Original article

Persistent premature mortality gap in dermatomyositis and polymyositis: a United Kingdom general population-based cohort study

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Abstract

Objective. DM and PM are associated with substantial morbidity and mortality. We aimed to examine recent trends.

Methods. Using The Health Improvement Network, we identified patients with incident DM/PM (defined by ≥ 1 Read diagnosis code) aged 18–89 years with ≥ 1 year of continuous enrolment prior to the cohort entry date and up to 10 comparators matched on age, sex and entry year. The cohort was divided in two based on the year of DM/PM diagnosis: the early cohort (1999–2006) and late cohort (2007–2014). We calculated multivariable hazard ratios (HR) for death using a Cox-proportional hazards model and multivariable rate differences (RD) using an additive hazard model.

Results. We identified 410 DM cases (mean age: 58 years, 66% female) and 407 PM cases (mean age: 59 years, 61% female). Both DM cohorts had excess mortality compared with the comparison cohorts (71.5 vs 12.9 deaths/1000 person-years [PY] in the early cohort and 49.1 vs 10.4 deaths/1000 PY in the late cohort). The multivariable HRs were 7.51 (95% CI: 4.20, 13.42) in the early cohort and 5.42 (95% CI: 3.11, 9.45) in the late cohort (P -value for interaction = 0.59), and multivariable RDs were 56.2 (95% CI: 31.8, 81.2) in the early cohort and 36.3 (95% CI: 19.6, 53.0) in the late cohort (P -value for interaction = 0.15). A similar trend existed in PM.

Conclusion. The premature mortality gap in DM/PM has not considerably improved in recent years, highlighting an unmet need for therapeutic improvement.

Key words: myositis, dermatomyositis, polymyositis, mortality

Rheumatology key messages

- The premature mortality gap in dermatomyositis (DM) and PM has persisted in recent years.
- DM and PM patients have over three-fold higher risk of mortality compared with matched comparators.
- This highlights a critical unmet need for new treatment strategies for DM and PM.

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Submitted 8 May 2020; accepted 7 September 2020

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Introduction

DM and PM are autoimmune idiopathic inflammatory myopathies (IIMs) that can cause muscle weakness, rashes and cardiopulmonary disease. IIMs are associated with increased morbidity (with up to 80% of treated patients reporting long-term disability), malignancy and mortality, with prior estimates of 5-year mortality ranging widely from 23% to 73% [1, 2]. Mortality in IIM has been examined in general population-based cohort studies from Scandinavian countries [1, 3, 4] and Taiwan

[5]. These studies have shown 1.5–7.7 times higher mortality risk with IIM compared with the general population, with major contributing factors including interstitial lung disease, malignancy and cardiovascular disease [1, 3–5].

Time trends in other rheumatic diseases, including RA [6] and granulomatosis with polyangiitis [7] have shown improvement in mortality in recent years. However, little is known about whether mortality has improved in IIM. We examined trends in mortality in DM and PM in early (1999–2006) and late (2007–2014) cohorts in a large general population database from the United Kingdom (UK).

Methods

Data source

We used The Health Improvement Network (THIN) database, which contains electronic medical records from general practitioners (GPs) in the UK. The THIN database contains ~4 million individuals (roughly 6% of the UK population) and has been shown to be representative of the general UK population in demographics and disease prevalence [8, 9]. Available information includes demographics, GP visit details, general health information (alcohol use, smoking and BMI), diagnostic codes from specialist referrals and hospitalizations, medications and laboratory test results. Diagnostic codes use the Read classification, a hierarchical clinical terminology system, and medications are coded according to Multilex classification, a standard drug terminology library that includes drug name and strength [7]. This study was approved by the THIN Scientific Review Committee.

Study design and case definition

We performed a matched cohort study to examine the relationship between incident DM and PM with the risk of all-cause mortality. We identified patients with incident DM or PM (defined by ≥ 1 Read diagnosis code, [Supplementary Table S1](#), available at *Rheumatology* online) between 18 and 89 years of age with at least 1 year of continuous enrolment prior to the cohort entry date. Read code diagnoses for rheumatic diseases have previously been validated in a similar UK database and found to have >80% accuracy [10]. The entry date was considered to be the date at which a first diagnosis of DM or PM was given. For each DM or PM case, we selected up to 10 comparators without DM or PM matched by age, sex, and database entry year. The cohort was then divided into two calendar time-based sub-cohorts, based on the year of diagnosis [the early cohort (1999–2006) and late cohort (2007–2014)] to evaluate trends in mortality. We chose these two time periods given that the majority of mortality studies in IIM were conducted prior to 2006 and in order to be able to compare changes in mortality in IIM to prior work

examining changes in mortality in RA during these same time periods [2, 6].

