascular disease on death certificates of subjects with SAID as the underlying CoD compared with the general population is in

agreement with previous evidence regarding the occurrence of complications, such as stroke and heart disease [17, 37, 38]. Mechanisms involved in the development of cardiovascular disease include the formation of atherosclerotic plaques via inflammation, most studied for SLE and systemic sclerosis, as well as procoagulant activity predominant in antiphospholipid syndrome. The role of treatment-related cardiac toxicity in SAID has been also described [38].

Our results corroborate previous findings regarding the importance of infections as a cause of death in patients with SAID [39, 40]. About 17% of the deceased with SAID in our study had an infection that contributed directly or indirectly to death, in line with a recent SAID mortality study [9]. General infections, pneumonia, genitourinary infections and, most of all, influenza were reported more frequently on death certificates with a mention of SAID. However, it is not known whether an infection can be attributed to disease activity or the effect of immunosuppressive drugs, therefore is a topic for further study. Our finding that pneumonia had more frequent report on death certificates with SAID only as an underlying CoD may imply that it is recognized as a particular lethal pathway for these patients.

Although 16% of our study population had a solid malignant neoplasm at the time of death, the rate of deaths with any mention of a solid neoplasm was substantially lower compared with the general population. This finding may seem surprising, as SAID cannot be considered as a protective factor, but is consistent with prior publications [19–21, 39]. A potential explanation may be surveillance bias, with SAID patients having more frequent visits to specialists, therefore getting an earlier detection and treatment of cancer. At the same time, cancer has high prominence in the death certification process, often resulting in fewer mentions of other diseases, because it might be assumed to have contributed to death on its own. On the contrary, malignant neoplasms of lymphoid, and haematopoietic tissue were more frequently reported as a cause of death in deceased with SAID, although still rare. A meta-analysis found that SLE and Sjögren syndrome are associated with occurrence of non-Hodgkin lymphoma [41]. Immunomodulatory therapies have been associated with development of lymphomas as a rare adverse effect.

In our study, several other conditions were associated with mention of SAID on the death certificate. The high number of mentions of musculoskeletal disease may be partially explained by the fact that musculoskeletal disease is often an inherent part of SAID. Disorders of the blood and blood-forming organs, as well as diseases of the genitourinary, the respiratory and the digestive system were associated with SAID, especially when SAID was reported as underlying CoD. This reflects to a large extent known complications, such as haemolytic anaemia in SLE [42], renal failure in ANCA-associated vasculitides and SLE [40, 42], lung failure in systemic sclerosis and dermatopolymyositis [27], and gastrointestinal ulcers or perforation in vasculitides and dermatopolymyositis [28]. Of note, skin and subcutaneous tissue disease, a not so well-studied complication or comorbidity, was found to have a strong association with SAID reporting on the death certificate. Antiphospholipid syndrome, vasculitides and Sjögren syndrome have been documented as SAIDs with potentially severe skin involvement [29]. Similarly, neurological disorders may occur more often in SAID patients in the form of peripheral neuropathy [43]. Endocrine, nutritional and metabolic diseases had a high occurrence in deceased with SAID, which was driven only via their reporting as an underlying CoD. This evidence reinforces the hypothesis that diseases such as hypothyroidism [44] and diabetes mellitus [45], may not act as a complication of SAID, but rather a comorbidity.

Although survival of patients with SAID has improved during recent years, our findings extend our knowledge on ways to further advance it. Clinically relevant comorbidities may be targets for secondary prevention, with complete vaccination coverage for influenza and pneumonia infections being the most prominent. In addition, it is recommended that physicians monitor closely the respiratory, renal and cardiovascular functions of the patients and treat early known complications that may become life-threatening. At the same time, more rare but severe conditions that may contribute to death directly or indirectly, such as musculoskeletal, skin and blood disorders, as well as lymphomas, should be taken into consideration when assessing the overall physical state and quality of life of the patients. Further research is needed to fully understand the mechanisms driving mortality in SAID patients and to define subgroups vulnerable for certain complications.

Finally, we presented a novel approach of using all death certificate information in order to assess how SAID relates to other diseases in affecting mortality in the general population. Whereas previous studies applied multiple-cause-of-death analysis to specific SAID diseases, we were the first to apply this approach to SAID as one class. Countries following the WHO model of death certificate and coding systematically all mentioned causes of death could adopt our method. Such results may be used also to monitor mortality related with SAIDs and inform policies to address them. This is relevant particularly in view of the forthcoming ICD-11 introduction [46], in which the problem of SAID classification is mitigated, but there is room for improvement, especially when new autoinflammatory diseases are being discovered. Mortality classification systems need more flexibility to allow for such new views on the grouping of diseases to be incorporated.

To our knowledge, this is the first study to investigate systemic autoimmune diseases as a group using the multiple-cause-of-death approach. Systemic autoimmune diseases compose a rare group of causes of death, but can contribute to mortality through various comorbidities. Reclassification of readily available data provides useful estimates of the mortality burden of systemic autoimmune diseases in the general population.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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