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Trends in age and sex-specific dilated cardiomyopathy mortality in Italy, 2005–2017

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Aims Data regarding the dilated cardiomyopathy (DCM)-related mortality and relative time trends in the Italian population remain scant. We sought to assess the DCM mortality rates and relative trends among the Italian population between 2005 and 2017.

Methods Annual death rates by sex and 5-year age group were extracted from the WHO global mortality database. The age-standardized mortality rates, with relative 95% confidence intervals (95% CIs), also stratified by sex, were calculated using the direct method. Joinpoint regression analyses were used to identify periods with statistically distinct log linear trends in DCM-related death rates. To calculate nationwide annual trends in DCM-related mortality, we assessed the average annual percentage change (AAPC) and relative 95% CIs.

Results In Italy, the DCM age-standardized annual mortality rate decreased from 4.99 (95% CI: 4.97–5.02) deaths per 100 000 to 2.51 (95% CI: 2.49–2.52) deaths per 100 000 population. Over the entire period, men had a higher DCM-related mortality rates than women. Moreover, the mortality rate increased with age, with a seemingly exponential distribution and showing a similar trend among men and women. Joinpoint regression analysis revealed a linear decrease in age-standardized DCM-related mortality from 2005 to 2017 [AAPC: −5.1% (95% CI: −5.9 to −4.3, $P < 0.001$)] in the entire Italian population. However, the decline was more pronounced among women [AAPC: −5.6 (95% CI: −6.4 to −4.8, $P < 0.001$)] compared with men [AAPC: −4.9 (95% CI: −5.8 to −4.1, $P < 0.001$)].

Conclusion In Italy, the DCM-related mortality rates linearly declined from 2005 to 2017.

Keywords: cardiomyopathies, dilated cardiomyopathy, mortality

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Introduction

Dilated cardiomyopathy (DCM) represents the final common response of the myocardium to different genetic and environmental injuries,[1] characterized by ventricular dilatation and contractile dysfunction in the absence of abnormal loading conditions or coronary artery disease (CAD).[2] Previous epidemiological investigations have reported a DCM prevalence ranging from 1 : 2500 to 1 : 250 and estimated a global increase of about 30% over the last 10 years.[3,4] Although the current available data have shown a significant improvement in DCM patients' survival, as well as a lower rate of cardiovascular events, estimates of survival rates attributed to DCM outside of the referral center populations remain scant.[5,6] For epidemiological purposes, national survey data remain essential for obtaining reliable estimates of the proportion of deaths attributable to a specific cardiovascular condition, to prevent excess morbidity and mortality inequalities, and to establish adequate preventive measures. Therefore, the aim of the present study is to describe the DCM mortality rates and relative trend among the Italian population between 2005 and 2017.

Materials and methods

Data source

Annual death rates by sex and 5-year age group (up to and including 85 and over) were extracted from the freely publicly available WHO global mortality database (latest update: September 1, 2022).[7] Specifically, the WHO database systematically collects data on all registered deaths in a country. On a regular basis, Member States transmit the information to the WHO using standard procedures, including plausibility check, agreement with previous years, and validation against the International Classification of Disease (ICD) 10th Revision codes.[8] Previous investigations have demonstrated acceptable accuracy in validating diagnoses of DCM in administrative

registries using ICD-10 codes with a positive predictive value (PPV) of about 80%.[9]

Definition of dilated cardiomyopathy-related death

Deaths were considered related to DCM if the ICD code specific for the disease (I42.0) was listed as the primary cause of death in the death certificates, defined as 'the disease or event that started the chain of events that led to death'.[7]

Data extraction

Two authors (M.Z. and G.R.) extracted the number of DCM-related deaths, total deaths, and population size from the WHO mortality database for the period from 2005 to 2017 (the last available year for the data regarding the Italian population). This period was chosen considering that evidence-based management guidelines and treatment for DCM were relatively standardized. The study did not require institutional review board approval, as the analysis was based on de-identified and publicly available data.