Assessment of outcome

The primary outcome was all-cause mortality (based on the death date recorded in THIN). Subject death triggers an update in the national Personal Demographics Service, which holds patient demographic data for the National Health Service. The change in status to 'deceased' immediately updates the subject's electronic medical records. Prior studies have shown that mortality rates from THIN agree well with national UK death rates [8].

Assessment of covariates

Covariates that could potentially influence mortality risk were assessed. We collected data from the THIN database including personal characteristics and lifestyle factors (BMI, smoking, alcohol use), healthcare utilization (number of GP office visits), socioeconomic deprivation index (SDI), comorbidities (e.g. hypertension, hyperlipidemia, ischaemic heart disease, diabetes, chronic kidney disease) and medications [e.g. anti-hypertensives and non-steroidal anti-inflammatory drugs (NSAIDs)] at the nearest possible measurement prior to the index date (full list of covariates in [Table 1](#)). The Charlson comorbidity index [11] prior to the index date was calculated.

Statistical analysis

Person-years (PY) of follow-up were computed for each subject from the index date to the first of any of the following events: death, migration out of the database, or the end of the follow-up period (either 31 December 2006, for the early cohort or 31 December 2014, for the late cohort, ensuring that the follow-up time was equal between the two cohorts to allow for a fair comparison). We calculated incidence rates of death for each group by dividing the number of cases of each outcome variable by the number of PY. The associations between myositis and all-cause mortality are expressed as incidence rate ratios with 95% CI. We used the Kaplan–Meier method to construct survival curves for the two calendar time-based sub-cohorts. Cox proportional hazard regression models were used to calculate hazard ratios (HR) for all-cause mortality, after accounting for matched clusters (age, sex and database entry year).

Our multivariable model adjusted for lifestyle factors (such as smoking and alcohol consumption), SDI, comorbidities (measured as Charlson comorbidity index and as individual comorbidities including hypertension, hyperlipidemia, diabetes, chronic kidney disease, ischaemic heart disease and stroke), medications for cardiovascular disease (including anti-hypertensives and aspirin), healthcare utilization (measured by number of GP visits), and BMI, as previously described [6, 7]. We then tested the significance of interaction between

TABLE 1 Baseline characteristics of participants with DM, PM and age-sex matched comparators according to calendar time-based sub-cohorts

