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Multiple myeloma in Brazil: an assessment of Global Burden Disease study 2019

Mieloma múltiplo no Brasil: uma avaliação do estudo da Carga Global de Doenças 2019

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ABSTRACT Multiple myeloma is the second most common hematological cancer; it accounts for approximately 10% of all hematologic malignancies and 1%-2% of all cancer diagnoses. From 1990 to 2019, an ecological study was conducted to describe and evaluate trends in Brazil's morbidity, mortality, and disease. The Global Burden of Disease data described age-standardized (+40 years) incidence, prevalence, mortality, disability-adjusted life years, and its components in Brazil and across its 27 federative units according to sex and Socio-demographic Index quintiles. Trends were estimated using linear regression and expressed as Average Annual Percentage Changes (AAPC) and 95% Confidence Intervals (CI). Ascending trends of the measures were found for both sexes in Brazil and its federative units. Mortality increased to a lesser extent than incidence (AAPC=1.3%; 95%CI=1.2-1.3 vs. AAPC=1.5%; 95%CI= 1.5-1.5 for men; AAPC=0.9%; 95%CI=0.9-0.9 vs. AAPC=1.1%; 95%CI=1.1-1.2 for women), resulting in higher rising trends in prevalence for both sexes. All the measures were significantly higher in high- and high-middle socio-demographic quintiles; however, higher ascending trends were found in lower socio-demographic quintiles. Aging, level of development, diagnosis, and treatment appear to explain Brazil's ascending multiple myeloma rates and their differences among the federative units.

KEYWORDS Multiple myeloma. Incidence. Mortality, disability-adjusted life years. Brazil.

RESUMO *O mieloma múltiplo é o segundo câncer hematológico mais comum; representa aproximadamente 10% de todas os cânceres hematológicos e 1%-2% de todos as neoplasias. Foi conduzido um estudo ecológico para descrever a morbidade, a mortalidade e a carga da doença no Brasil e suas 27 unidades federativas e avaliar tendências entre 1990-2019. Dados do estudo da Carga Global de Doenças foram avaliados para descrever medidas ajustadas por idade: incidência, prevalência, mortalidade, anos de vida ajustados pela incapacidade e seus componentes de acordo com sexo e Índice Sociodemográfico. As tendências foram estimadas usando regressão linear e expressas como Variação Percentual Anual Média (AAPC) e Intervalos de Confiança (IC) 95%. Tendências ascendentes das medidas foram observadas. A mortalidade aumentou em menor extensão comparada à incidência (AAPC=1,3%; IC95%=1,2-1,3 vs. AAPC=1,5%; IC95%=1,5-1,5 homens; AAPC=0,9%; IC95%=0,9-0,9 vs. AAPC=1,1%; IC95%=1,1-1,2 mulheres), resultando em tendências crescentes da prevalência para ambos os sexos. Todas as medidas foram mais altas nos quintis do índice sociodemográfico alto e médio-alto; tendências ascendentes mais altas foram encontradas em quintis do índice sociodemográfico mais baixos. Envelhecimento, nível de desenvolvimento, acesso ao diagnóstico e tratamento parecem explicar as medidas ascendentes do mieloma múltiplo no Brasil e suas diferenças entre as unidades federativas.*

PALAVRAS-CHAVE *Mieloma múltiplo. Incidência. Mortalidade. Anos de vida ajustados pela incapacidade. Brasil.*

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Introduction

Multiple Myeloma (MM) is an incurable hematological malignancy that primarily affects older adults[1]. It is characterized by the proliferation of clonal plasma cells in the bone marrow, resulting in damage to end organs (hypercalcemia, renal failure, anemia, or lytic bone lesions – CRAB features)[1,2]. MM usually evolves from asymptomatic conditions of Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering MM (SMM) to symptomatic MM at progression rates of approximately 1% and 10% per year, respectively[1]. Known risk factors for MM are aging, male sex, black race, genetic factors[1,2], family history of MM[3], high Body Mass Index (BMI)[4], and occupational exposures, such as pesticides[5,6].

MM is the second most common hematological cancer; it accounts for approximately 10% of all hematologic malignancies and 1%-2% of all cancer diagnoses. Globally, from 1990 to 2019, the age-standardized incidence rate of MM has increased from 1.73 cases per 100,000 to 1.92 cases per 100,000, with a significant age-standardized prevalence increase [4.21 (95% Uncertainty Interval – UI, 3.86-4.64) to 5.55 (95% UI, 4.89-6.18)] and the downward tendency of age-standardized mortality rates since the early 2000's[4]. These reflect the global disease burden estimated at 2.5 million Disability-Adjusted Life Years (DALYs) in 2019, corresponding to an age-standardized rate of 30.26 DALYs per 100,000[7].