Statistical analysis

DCM age-standardized mortality rates (ASMRs) per 100 000 people with the relative 95% confidence interval (95% CI) were calculated by standardizing the related deaths using the annual national population totals and the European Standard Population (ESP) with the direct method.[10] To calculate nationwide annual trends in DCM-related mortality, we assessed the annual percentage change (APC) as well as the average annual percentage change (AAPC) and relative 95% CIs. Joinpoint regression software determines the inflection points for each population of interest, and accordingly across the study period, time intervals of interest vary. A negative slope was defined as one in which the APC was significantly negative, conferring a decreasing trend while a positive one reflected an increasing trend. Statistical analyses were performed using Joinpoint regression (Joinpoint, version 4.6.0.0, National Cancer Institute, USA). Statistical significance was set at a *P*-value of 0.05 or less.

Results

Population and global nationwide mortality

Between 2005 and 2017, the Italian population increased from 58 462 375 (30 085 571 women) to 60 795 612 (31 294 022 women). The total number of deaths recorded was 7 804 106, of which 31 533 [0.40% (37.0% women, $n = 11\,675$)] had been primarily attributed to DCM according to the Italian death certificates.

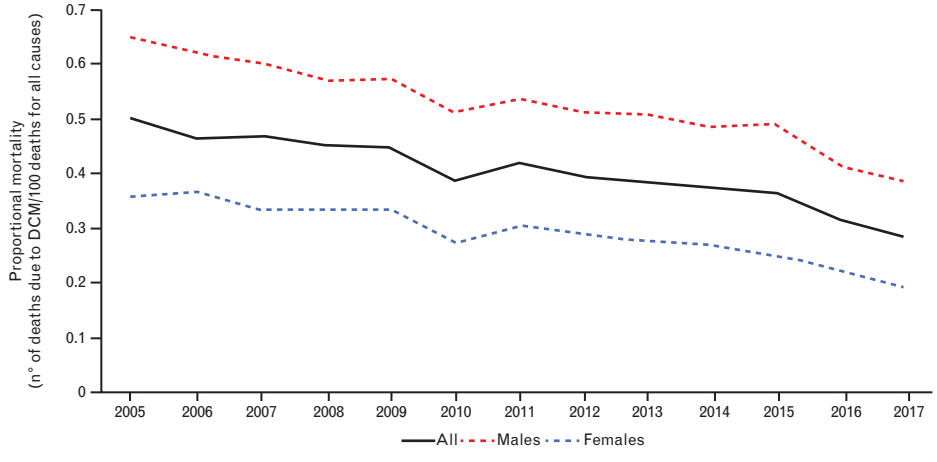
Proportional mortality

Less than 1% of total deaths were attributed to DCM; more precisely, the proportional DCM-related mortality rates decline from 0.50 to 0.28% in the entire population, showing a similar trend in both sexes (from 0.65 to 0.38% in men and from 0.35 to 0.19% in women, respectively) (Fig. 1). The crude DCM-related mortality rates declined from 4.89 (95% CI: 4.85–4.92) to 3.09 (95% CI: 3.07–3.11) deaths per 100 000 population.

Age-group dilated cardiomyopathy-related deaths

Table 1 summarizes the population size, number of DCM-related deaths, crude DCM-related mortality by age group and in the entire population, as well as the ASMR. Over the study period, the DCM age-standardized annual mortality rate decreased from 4.99 (95% CI: 4.97–5.02) deaths per 100 000 to 2.51 (95% CI: 2.49–2.52) deaths per 100 000

Fig. 1



Proportional mortality for dilated cardiomyopathy in Italy between 2005 and 2017.