Characteristic	1996–2006			2007–2014			1996–2006			2007–2014				
	Dermato-myositis (n = 186)	Comparators (n = 1665)	Dermato-myositis (n = 224)	Comparators (n = 2008)	Poly-myositis (n = 197)	Comparators (n = 1764)	Dermato-myositis (n = 186)	Comparators (n = 1665)	Dermato-myositis (n = 224)	Comparators (n = 2008)	Poly-myositis (n = 197)	Comparators (n = 1764)	Dermato-myositis (n = 210)	Comparators (n = 1884)
Age, years (mean (s.d.))	57 (15)	57 (14)	58 (16)	58 (16)	59 (14)	59 (14)	57 (15)	57 (14)	58 (16)	58 (16)	59 (14)	59 (14)	59 (16)	59 (16)
Female sex (n, %)	120 (64%)	1080 (65%)	149 (66%)	1340 (67%)	117 (59%)	1052 (60%)	120 (64%)	1080 (65%)	149 (66%)	1340 (67%)	117 (59%)	1052 (60%)	130 (62%)	1164 (62%)
Socioeconomic deprivation index score ^a (median, IQR)	3.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	3.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)
BMI, kg/m ² [mean (s.d.)]	27 (5)	27 (5)	27 (5)	27 (6)	27 (5)	26 (5)	27 (5)	27 (5)	27 (5)	27 (6)	27 (5)	26 (5)	28 (5)	27 (5)
Smoking history (n, %)														
Never	94 (51%)	816 (49%)	127 (57%)	1138 (57%)	98 (50%)	873 (50%)	94 (51%)	816 (49%)	127 (57%)	1138 (57%)	98 (50%)	873 (50%)	126 (60%)	1062 (56%)
Former	35 (19%)	288 (17%)	58 (26%)	476 (24%)	37 (19%)	306 (17%)	35 (19%)	288 (17%)	58 (26%)	476 (24%)	37 (19%)	306 (17%)	58 (28%)	449 (24%)
Current	39 (21%)	354 (21%)	38 (17%)	356 (18%)	47 (24%)	342 (19%)	39 (21%)	354 (21%)	38 (17%)	356 (18%)	47 (24%)	342 (19%)	25 (12%)	331 (18%)
Alcohol use (n, %)														
Never	29 (16%)	226 (14%)	48 (21%)	340 (17%)	31 (16%)	241 (14%)	29 (16%)	226 (14%)	48 (21%)	340 (17%)	31 (16%)	241 (14%)	36 (17%)	309 (16%)
Former	3 (2%)	19 (1%)	7 (3%)	38 (2%)	2 (1%)	15 (1%)	3 (2%)	19 (1%)	7 (3%)	38 (2%)	2 (1%)	15 (1%)	6 (3%)	36 (2%)
Current	120 (65%)	1055 (63%)	145 (65%)	1378 (69%)	137 (70%)	1106 (63%)	120 (65%)	1055 (63%)	145 (65%)	1378 (69%)	137 (70%)	1106 (63%)	147 (70%)	1270 (67%)
Charlson comorbidity index (median, IQR)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)	1 (1, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)	1 (1, 1)	0 (0, 0)	1 (1, 2)	0 (0, 0)
GP visits (median, IQR)	4 (2, 7)	1 (0, 4)	5 (3, 9)	2 (1, 5)	5 (2, 8)	2 (0, 4)	4 (2, 7)	1 (0, 4)	5 (3, 9)	2 (1, 5)	5 (2, 8)	2 (0, 4)	6 (3, 9)	2 (0, 5)
Hypertension (n, %)	56 (30%)	375 (23%)	71 (32%)	570 (28%)	59 (30%)	459 (26%)	56 (30%)	375 (23%)	71 (32%)	570 (28%)	59 (30%)	459 (26%)	74 (35%)	567 (30%)
Hyperlipidemia (n, %)	12 (7%)	105 (6%)	29 (13%)	201 (10%)	19 (10%)	112 (6%)	12 (7%)	105 (6%)	29 (13%)	201 (10%)	19 (10%)	112 (6%)	31 (15%)	183 (10%)
Diabetes (n, %)	15 (8%)	90 (5%)	17 (8%)	143 (7%)	15 (8%)	113 (6%)	15 (8%)	90 (5%)	17 (8%)	143 (7%)	15 (8%)	113 (6%)	20 (10%)	143 (8%)
Chronic kidney disease (n, %)	1 (1%)	13 (1%)	21 (9%)	139 (7%)	5 (3%)	22 (1%)	1 (1%)	13 (1%)	21 (9%)	139 (7%)	5 (3%)	22 (1%)	22 (11%)	165 (9%)
Ischaemic heart disease (n, %)	13 (7%)	104 (6%)	25 (11%)	138 (7%)	28 (14%)	137 (8%)	13 (7%)	104 (6%)	25 (11%)	138 (7%)	28 (14%)	137 (8%)	27 (13%)	135 (7%)
Stroke (n, %)	3 (2%)	30 (2%)	5 (2%)	33 (2%)	3 (2%)	37 (2%)	3 (2%)	30 (2%)	5 (2%)	33 (2%)	3 (2%)	37 (2%)	6 (3%)	44 (2%)
Diuretic (n, %)	46 (25%)	250 (15%)	54 (24%)	314 (16%)	57 (29%)	326 (19%)	46 (25%)	250 (15%)	54 (24%)	314 (16%)	57 (29%)	326 (19%)	52 (25%)	306 (16%)
Beta blocker (n, %)	22 (12%)	188 (11%)	30 (13%)	231 (12%)	33 (17%)	227 (13%)	22 (12%)	188 (11%)	30 (13%)	231 (12%)	33 (17%)	227 (13%)	30 (14%)	243 (13%)
Calcium channel blocker (n, %)	22 (12%)	163 (10%)	40 (18%)	238 (12%)	28 (14%)	176 (10%)	22 (12%)	163 (10%)	40 (18%)	238 (12%)	28 (14%)	176 (10%)	39 (19%)	243 (13%)
ACE inhibitor (n, %)	27 (15%)	154 (9%)	37 (17%)	312 (16%)	32 (16%)	186 (11%)	27 (15%)	154 (9%)	37 (17%)	312 (16%)	32 (16%)	186 (11%)	41 (20%)	277 (15%)
ARB (n, %)	8 (4%)	53 (3%)	13 (6%)	105 (5%)	16 (8%)	75 (4%)	8 (4%)	53 (3%)	13 (6%)	105 (5%)	16 (8%)	75 (4%)	19 (9%)	111 (6%)
Aspirin (n, %)	23 (12%)	164 (10%)	41 (18%)	236 (12%)	38 (19%)	230 (13%)	23 (12%)	164 (10%)	41 (18%)	236 (12%)	38 (19%)	230 (13%)	44 (21%)	244 (13%)
NSAIDs (n, %)	63 (34%)	324 (20%)	75 (34%)	296 (15%)	84 (43%)	306 (17%)	63 (34%)	324 (20%)	75 (34%)	296 (15%)	84 (43%)	306 (17%)	76 (36%)	302 (16%)