Although MM still has no cure, the disease is treatable. Increasing survival rates have been attributed to the availability of Autologous Stem Cell Transplantation (ASCT)[8,9] and to the Introduction of Immunomodulatory Drugs – IMiDs (e.g., thalidomide and its analog lenalidomide) and Proteasome Inhibitor – PI drugs (e.g., bortezomib) in the MM treatment in the early 2000's[10,11]. These drug classes are recommended to be used in the induction therapy followed by ASCT in transplant-eligible newly diagnosed MM patients and preferred first- line therapy for patients unsuitable for transplantation in developed countries[12,13].

Despite the advances in the MM treatment, there are marked inequalities concerning access to ASCT[8,9] and drug availability worldwide[10,14]. In Brazil, thalidomide (2002) and bortezomib (2020) have been made available free of charge through the national Unified Health System (Sistema Único de Saúde – SUS) for patients treated in public (High-Complexity Oncology Centers – CACONs and High-Complexity Oncology Units – UNACONs) and private specialized health centers. Lenalidomide was approved for MM treatment in Brazil in 2017[15]; however, it was not incorporated into SUS and made accessible without costs for use[16].

Some studies have provided valuable knowledge on MM epidemiology and addressed the influence of factors such as population growth, aging, structure of health care system, and treatment availability on the burden of disease in high- to low-income countries[3,4,10,17,18]. Age-standardized mortality rates have decreased in high Socio-demographic Index (SDI) countries yet have shown a rising trend in low- to high-middle SDI countries[4,10] as in many countries of Latin America[3]. Age-standardized incidence rates have increased globally. Particularly in low- to middle-SDI regions, the increase in incidence rates has been regarded as due to aging and population growth[10]. In addition, the authors pointed out that disparities in access to treatment (ASCT and novel therapies) and early diagnosis could explain the geographical heterogeneity of MM. The pattern of disease is also different between sexes, affecting mainly men. Although some risk factors for MM have been established (e.g., race, family history of MM, BMI, and occupational exposures), further investigation on etiologic factors is still needed[4-6,10].

MM estimates are not released periodically in Brazil; thus, reporting epidemiological patterns of the disease is crucial to inform national health decision-making and planning and to guide research. Therefore, we performed a

comprehensive analysis of the Global Burden of Disease (GBD) study 2019 to describe the epidemiological pattern of MM in Brazil. Our objective was to report age-standardized (+40 years) incidence, mortality, DALY, years of life lost (YLL) and years lived with disability (YLD) and assess trends in morbidity, mortality, and burden of MM from 1990 to 2019, by age and SDI group in Brazil, across its 27 federative units.

Material and methods

This is a time-series ecological study using data from the GBD study. Data on MM were obtained to calculate incidence, prevalence, mortality, DALY, and its components – YLL and YLD of MM in Brazil between 1990 and 2019. Data were extracted from the Global Health Data Exchange (GHDx) query tool[7,19]. C88 and C90 codes of the International Disease Classification, tenth revision (ICD-10) were considered for MM definition.

GBD uses standard approaches for data correction. In the case of mortality, the main adjustments include the redistribution of unspecific codes (garbage codes) or codes that cannot be considered the underlying cause of death. Mortality was adjusted for all-cause mortality separately estimated through a process called 'CodCorrect', as reported by other authors[10,20,21]. Incidence data were derived from population-based cancer registries, as described elsewhere[10].

GBD calculates DALYs for MM as the sum of the YLL. YLL is calculated by the difference between a standard life expectancy and the age at death, and YLD is obtained by multiplying the prevalence by disability weights for mutually exclusive sequelae of MM[10].

We used age-standardized (40+ years) measures to calculate incidence, mortality rates DALYs, YLL, and YLD, and prevalence over the 30-year study period, according to sex and federative units and SDI group. SDI is a composite indicator based on the total fertility rate under the age of 25, mean education for those ages 15 and older, and lag-distributed income per capita. It varies from 0 (minimum level of development) to 1 (maximum level of development), allowing the comparison of the level of development relevant to health across Brazilian federative units[22]. We calculated SDI quintiles annually between 1990 and 2019 for Brazil and all its 27 federative units, which were categorized into five groups: low-, low-middle-, middle- , highmiddle-, and high-quantile.