Table 1 Annual dilated cardiomyopathy-related mortality rates in Italy, 2005–2017

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Number of deaths (DCM)	2842	2759	2683	2623	2644	2290	2499	2433	2333	2247	2357	1968	1875
	Crude DCM-related mortality rate by age group												
Age–class (years)													
<1	0.27	0.27	0.54	0.53	0.35	0.18	0.45	0.28	0.47	0.58	0.60	0.10	0.21
1–4	0.00	0.18	0.06	0.06	0.12	0.00	0.00	0.06	0.00	0.06	0.12	0.13	0.13
5–9	0.04	0.04	0.04	0.00	0.00	0.00	0.00	0.04	0.04	0.03	0.00	0.07	0.04
10–14	0.07	0.07	0.07	0.04	0.04	0.04	0.11	0.18	0.04	0.00	0.00	0.11	0.00
15–19	0.07	0.10	0.00	0.03	0.03	0.10	0.18	0.00	0.04	0.03	0.07	0.14	0.07
20–24	0.10	0.03	0.03	0.03	0.06	0.10	0.03	0.00	0.00	0.03	0.03	0.10	0.03
25–29	0.18	0.08	0.11	0.20	0.17	0.20	0.06	0.15	0.06	0.12	0.12	0.06	0.00
30–34	0.24	0.15	0.13	0.14	0.21	0.19	0.13	0.16	0.14	0.19	0.14	0.11	0.06
35–39	0.23	0.33	0.37	0.08	0.21	0.17	0.13	0.13	0.22	0.23	0.19	0.17	0.08
40–44	0.72	0.57	0.51	0.34	0.56	0.42	0.37	0.23	0.41	0.19	0.35	0.27	0.17
59–49	1.07	1.03	0.94	0.97	0.74	0.61	0.74	0.89	0.61	0.64	0.71	0.47	0.47
50–54	2.00	1.70	1.54	1.45	1.22	1.17	0.83	1.26	0.87	0.66	0.85	0.83	0.84
55–59	3.00	2.41	2.69	2.33	2.27	2.21	2.03	1.81	1.81	1.78	1.65	1.61	1.48
60–64	4.54	4.40	3.90	3.63	4.13	3.06	2.56	2.70	2.91	2.53	3.60	2.56	2.08
65–69	7.16	7.53	6.08	5.52	6.08	5.25	5.78	4.50	5.00	4.05	4.28	4.05	3.73
70–74	12.64	10.88	11.22	10.41	9.93	8.47	9.02	8.59	7.43	7.79	8.52	6.07	5.56
75–79	22.95	22.48	20.13	18.00	17.25	15.44	17.39	15.05	13.55	13.20	13.35	10.93	9.61
80–84	34.94	32.02	32.00	31.20	29.96	25.31	26.40	27.82	25.97	23.64	24.23	19.00	18.57
>85	55.29	51.85	49.78	51.26	49.93	40.71	48.64	45.57	42.70	40.70	39.34	33.58	33.17
Crude DCM-	4.89	4.67	4.54	4.38	4.39	3.78	4.2	4.08	3.87	3.69	3.88	3.24	3.09
Age-standardized related mortality rate	**4.99**	**4.66**	**4.4**	**4.2**	**4.14**	**3.51**	**3.8**	**3.6**	**3.36**	**3.16**	**3.28**	**2.69**	**2.51**

The colors represent the value of the observed crude and age-standardized annual dilated cardiomyopathy mortality rates, ranging from green (the lowest) to red (the highest).

population. Notably, over the entire period, men had higher DCM-related mortality rates than women. However, the mortality rate increased with age, with a seemingly exponential distribution and showing a similar trend among men and women, as evidenced by the heatmaps (Tables 2 and 3; Fig. 2).

Average annual percentage changes: overall trends in mortality

Joinpoint regression analysis revealed a linear significant decrease in age-standardized DCM-related mortality from 2005 to 2017 [AAPC: −5.1% (95% CI: −5.9 to −4.3, $P < 0.001$)] in the entire Italian population (Fig. 3). However, the decline was more pronounced among women [AAPC: −5.6 (95% CI: −6.4 to −4.8, $P < 0.001$)] compared with men [AAPC: −4.9 (95% CI: −5.8 to −4.1, $P < 0.001$)] (Fig. 4).

Discussion

Our study provides updated data regarding the DCM-related mortality rates among the Italian population, outside the referral centers, using the WHO mortality database. Less than 1% of total deaths in Italy between 2005 and 2017 were attributed to DCM. Moreover, DCM-related mortality increased with age with an apparent exponential distribution. Finally, there was a significant linear decrease in age-standardized DCM-related mortality, with a greater reduction observed in women compared with men.