^aSocioeconomic deprivation index score was measured by the Townsend deprivation index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; GP: general practitioner; IQR: interquartile range.

TABLE 2 Association between DM and all-cause mortality according to time period

	1999–2006		2007–2014		P-value for interaction
	DM (n = 186)	Comparators (n = 1665)	DM (n = 224)	Comparators (n = 2008)	
Mean follow-up time, years	2.5 (2.0)	2.9 (2.1)	3.0 (2.20)	3.4 (2.2)	
Total follow-up time, PY	462	4810	673	6766	
Number of deaths	33	62	33	70	
Mortality rate/1000 PY	71.5 (49.2, 100.3)	12.9 (9.9, 16.5)	49.1 (33.8, 68.9)	10.4 (8.1, 13.1)	
Age, sex and entry year matched HR	7.41 (4.63, 11.86)	1.00 (ref)	5.71 (3.65, 8.92)	1.00 (ref)	0.33
Multivariable HR ^a	7.51 (4.20, 13.42)	1.00 (ref)	5.42 (3.11, 9.45)	1.00 (ref)	0.59
Age, sex and entry year matched rate difference/1000 PY	58.6 (34.0, 83.1)	0.0 (ref)	38.7 (21.8, 55.6)	0.0 (ref)	0.18
Multivariable-adjusted rate difference/1000 PY	56.2 (31.8, 81.2)	0.0 (ref)	36.3 (19.6, 53.0)	0.0 (ref)	0.15

^aIn addition to the matching variables, multivariable models were adjusted for the number of general practitioner visits, BMI, socioeconomic deprivation index, smoking status (i.e. never, former or current smokers), alcohol consumption (i.e. never, former or current drinkers), Charlson comorbidity index, comorbidities and medication use prior to the index date. Rates or rate differences (95% CI). HR: hazard ratio; PY: person-years; Ref: reference.

FIG. 1 Survival according to presence of dermatomyositis in early cohort (1999–2006) and late cohort (2007–2014)

myositis and time period by adding the time period variable and interaction terms to the models. We also calculated the absolute rate difference using an additive hazard model [12] for the two sub-cohorts and tested the additive interaction between myositis and time period. Our primary analysis used imputed missing values for BMI, smoking status, alcohol consumption and SDI, employing a sequential regression method, as previously described (IVEware for SAS, version 9.4, SAS Institute, Cary, NC, USA) [13]. To minimize random error, we imputed five datasets and then combined estimates from these datasets [14]. Given the changing

classification of DM and PM over time [15], we conducted a sensitivity analysis using the combined cohort of DM and PM to create an IIM cohort. We calculated 95% CIs for all HRs. All *P*-values were two-sided with a significance level set at 0.05.