A direct method was employed to standardize all health indicators, using the world population as a reference. All rates were expressed per 100,000. The Average Annual Percentage Change (AAPC), with a 95% Confidence Interval (CI), was calculated to identify trends for MM measures in Brazil and its federative units by sex and SDI quintiles. AAPC is the weighted average of the angular coefficients of the regression line, with weights equal to the length of each segment throughout the interval. An increase or decrease in trend is statistically significant when different from 0 ($p < 0.05$) and stable when equal to 0 ($p > 0.05$)[23]. Trend analysis was carried out by linear regression using the Joinpoint regression program, version 4.9.1.0 – April 11, 2022, from the Surveillance, Epidemiology and End Results program (SEER) of the National Cancer Institute[24].

This study complies with the Resolution nº 466/2012[25], which regulates human subject research in Brazil. The Ethics Committee of the Universidade Federal de Minas Gerais approved the study (CAAE 62803316.7.0000.5149, Opinion Number 1.873.624).

Results

Incidence and prevalence

In Brazil, 1,240 and 4,843 new cases (+40 years, both sexes) of MM were registered in

1990 and 2019, respectively. There was a rising trend in the incidence of MM for both sexes over the period. Men had the largest incidence (from 4.40/100,000 in 1990 to 6.78/100,000 in 2019 – AAPC= 1.5; 95%CI=1.5-1.5) compared to women (3.97/100,000 in 1990 and 5.50/100,000 in 2019 – AAPC= 1.1; 95%CI=1.1;1.12) (*table 1*). In all federative units, there was an upward incidence trend from 1990 to 2019 for both sexes (*table 1*). The lowest rates among men were found in the state of Amapá (2.21/100,000 in 1990 vs. 3.96/100,000 in 2019) and the highest in the Distrito Federal (8.55/100,000 in 1990 vs. 10.35/100,000 in 2019). The most pronounced increasing trends in incidence were observed in Bahia and the least one in the Distrito Federal. In women, the lowest rates were in Maranhão in 1990 (2.08/100,000) and Pará in 2019 (2.92/100,000); the highest incidences were observed in the Distrito Federal in both periods (7.01 and 8.56/100,000 in 1990 and 2019, respectively). Incidence rose for all SDI groups; the most increasing trends were found in the low- and low-middle SDI quintiles for men (AAPC= 2.2; 95%CI=2.1-2.3 AAPC= 2.2; 95%CI=2.1-2.2, respectively) and in the low SDI quintile for women (AAPC= 1.9; 95%CI=1.9-2.2) (*figure 1A*, *table 4*).

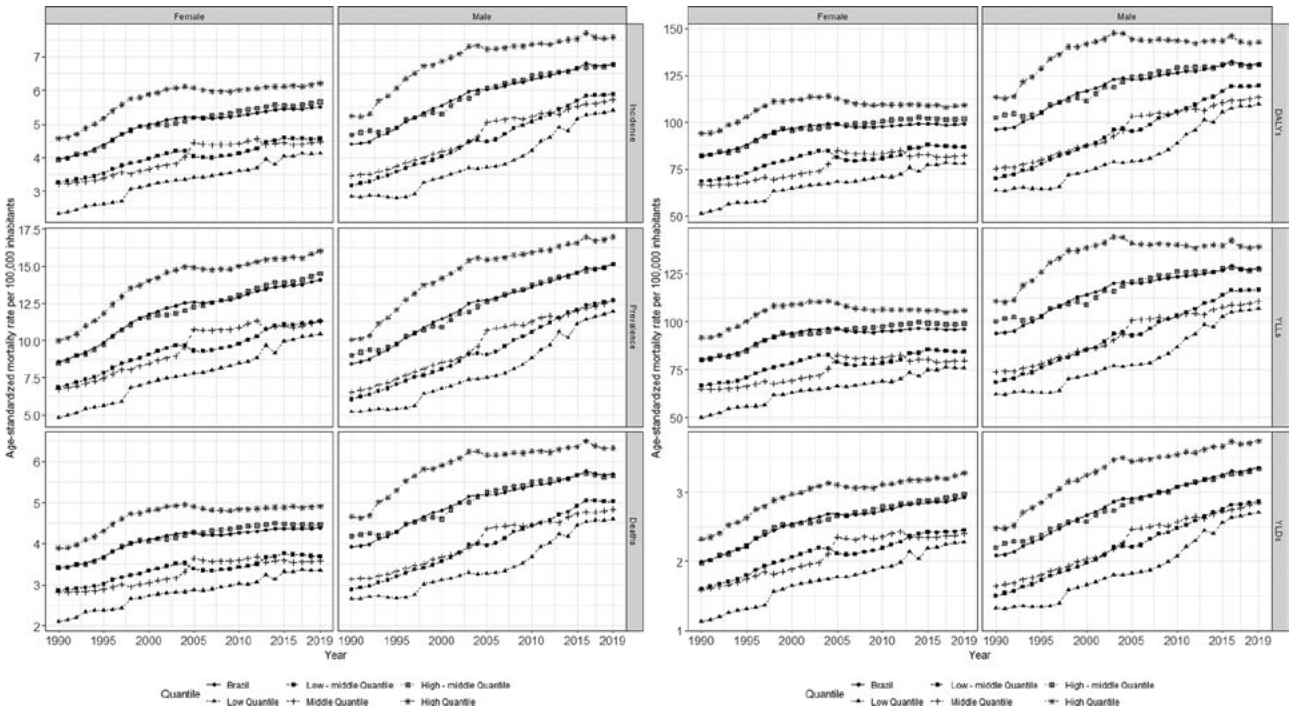
The number of prevalent cases (+40 years) of MM for both sexes was 2,649 in 1990 and 11,820 in 2019. Prevalence among men in Brazil was 8.45/100,000 in 1990 and 15.10/100.000 in 2019, corresponding to an ascending trend of 2.0% per year (95%CI=2.0-2.1). Among women, annual changes in prevalence increased by 1.7% (95%CI=1.7-1.8) (8.58/100,000 in 1990 and 14.12/100.000 in 2019) (*table 1*). The lowest rates in men were found in Amapá e and the highest in the Distrito Federal. In women, the lowest prevalence rates were in Maranhão (1990) and Pará (2019) and the largest in the Distrito Federal in both periods. Increasing trends in the prevalence rates were observed for all Brazilian States over the period, with the higher rising trends registered in Maranhão and the lowest ones in Rio de Janeiro, Goiás, and the Distrito Federal (*table 1*). There were increasing prevalence trends for all SDI groups, with the low-SDI quintile group having the highest changes for both sexes (*figure 1A*, *table 4*).