Currently available data on DCM-related mortality predominantly come from referral centers, thus introducing a selection bias in the assessed population. This study addresses the knowledge gap on national mortality trends among patients with DCM in Italy. The strength of this analysis lies in the use of nationwide Italian registry data on DCM-related outcomes over a long-time interval as opposed to data from tertiary referral centers. Using an approach accounting for the independent prognostic role of age of DCM onset, the observed linear decrease in the ASMR confirmed a significant reduction in cardiovascular events in DCM patients, resulting in a significant increase in overall survival. Furthermore, our results demonstrate that the magnitude of the reduction in DCM-related[11–15] mortality is not surprisingly higher in the general population than in the reference centers.[6] Patients referred to third-level centers commonly have more a advanced disease stage or challenging clinical scenario for which the expert management of referral centers is required. These findings support how establishing a dedicated hub and spoke network system may have a deep impact on the management and outcome of patients with DCM.

This improvement could be partly explained by the diffusion of the integration of advanced noninvasive cardiac imaging to guide clinical management and decision-making that has deeply transformed the approach to prognostic stratification. The exemplar case is represented by cardiac magnetic resonance (CMR), which provides

Table 2 Annual dilated cardiomyopathy-related mortality rates for men in Italy, 2005–2017

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Number of deaths	1790	1721	1697	1634	1646	1463	1562	1512	1484	1408	1513	1244	1204
	Crude DCM-related mortality rate by age group												
Age–class (years)													
<1	0.35	0.18	0.52	0.52	0.51	0.00	0.52	0.18	0.74	0.57	0.39	0.20	0.21
1–4	0.00	0.24	0.00	0.00	0.11	0.00	0.00	0.12	0.00	0.12	0.12	0.00	0.13
5–9	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.07	0.00	0.07	0.07
10–14	0.14	0.07	0.00	0.07	0.07	0.00	0.14	0.00	0.07	0.00	0.00	0.07	0.00
15–19	0.07	0.14	0.00	0.07	0.00	0.21	0.14	0.00	0.07	0.00	0.14	0.29	0.07
20–24	0.13	0.00	0.06	0.06	0.06	0.13	0.06	0.00	0.00	0.00	0.06	0.19	0.00
25–29	0.31	0.16	0.16	0.33	0.28	0.34	0.06	0.30	0.12	0.24	0.18	0.12	0.00
30–34	0.31	0.22	0.13	0.18	0.32	0.34	0.10	0.11	0.27	0.33	0.22	0.17	0.00
35–39	0.38	0.49	0.66	0.12	0.21	0.25	0.22	0.27	0.27	0.32	0.29	0.25	0.15
40–44	1.09	1.00	0.90	0.52	0.84	0.69	0.63	0.34	0.75	0.25	0.46	0.51	0.35
45–49	1.91	1.64	1.55	1.55	1.28	0.98	1.20	1.43	1.07	1.01	1.10	0.78	0.87
50–54	3.02	2.97	2.64	2.64	2.18	1.99	1.44	1.94	1.49	1.07	1.30	1.31	1.46
55–59	4.84	3.92	4.53	3.35	3.82	3.26	3.06	2.85	3.19	2.74	2.69	2.78	2.47
60–64	7.71	7.02	6.42	6.16	7.18	5.07	4.04	4.52	4.56	4.51	5.99	4.01	3.61
65–69	11.55	10.91	9.60	9.32	9.85	8.58	9.32	7.18	8.26	5.98	6.65	6.49	5.97
70–74	21.26	17.74	18.37	16.30	16.06	13.28	14.95	14.18	11.95	11.69	13.45	9.61	8.55
75–79	37.19	38.05	31.60	28.72	26.99	24.39	28.64	25.13	20.89	21.62	21.14	16.69	16.23
80–84	56.56	50.28	54.88	51.16	48.90	40.92	44.89	43.52	42.43	38.56	38.51	29.50	30.85
>85	79.08	77.60	75.27	78.27	72.51	68.42	71.02	69.30	68.05	63.46	65.03	52.83	49.45
Crude DCM-related mortality rate	6.38	6.03	5.90	5.64	5.65	4.99	5.44	5.26	5.09	4.79	5.14	4.23	4.10
Age-standardized related mortality rate	7.86	7.35	7.07	6.68	6.50	5.69	6.02	5.69	5.41	5.01	5.27	4.23	4.00