Results

Dermatomyositis

At baseline, our study population included 186 DM patients and 1665 matched comparators without IIM in

TABLE 3 Association between PM and all-cause mortality according to time period

	1999–2006		2007–2014		P-value for interaction
	PM (n = 197)	Comparators (n = 1764)	PM (n = 210)	Comparators (n = 1884)	
Mean follow-up time, years	2.8 (2.1)	3.0 (2.1)	3.5 (2.6)	3.7 (2.5)	
Total follow-up time, PY	546	5250	727	6956	
Number of deaths	23	81	25	91	
Mortality rate/1000 PY	42.1 (26.7, 63.2)	15.4 (12.3, 19.2)	34.4 (22.3, 50.8)	13.1 (10.5, 16.1)	
Age, sex and entry year matched HR	2.98 (1.83, 4.87)	1.00 (ref)	3.41 (2.13, 5.46)	1.00 (ref)	0.46
Multivariable HR ^a	3.48 (1.93, 6.28)	1.00 (ref)	3.32 (1.85, 5.94)	1.00 (ref)	0.98
Age, sex and entry year matched rate difference/1000 PY	26.7 (9.2, 44.3)	0.0 (ref)	21.3 (7.6, 35.1)	0.0 (ref)	0.63
Multivariable-adjusted rate difference/1000 PY	24.0 (6.1, 41.9)	0.0 (ref)	19.3 (5.8, 32.8)	0.0 (ref)	0.77

^aIn addition to the matching variables, multivariable models were adjusted for the number of general practitioner visits, BMI, socioeconomic deprivation index, smoking status (i.e. never, former or current smokers), alcohol consumption (i.e. never, former or current drinkers), Charlson comorbidity index, comorbidities, and medication use prior to the index date. Rates or rate differences (95% CI). HR: hazard ratio; PY: person-years; Ref: reference.

FIG. 2 Survival according to presence of PM in early cohort (1999–2006) and late cohort (2007–2014)

the early cohort (1996–2006) and 224 DM patients and 2008 matched comparators in the late cohort (2007–2014) (Table 1). In the early cohort, the average age was 57 years, and 64% were female. In the late cohort, the average age was 58 years, and 66% were female. The early and late DM cohorts had similar socioeconomic deprivation index scores, BMI and Charlson comorbidity index scores. There tended to be more hyperlipidemia [13% (95% CI: 9%, 17%) vs 7% (95% CI: 3%, 10%)], chronic kidney disease [9% (95% CI: 6%, 13%) vs 1% (95% CI: 0.1%, 2%)], ischaemic heart

disease [11% (95% CI: 7%, 15%) vs 7% (95% CI: 3%, 11%)] and use of calcium channel blockers [18% (95% CI: 13%, 23%) vs 12% (95% CI: 7%, 17%)] and aspirin [18% (95% CI: 13%, 23%) vs 12% (95% CI: 8%, 17%)] in the late DM cohort compared with the early DM cohort. DM patients in the early cohort tended to have more GP visits than the comparison cohort [median 4 (IQR: 2, 7) vs 1 (IQR: 0, 4)]. Similarly, patients in the late DM cohort tended to have more GP visits than the comparison cohort [median 5 (IQR: 3, 9) vs 2 (IQR: 1, 5)].

In the early time period (1999–2006), there were 33 deaths in the DM cohort ($n=186$) over a mean follow-up time of 2.5 years, and 62 deaths in the matched comparison cohort ($n=1665$) over a mean follow-up time of 2.9 years (Table 2). This corresponded to a mortality rate (per 1000 PY) of 71.5 (95% CI: 49.2, 100.3) in the early DM cohort, in comparison to a mortality rate of 12.9 (95% CI: 9.9, 16.5) in the matched comparison cohort. In the late time period (2007–2014), there were 33 deaths in the DM cohort ($n=224$) over a mean follow-up time of 3 years, and 70 deaths in the matched comparison cohort ($n=2008$) over a mean follow-up time of 3.4 years. This corresponded to a mortality rate (per 1000 PY) of 49.1 (95% CI: 33.8, 68.9) in the late DM cohort, in comparison to a mortality rate of 10.4 (95% CI: 8.1, 13.1) in the matched comparison cohort.

The multivariable HR for death in the early DM cohort was 7.51 (95% CI: 4.20, 13.42). In the late DM cohort, there was no significant decrease in the risk of death compared with the early cohort (HR 5.42, 95% CI: 3.11, 9.45, P -value for interaction = 0.59) (Fig. 1 and Table 2). The multivariable-adjusted rate difference per 1000 PY was 56.2 (95% CI: 31.8, 81.2) in the early DM cohort and numerically lower at 36.3 (95% CI: 19.6, 53.0) in the late DM cohort, a statistically insignificant difference (P -value for interaction = 0.15) (Table 2).