Table 1. Age-standardized incidence rate and prevalence per 100,000 and Average Annual Percent Change (AAPC) by sex, according to Federative unit and Brazil, 1990-2019

	Incidence						Prevalence					
	Male			Female			Male			Female		
	Years		AAPC	Years		AAPC	Years		AAPC	Years		AAPC
Federative unit	**1990**	**2019**	**(95%CI)**	**1990**	**2019**	**(95%CI)**	**1990**	**2019**	**(95%CI)**	**1990**	**2019**	**(95%CI)**
Acre	2.45	4.64	2.2 (2.1;2.3)	2.44	3.87	1.6 (1.6;1.7)	4.32	9.67	2.8 (2.7;2.9)	4.91	9.37	2.2 (2.2;2.3)
Alagoas	2.73	4.64	1.9 (1.8;1.9)	2.56	3.71	1.3 (1.2;1.3)	4.92	10.02	2.5 (2.4;2.5)	5.04	9.04	2.0 (2.0;2.1)
Amapá	2.21	3.96	2.0 (2.0;2.1)	2.57	4.57	2.0 (1.9;2.1)	4.26	8.51	2.4 (2.3;2.5)	5.62	11.34	2.4 (2.4;2.5)
Amazonas	2.74	4.45	1.7 (1.7;1.8)	2.40	3.34	1.1 (1.1;1.2)	5.15	9.73	2.2 (2.2;2.3)	4.98	8.37	1.9 (1.8;1.9)
Bahia	2.98	6.61	2.8 (2.7;2.9)	3.34	4.93	1.3 (1.3;1.4)	5.67	14.42	3.3 (3.2;3.4)	6.96	12.38	2.0 (1.9;2.0)
Ceará	3.30	6.02	2.1 (2.1;2.2)	3.12	4.52	1.3 (1.2;1.3)	6.46	13.67	2.7 (2.6;2.7)	6.73	11.73	2.0 (1.9;2.0)
Distrito Federal	8.55	10.35	0.6 (0.5;0.8)	7.01	8.56	0.7 (0.6;0.7)	15.96	24.20	1.4 (1.2;1.6)	15.26	23.38	1.4 (1.3;1.5)
Espírito Santo	4.21	7.34	1.9 (1.9;2.0)	3.91	5.87	1.4 (1.4;1.4)	8.11	16.39	2.5 (2.4;2.6)	8.48	15.20	2.0 (2.0;20)
Goiás	4.82	6.72	1.2 (1.1;1.2)	4.36	5.39	0.7 (0.7;0.8)	9.39	15.17	1.6 (1.6;1.7)	9.29	13.91	1.4 (1.4;1.5)
Maranhão	2.87	5.13	2.0 (1.9;2.1)	2.08	3.72	2.1 (2.0;2.2)	5.12	10.74	2.6 (2.5;2.7)	4.31	9.11	2.7 (2.6;2.8)
Mato Grosso	2.85	4.51	1.7 (1.6;1.8)	3.04	4.32	1.2 (1.2;1.3)	5.38	10.00	2.2 (2.1;2.3)	6.43	10.82	1.8 (1.8;1.9)
Mato Grosso do Sul	3.76	5.88	1.5 (1.4;1.7)	3.60	4.88	1.1 (1.1;1.1)	7.22	12.76	2.0 (1.9;2.0)	7.75	11.96	1.5 (1.5;1.6)
Minas Gerais	5.04	7.14	1.2 (1.1;1.2)	4.12	5.88	1.2 (1.2;1.3)	9.67	16.08	1.7 (1.7;1.8)	8.81	15.22	1.9 (1.8;1.9)