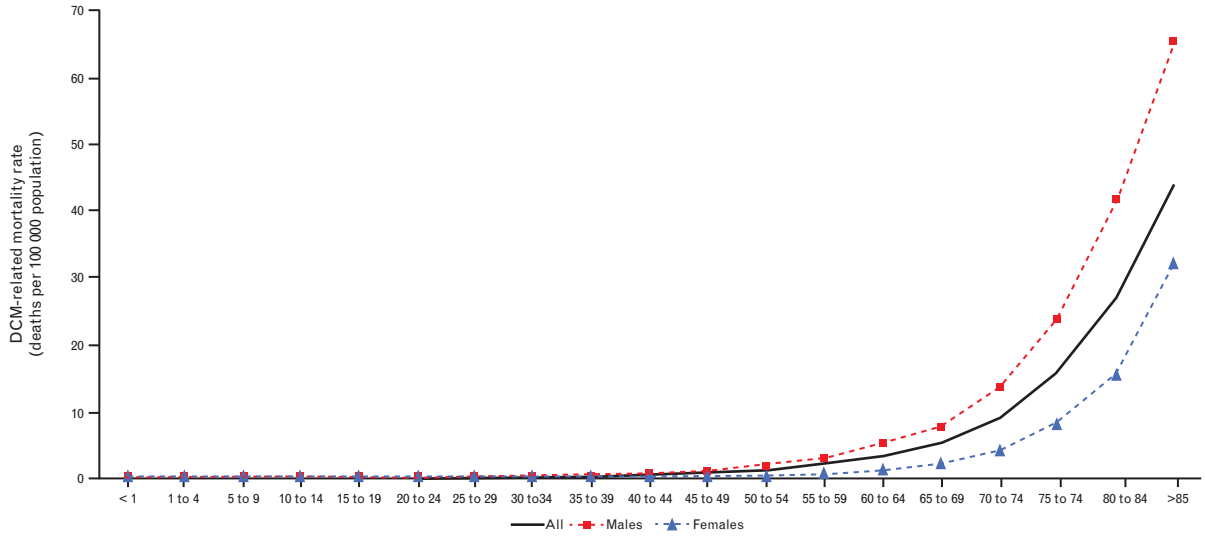
The colors represent the value of the observed crude and age-standardized annual dilated cardiomyopathy mortality rates, ranging from green (the lowest) to red (the highest).

Table 3 Annual dilated cardiomyopathy-related mortality rates for women in Italy, 2005–2017