Polymyositis

At baseline, our study population included 197 PM patients and 1764 matched comparators in the early cohort (1996–2006) and 210 PM patients and 1884 matched comparators in the late cohort (2007–2014) (Table 1). In the early cohort, the average age was 59 years, and 59% were female. In the late cohort, the average age was 59 years, and 62% were female. The early and late PM cohorts had similar socioeconomic deprivation index scores and BMI. There tended to be more hypertension (35% [95% CI: 29%, 42%] vs 30% [95% CI: 24%, 36%]), hyperlipidemia (15% [95% CI: 10%, 20%] vs 10% [95% CI: 6%, 14%]), chronic kidney disease (11% [95% CI: 6%, 15%] vs 3% [95% CI: 0.3%, 5%]) and use of calcium channel blockers (19% [95% CI: 13%, 24%] vs 14% [95% CI: 9%, 19%]) in the late PM cohort compared with the early PM cohort, similar to the trend seen in the DM cohorts. The early PM cohort tended to have more GP visits compared with the comparison cohort (median 5 [IQR: 2, 8] vs 2 [IQR: 0, 4]). Similarly, the late PM cohort tended to have more GP visits compared with the comparison cohort (median 6 [IQR: 3, 9] vs 2 [IQR: 0, 5]).

In the early time period (1999–2006), there were 23 deaths in the PM cohort ($n=197$) over a mean follow-up time of 2.8 years, and 81 deaths in the matched comparison cohort ($n=1764$) over a mean follow-up time of 3.0 years (Table 3). This corresponded to a mortality rate (per 1000 PY) of 42.1 (95% CI: 26.7, 63.2) in the early PM cohort, in comparison to a mortality rate of 15.4 (95% CI: 12.3, 19.2) in the matched comparison cohort. In the late time period (2007–2014), there were 25

deaths in the PM cohort ($n=210$) over a mean follow-up time of 3.5 years, and 91 deaths in the matched comparison cohort ($n=1884$) over a mean follow-up time of 3.7 years. This corresponded to a mortality rate (per 1000 PY) of 34.4 (95% CI: 22.3, 50.8) in the late PM cohort, in comparison to a mortality rate of 13.1 (95% CI: 10.5, 16.1) in the matched comparison cohort.

The multivariable HR for death in the early PM cohort was 3.48 (95% CI: 1.93, 6.28). In the late PM cohort, there was no statistically significant decrease in the risk of death (multivariable HR 3.32, 95% CI: 1.85, 5.94, P -value for interaction = 0.98) (Fig. 2 and Table 3). The multivariable-adjusted rate difference per 1000 PY was 24.0 (95% CI: 6.1, 41.9) in the early PM cohort and numerically lower at 19.3 (95% CI: 5.8, 32.8) in the late PM cohort, a statistically insignificant difference (P -value for interaction = 0.77) (Table 3).

Idiopathic inflammatory myositis

In the combined IIM cohort sensitivity analysis, baseline characteristics were similar to the individual DM and PM cohorts (Supplementary Table S2, available at *Rheumatology* online). The multivariable HR for death in the early IIM cohort was 4.71 (95% CI: 3.17, 7.01). In the late cohort, there was no statistically significant decrease in risk of death (multivariable HR 4.03, 95% CI: 2.71, 6.00, P -value for interaction = 0.70), similar to the primary analyses (Supplementary Table S3 and Supplementary Fig. S1, available at *Rheumatology* online). The multivariable adjusted rate difference per 1000 PY was 24.0 (95% CI: 6.1, 41.9) in the early IIM cohort and numerically lower at 19.3 (95% CI: 5.8, 32.8) in the late IIM cohort, a statistically insignificant difference (P -value for interaction = 0.77).

Discussion

In this general population-based cohort study, we found that excess all-cause mortality did not significantly improve among DM and PM patients in recent years (2007–2014 vs 1999–2006) compared with matched comparators. Although overall mortality rates were lower in DM and PM in the late cohorts, this trend was parallel to the improvement in mortality seen over time in the general population. The persistent excess mortality associated with DM and PM is in contrast to recent improving mortality trends seen in RA [6] and granulomatosis with polyangiitis [7], highlighting the need for improved management and treatment strategies in IIM.