Pará	2.61	4.25	1.7 (1.6;1.8)	2.26	2.92	0.9 (0.8;0.9)	4.80	9.04	2.2 (2.1;2.3)	4.59	7.07	1.5 (1.5;1.5)
Paraíba	3.46	5.78	1.8 (1.7;1.9)	3.46	4.55	1.0 (0.9;1,0)	6.78	13.04	2.3 (2.2;2.4)	7.39	11.62	1.6 (1.6;1.6)
Paraná	4.15	6.94	1.8 (1.7;1.9)	3.71	5.58	1.5 (1.4;1.5)	7.87	15.37	2.3 (2.3;2.4)	7.76	14.19	2.1 (2.1;2.2)
Pernambuco	3.02	5.93	2.4 (2.3;2.5)	3.12	4.83	1.5 (1.4;1.6)	5.54	12.57	2.9 (2.8;3.0)	6.32	11.70	2.2 (2.1;2.3)
Piauí	2.97	4.43	1.4 (1.3;1.4)	2.70	3.59	1.0 (1.0;1.0)	5.67	9.77	1.9 (1.8;2.0)	5.76	9.06	1.6 (1.6;1.6)
Rio de Janeiro	5.22	7.28	1.2 (1.1;1.2)	4.66	5.96	0.8 (0.8;0.9)	9.79	15.75	1.7 (1.6;1.7)	9.96	14.88	1.4 (1.3;1.4)
Rio Grande do Norte	3.57	6.17	1.8 (1.7;1.9)	3.47	5.16	1.4 (1.3;1.4)	6.98	13.84	2.3 (2.2;2.4)	7.52	13.42	2.0 (2.0;20)
Rio Grande do Sul	4.91	7.52	1.5 (1.4;1.5)	4.09	5.61	1.1 (1.1;1.2)	9.59	17.13	2.0 (2.0;2.1)	9.18	14.67	1.6 (1.6;1.7)
Rondônia	3.34	4.86	1.4 (1.2;1.6)	2.88	3.60	0.8 (0.8;0.9)	5.88	10.57	2.1 (2.0;2.3)	5.57	8.84	1.6 (1.5;1.7)
Roraima	3.79	5.16	1.1 (1.0;1.2)	3.57	5.25	1.4 (1.3;1.5)	6.84	11.02	1.7 (1.6;1.7)	7.34	12.74	1.9 (1.9;2.0)
Santa Catarina	4.70	7.10	1.5 (1.4;1.6)	4.26	5.77	1.1 (1.0;1.1)	9.05	16.41	2.1 (2.0;2.1)	9.24	15.50	1.8 (1.8;1.8)
São Paulo	5.65	7.84	1.1 (1.1;1.2)	4.88	6.61	1.1 (1.0;1.1)	10.94	17.62	1.6 (1.6;1.7)	10.80	17.08	1.6 (1.5;1.6)
Sergipe	2.80	4.66	1.7 (1.7;1.8)	3.22	4.18	0.9 (0.9;0.9)	5.14	10.09	2.3 (2.2;2.4)	6.51	10.34	1.6 (1.6;1.6)
Tocantins	3.09	6.20	2.5 (2.4;2.5)	2.18	3.19	1.3 (1.2;1.3)	5.71	13.51	3.0 (3.0;3.1)	4.52	8.06	2.0 (1.9;2.1)
Brazil	**4.40**	**6.78**	**1.5 (1.5;1.5)**	**3.97**	**5.50**	**1.1 (1.1;1.2)**	**8.45**	**15.10**	**2.0 (2.0;2.1)**	**8.58**	**14.12**	**1.7 (1.7;1.8)**

Source: GHDx[19].
AAPC: Average Annual Percent Change; CI: Confidence Interval.