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Number of deaths	1052	1038	986	989	998	827	937	921	849	839	844	724	671
	Crude DCM-related mortality rate by age group												
Age–class (years)													
<1	0.19	0.37	0.56	0.55	0.18	0.36	0.37	0.38	0.20	0.60	0.83	0.00	0.22
1–	0.00	0.12	0.12	0.12	0.12	0.00	0.00	0.00	0.00	0.00	0.13	0.26	0.13
5–9	0.08	0.08	0.07	0.00	0.00	0.00	0,00	0.07	0.07	0.00	0.00	0.07	0.00
10–14	0.00	0.07	0.15	0.00	0.00	0.07	0.07	0.37	0.00	0.00	0.00	0.14	0.00
15–19	0.07	0.07	0.00	0.00	0.07	0.00	0.21	0.00	0.00	0.07	0.00	0.00	0.07
20–24	0.07	0.06	0.00	0.00	0.07	0.07	0.00	0.00	0.00	0.07	0.00	0.00	0.07
25–29	0.05	0.00	0.06	0.06	0.06	0.06	0.06	0.00	0.00	0.00	0.06	0.00	0.00
30–34	0.18	0.09	0.13	0.09	0.09	0.05	0.16	0.21	0.00	0.06	0.06	0.06	0.12
35–39	0.08	0.17	0.08	0.04	0.21	0.08	0.04	0.00	0.18	0.14	0.10	0.10	0.00
40–44	0.35	0.13	0.12	0.16	0.28	0.16	0.12	0.21	0.08	0.12	0.25	0.04	0.00
45–49	0.25	0.43	0.33	0.40	0.22	0.25	0.29	0.37	0.16	0.28	0.32	0.16	0.08
50–54	1.01	0.47	0.33	0.30	0.29	0.38	0.24	0.60	0.27	0.26	0.42	0.37	0.24
55–59	1.23	0.96	0.93	1.36	0.79	1.21	1.05	0.82	0.50	0.88	0.67	0.52	0.55
60–64	1.62	1.97	1.55	1.27	1.28	1.18	1.19	1.00	1.38	0.69	1.38	1.21	0.67
65–69	3.29	4.55	2.96	2.13	2.72	2.26	2.59	2.08	2.05	2.29	2.11	1.83	1.70
70–74	5.69	5.32	5.37	5.55	4.83	4.44	4.01	3.85	3.58	4.45	4.28	3.01	2.96
75–79	12.96	11.51	11.94	10.25	10.13	8.81	8.94	7.39	7.91	6.64	7.22	6.37	4.32
80–84	22.97	21.61	19.00	19.42	18.59	15.76	14.88	17.87	15.36	13.86	14.71	11.88	10.10
>85	45.42	41.24	39.18	39.88	40.31	28.80	38.96	35.17	31.46	30.48	27.61	24.63	25.49
Crude DCM-related mortality rate	3.50	3.41	3.19	3.20	3.21	2.65	3.04	2.98	2.72	2.67	2.69	2.31	2.15
Age-standardized related mortality rate	3.01	2.84	2.61	2.53	2.48	2.04	2.26	2.16	1.94	1.89	1.89	1.59	1.42

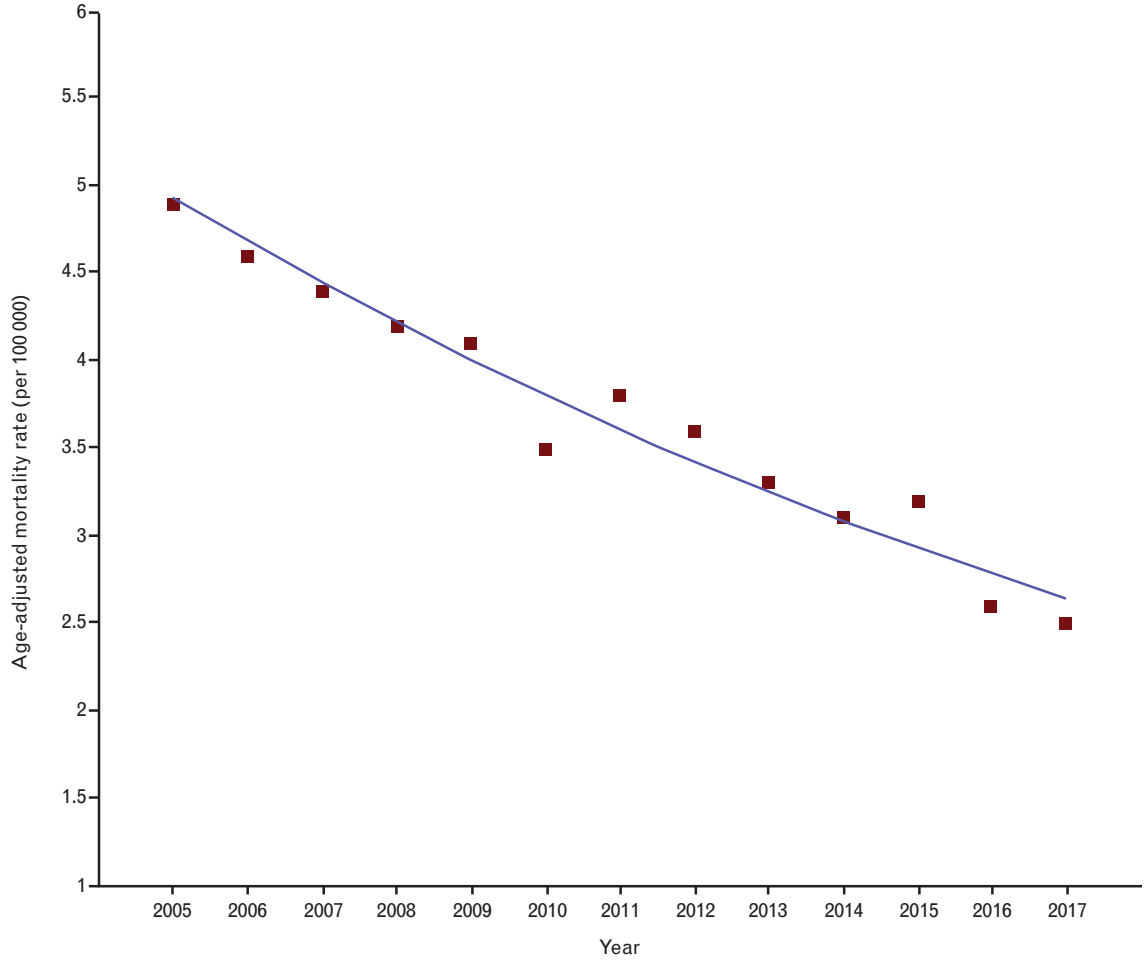
The colors represent the value of the observed crude and age-standardized annual dilated cardiomyopathy mortality rates, ranging from green (the lowest) to red (the highest).