Our results show higher mortality in DM compared with PM, and in both DM and PM compared with the general population. This finding agrees with population-based Scandinavian and Taiwanese cohort studies [1, 3–5]. A study from Finland from 1969 to 1985 showed that subjects with DM or PM had three times the risk of death compared with the general population [1]. Similarly, a more recent study from the Swedish National Patient Register from 2002–2011 found that

subjects with IIM (including DM, PM and inclusion body myositis) had 3.7 times the risk of death compared with the general population, with the highest mortality in the first year after IIM diagnosis [4]. Lastly, a population-based study from Taiwan from 2003–2007 showed standardized mortality ratios of 7.68 and 5.29 for DM and PM, respectively [5]. Our study extends from the prior literature by showing that this mortality gap has persisted in recent years.

The mechanisms behind the persistent mortality gap in IIM remain unclear. In contrast to other rheumatic diseases where mortality has improved over time, therapeutics for IIM remain limited to evidence from observational data rather than large randomized controlled trials [16]. In addition to few therapeutic advances, prior studies have implicated malignancy, interstitial lung disease (ILD) and cardiovascular complications as important drivers of morbidity and mortality in IIM. A Japanese cohort study of 197 patients showed a 5-year survival of 77% in DM and 91% in PM, with ILD representing the main cause of death [17]. A Dutch cohort study of 268 biopsy-proven myositis patients showed that 10% had disease-related death, most commonly due to ILD or malignancy [18]. Additionally, a cohort of 831 patients from the Johns Hopkins myositis center showed that myositis patients with ILD have significantly higher mortality compared with those without ILD (HR 2.13, 95% CI: 1.06, 4.25) [19]. Lastly, a prior study using a population-based database from British Columbia showed that risk of myocardial infarction (but not ischaemic stroke) was higher in subjects with PM and DM compared with comparators, particularly in the first year following PM/DM diagnosis [20]. These prior studies implicate malignancy, ILD and comorbidities including cardiovascular disease as important mechanisms behind the persistent mortality gap in IIM, and future IIM management strategies should emphasize screening for malignancy and cardiovascular disease in addition to novel therapeutic strategies.

Our study is one of the first studies evaluating recent mortality trends in DM and PM and has several strengths. Given that the THIN database is representative of the general UK population, our results are likely generalizable. Documentation of death in THIN has previously been shown to be accurate [8]. We used incident (rather than prevalent) cohorts and adjusted for several lifestyle factors and comorbidities that could confound the relationship between DM/PM and mortality. However, potential limitations of our study deserve comment. Our study was observational and therefore may be affected by residual or unmeasured confounding. Our study relied on physician diagnosis of IIM, which can be complex due to the heterogeneity of the disease [4]. Although the THIN database has been previously shown to be representative of the general UK population in demographics and disease prevalence, given the rarity of DM and PM, our analysis may have been underpowered for modest differences over time. To that end, further studies with larger sample sizes would be

valuable. Lastly, we did not have sufficient detail on the underlying causes of death, precluding cause-specific analyses. Regardless, all-cause mortality trends are critically important as they reflect the net health outcome of risks associated with IIM.

In conclusion, we found that there has been no significant improvement in excess mortality risk in DM and PM compared with matched comparators in a general population-based cohort. Given the persistent higher mortality over time in IIM compared with the general population, advances in disease-specific therapies are needed, in addition to screening for ILD, malignancy and cardiovascular disease, in order to achieve sustained improvement in outcomes.

Acknowledgements

The authors' work was supported by the National Institutes of Health (T32-AR-007258 to K.M.D. and P50-AR-060772 to H.K.C.), Canadian Institutes of Health Research Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Awards to L.L., and British Columbia Lupus Society Scholar Award and Walter & Marilyn Booth Research Scholar to J.A.A.-Z.

K.M.D., L.L., N.L., A.O., J.A.A.-Z., and H.K.C. conceptualized and designed the study and interpreted the data. All authors contributed to drafting the article and critically revising the manuscript for important intellectual content, and all authors approved the final version of the article for publication.

Disclosure statement: H.K.C. reports research support from AstraZeneca, and consultancy fees from Takeda, Selecta, GlaxoSmithKline, and Horizon. A.O. reports research support from Pfizer, Amgen, and Novartis, and consultancy fees from Abbvie, Amgen, Bristol Myers Squibb, Celgene, Corrona, Janssen, Lilly, Pfizer, and Novartis. The other authors report no conflicts of interest.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Data availability statement

The data underlying this article were accessed from The Health Improvement Network, <https://www.the-health-improvement-network.com/en/>.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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