Figure 1. Age-standardized measures per 100,000, by sex according to Socio-demographic Index (SDI) quintiles. Brazil, 1990-2019. (A) incidence, prevalence, and mortality; (B) Disability-Adjusted Life Years (DALYs), Years of Life Lost (YLLs), and Years Lived with Disability (YLDs)



Source: GHDx[19].

Mortality

Higher mortality rates of MM were observed in Brazil in 2019 for men and women; however, showing a slightly lower upward trend in comparison to incidence. Incidence increased in men from 3.93/100,000 in 1990 to 5.68/100,000 in 2019 (AAPC=1.3; 95%CI=1.2-1.3), whereas an annual increase of 0.9% (95%CI=0.9-0.9) from 1990 to 2019 was found for women (*table 2*). The number of deaths due to MM (+40 years, both sexes) was 1,059 in 1990 and 3,907 in 2019.

The lowest mortality rates for men were observed in Amapá (1.99/100,000 in 1990 and 3.40/100,000 in 2019) and the highest in the Distrito Federal (7.78/100,000 in 1990 and 8.50/100,000 in 2019). In women, the lowest rates were in Tocantins in 1990 (1.92/100,000) and in Pará in 2019 (2.38/100,000); the highest were found in the Distrito Federal in both periods (6.02/100,000 in 1990 and 6.58 /100,000 in 2019). There was an upward trend of mortality in all federative units for men and women, varying from 0.3 (95%CI=0.2-0.4) in the Distrito Federal to 2.5 (95%CI=2.5-2.6) in Bahia and from 0.3 (95%CI=0.3-0.4) in the Distrito Federal to 1.8 (95%CI=1.8-1.9) in Amapá and Maranhão (AAPC=1.8; 95%CI=1.7-1.9) (*table 2*). Upward mortality trends were observed for all SDI quintiles, being the changes more pronounced in the low-SDI quintile for men and women (*figure 1A*, *table 4*).

Table 2. Age-standardized mortality rate and Disability-Adjusted Life Years (DALYs) per 100,000 and Average Annual Percent Change (AAPC) by sex, according to Federative unit and Brazil, 1990-2019