Fig. 2



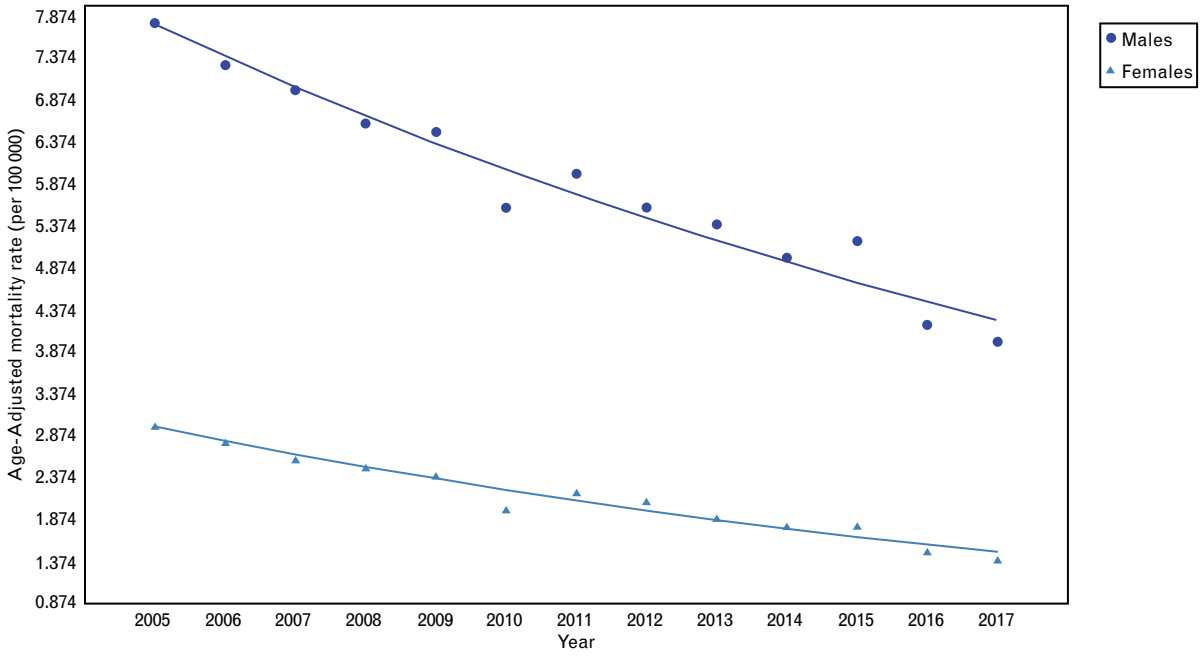
Dilated cardiomyopathy-related mortality rates in Italy by age group and sex, 2005–2017.