	Mortality						DALYs					
	Male			Female			Male			Female		
	Years		AAPC	Years			Years		AAPC	Years		AAPC
Federative unit	**1990**	**2019**	**(95%CI)**	**1990**	**2019**	**AAPC (95%CI)**	**1990**	**2019**	**(95%CI)**	**1990**	**2019**	**(95%CI)**
Acre	2.31	4.05	1.9 (1.9;2.0)	2.19	3.17	1.4 (1.3;1.5)	52.02	92.29	2.0 (1.9;2.1)	51.27	73.50	1.3 (1.2;1.4)
Alagoas	2.55	3.96	1.5 (1.5;1.6)	2.30	3.01	0.9 (0.9;1.0)	61.74	97.43	1.6 (1.5;1.6)	54.99	71.99	0.9 (0.9;1.0)
Amapá	1.99	3.40	1.9 (1.8;2.0)	2.21	3.68	1.8 (1.8;1.9)	46.14	79.11	1.9 (1.8;1.9)	51.97	86.12	1.8 (1.7;1.9)
Amazonas	2.50	3.78	1.5 (1.4;1.6)	2.14	2.70	0.8 (0.8;0.9)	59.46	89.09	1.4 (1.4;1.5)	49.53	62.49	0.8 (0.7;0.9)
Bahia	2.73	5.63	2.5 (2.5;2.6)	2.94	3.98	1.0 (1.0;1.1)	66.64	135.67	2.5 (2.4;2.5)	70.78	95.29	1.0 (1.0;1.1)
Ceará	2.97	5.03	1.9 (1.8;2.0)	2.71	3.57	1.0 (0.9;1.0)	71.76	118.84	1.8 (1.7;1.9)	64.07	82.67	0.9 (0.9;0.9)
Distrito Federal	7.78	8.50	0.3 (0.2;0.4)	6.02	6.58	0.3 (0.3;0.4)	170.18	180.50	0.2 (0.0;0.4)	137.05	140.51	0.1 (0.0;0.1)
Espírito Santo	3.70	6.19	1.8 (1.7;1.8)	3.39	4.65	1.1 (1.1;1.2)	89.68	141.94	1.5 (1.4;1.7)	81.46	106.47	0.9 (0.9;1.0)
Goiás	4.29	5.61	0.9 (0.9;1.0)	3.75	4.28	0.4 (0.4;0.5)	105.88	132.12	0.7 (0.7;0.8)	89.93	97.75	0.3 (0.3;0.3)
Maranhão	2.73	4.62	1.8 (1.6;1.9)	1.91	3.17	1.8 (1.7;1.9)	65.66	108.96	1.8 (1.6;1.9)	48.75	75.30	1.5 (1.5;1.6)
Mato Grosso	2.57	3.79	1.5 (1.4;1.6)	2.66	3.47	0.9 (0.9;1.0)	61.68	89.81	1.4 (1.3;1.5)	62.73	79.61	0.8 (0.8;0.9)
Mato Grosso do Sul	3.38	5.00	1.5 (1.4;1.6)	3.09	3.96	0.9 (0.9;0.9)	81.59	117.59	1.3 (1.2;1.5)	74.27	90.37	0.7 (0.7;0.8)
Minas Gerais	4.49	5.93	1.0 (0.9;1.0)	3.56	4.63	0.9 (0.9;0.9)	110.79	137.36	0.7 (0.6;0.8)	85.77	105.45	0.7 (0.7;0.7)
Pará	2.40	3.66	1.5 (1.5;1.6)	2.00	2.38	0.6 (0.6;0.7)	56.61	86.18	1.5 (1.4;1.5)	46.79	55.34	0.6 (0.5;0.6)
Paraíba	3.10	4.80	1.5 (1.4;1.6)	2.98	3.59	0.7 (0.6;0.7)	75.60	116.21	1.5 (1.4;1.5)	70.79	83.84	0.6 (0.6;0.6)
Paraná	3.73	5.87	1.6 (1.6;1.8)	3.25	4.46	1.2 (1.1;1.2)	90.29	135.17	1.4 (1.3;1.5)	75.97	101.29	1.0 (1.0;1.1)
Pernambuco	2.76	5.10	2.1 (2.0;2.3)	2.77	3.95	1.3 (1.2;1.4)	67.56	120.61	2.0 (2.0;2.2)	66.39	91.71	1.1 (1.0;1.2)
Piauí	2.69	3.76	1.2 (1.1;1.3)	2.36	2.90	0.7 (0.7;0.8)	63.45	89.70	1.2 (1.2;1.3)	55.41	68.20	0.7 (0.7;0.8)
Rio de Janeiro	4.66	6.16	1.0 (0.9;1.1)	4.02	4.80	0.6 (0.6;0.7)	116.20	141.58	0.7 (0.6;0.8)	98.97	107.80	0.3 (0.2;0.3)
Rio Grande do Norte	3.24	5.17	1.6 (1.5;1.7)	2.98	4.09	1.1 (1.0;1.1)	76.78	121.09	1.5 (1.5;1.6)	70.93	94.94	1.0 (1.0;1.0)
Rio Grande do Sul	4.34	6.20	1.2 (1.2;1.3)	3.44	4.39	0.9 (0.8;0.9)	103.94	141.33	1.1 (1.0;1.1)	81.96	98.03	0.6 (0.6;0.7)
Rondônia	3.11	4.12	1.1 (1.0;1.2)	2.61	2.91	0.5 (0.3;0.6)	71.29	96.67	1.1 (1.1;1.3)	58.19	66.73	0.5 (0.4;0.6)
Roraima	3.50	4.43	0.8 (0.8;0.9)	3.17	4.32	1.2 (1.1;1.2)	79.89	101.51	0.8 (0.8;0.9)	73.93	96.89	1.0 (0.9;1.0)
Santa Catarina	4.20	5.85	1.2 (1.1;1.3)	3.64	4.49	0.7 (0.7;0.8)	98.45	131.58	1.0 (0.9;1.0)	84.44	100.47	0.6 (0.5;0.7)
São Paulo	5.02	6.55	0.9 (0.8;1.0)	4.12	5.20	0.8 (0.8;0.9)	121.93	145.72	0.6 (0.5;0.7)	100.12	114.58	0.5 (0.4;0.5)
Sergipe	2.60	3.95	1.4 (1.4;1.5)	2.90	3.42	0.6 (0.5;0.6)	60.50	94.71	1.5 (1.4;1.6)	66.76	79.19	0.6 (0.5;0.6)
Tocantins	2.85	5.34	2.2 (2.1;2.3)	1.92	2.55	0.9 (0.9;1.0)	64.52	122.61	2.3 (2.2;2.3)	44.10	59.53	1.0 (1.0;1.1)
Brazil	**3.93**	**5.68**	**1.3 (1.2;1.3)**	**3.42**	**4.38**	**0.9 (0.9;0.9)**	**96.18**	**131.18**	**1.1 (1.1;1.2)**	**82.38**	**99.22**	**0.6 (0.6;0.7)**

Source: GHDx[19].
AAPC: Average Annual Percent Change; CI: Confidence Interval; DALYs: Disability-Adjusted Life Years.