Fig. 3



Time trend in age-adjusted dilated cardiomyopathy-related mortality rates between 2005 and 2017 in the overall Italian population.

Fig. 4



Time trend in age-adjusted dilated cardiomyopathy-related mortality rates by sex between 2005 and 2017 in the Italian population.

important diagnostic and prognostic information, aiding clinicians in addressing specific treatments (i.e. device therapy) in patients with ventricular reverse remodeling or increased arrhythmic risk.[16] In this regard, clinical benefits are also due to the use of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) in the treatment of DCM patients.[17] Furthermore, the prognosis for DCM has improved substantially during the last decades also due to earlier diagnoses through systematic familial screening, as well as the novel findings derived from the analysis of interactions between genotype and clinical phenotype.[18]

Our study confirms and expands the knowledge on 'gender differences' in DCM-related outcomes. In our analysis, women had the greatest reduction in DCM-related mortality rates. This finding is in line with previous studies reporting a more favorable long-term outcome in women affected by DCM and myocarditis experiencing lower rates of cardiovascular and arrhythmic events compared with men.[19,20] Several factors have been hypothesized to be involved in sex differences, including a higher percentage of men diagnosed with DCM compared with women,[21] and the potential role of sex hormones in cardiac remodeling with a protective effect exerted by estrogens on the development of adverse cardiac remodeling as opposed to testosterone.[22–24] Although available data suggest that female sex is an independent prediction of cardiovascular outcomes,[25,26] current understanding of the sex-related mechanism(s) in cardiovascular diseases is a gray area requiring further dedicated research (Supplementary file 1, http://links.lww.com/JCM/A555, Supplementary file 2, http://links.lww.com/JCM/A556).

Limitations

To our knowledge, this is the first study to report the DCM-related mortality trend in a European country using nationwide data and outside referral centers. Our analysis has several limitations. In the present investigation, we were not able to also perform dedicated sub-analyses considering the change in cardiovascular comorbidities, which were not provided by the WHO data set, as well as the incidence of DCM in the Italian population. Indeed, the real number of DCM cases is difficult to assess, as most of the data are generally derived from referral center and/or autoptic studies, and therefore they are not representative of the entire population. Furthermore, being that our results are based on a large administrative data set, we were not able to classify patients according to their specific risk of adverse events. Indeed, etiological characterization of DCM patients (i.e. genetically determined, post myocarditis, alcohol, chemotherapy, or tachycardia-induced) and data reflecting the functional status of the heart [such as left ventricular ejection fraction, New York Heart Association (NYHA) functional class, medications, valvular disease, or previous implantation of ICDs or CRT]

represent an important aspect for prognostication.[6] These characteristics are not available in the WHO mortality data set. Moreover, we cannot assess the contribution of life-threatening arrhythmic events or sudden cardiac death; indeed, the used database only reports the leading cause of death without specific data regarding other contributing factors or underlying disease. Similarly, no information was available regarding the competing causes of death. However, the above-mentioned limitations represent a major issue when large administrative data are used for epidemiological analyses. Finally, the use of ICD-10 codes on death certificates may be associated with miscoding, which may have biased our results.

Conclusion

Our study provides an updated analysis on DCM-related mortality attributable to DCM in Italy, which linearly declined from 2005 to 2017 and resulted higher than that observed in referral centers for DCM. Continued monitoring of trends in cardiomyopathies is important to ensure appropriate diagnostic and therapeutic strategies improving the development of public health approaches to prevent DCM mortality.

Conflicts of interest

There are no conflicts of interest.

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