YLD, YLL and DALY

DALY and its components – YLD and YLL had ascending trends in Brazil and its federative units from 1990 to 2019, except YLL in the Distrito Federal, which remained constant over the years among women (*tables 2 and 3*). YLD for men rose from 2.08/100.000 in 1990 to 3.37/100.000 in 2019 (AAPC= 1.7; 95%CI= 1.7-1.8) in Brazil, whereas for women it varied

from 1.99/100.000 in 1990 to 2.93/100.000 (AAPC= 1.3; 95%CI= 1.3-1.4). Compared to YLD, slighter upward trends were found for YLL in men (AAPC= 1.1; 95%CI=1.0-1.1) and women (AAPC= 0.6; 95%CI=0.6-0.6) (*tables 2 and 3*), corresponding to increased DALYs for men (96.18/100,000 vs. 131.18/100.000; AAPC= 1.1 95%CI=1.1-1.2) and for women (82.38/100,000 vs. 99.22/100.000; AAPC= 0.6; 95%CI=0.6-0.7) from 1990 to 2019 (*tables 2 and 3*). The number of DALYs (+40 years, both sexes) was 27,736 in 1990 and 92,224 in 2019, corresponding to 27,123 YLL and 613 YLD in 1990 and 89,714 YLL and 2,510 YLD in 2019.

The lowest DALYs for men in both periods were found in Amapá, while the highest DALYs were found in the Distrito Federal. Among women, the lowest DALYs were observed in Tocantins in 1990 and Pará in 2019, and the highest in the Distrito Federal in both years (*table 2*). Ascending trends of DALYs, YLL, and YLD were found for both sexes in all SDI quintiles (*figure 1B*, *table 4*).

Table 3. Age-standardized Years Lived with Disability (YLDs) and Age-standardized Years of Life Lost (YLLs) per 100,000 and Average Annual Percent Change (AAPC) by sex, according to Federative unit and Brazil, 1990-2019

	YLD						YLL					
	Male			Female			Male			Female		
	Years		AAPC	Years		AAPC	Years		AAPC	Years		AAPC
Federative unit	1990	2019	(95%CI)	1990	2019	(95%CI)	1990	2019	(95%CI)	1990	2019	(95%CI)
Acre	1.10	2.28	2.6 (2.5;2.8)	1.17	2.11	2.0 (1.9;2.1)	50.90	90.01	2.0 (1.9;2.1)	50.11	71.40	1.3 (1.2;1.4)
Alagoas	1.24	2.38	2.3 (2.2;2.3)	1.21	2.02	1.8 (1.7;1.8)	60.47	95.04	1.6 (1.5;1.6)	53.79	69.98	0.9 (0.9;0.9)
Amapá	1.07	2.04	2.3 (2.2;2.3)	1.29	2.46	2.2 (2.1;2.3)	45.07	77.06	1.9 (1.8;1.9)	50.66	83.66	1.8 (1.7;1.9)
Amazonas	1.28	2.32	2.1 (2.1;2.2)	1.18	1.85	1.6 (1.6;1.7)	58.15	86.77	1.4 (1.4;1.5)	48.34	60.66	0.8 (0.7;0.8)
Bahia	1.41	3.19	2.8 (2.7;2.9)	1.62	2.66	1.7 (1.7;1.8)	65.24	132.48	2.5 (2.4;2.5)	69.13	92.64	1.0 (0.9;1.0)
Ceará	1.57	2.96	2.3 (2.2;2.4)	1.55	2.51	1.7 (1.7;1.7)	70.19	115.89	1.8 (1.7;1.9)	62.53	80.15	0.9 (0.8;0.9)
Distrito Federal	3.76	5.19	1.1 (0.9;1.3)	3.29	4.61	1.2 (1.1;1.3)	166.45	175.31	0.2 (0.0;0.4)	133.76	135.87	0 (-0.1;0.1)
Espírito Santo	2.04	3.61	2.0 (1.9;2.1)	1.98	3.07	1.5 (1.5;1.6)	87.65	138.34	1.5 (1.4;1.6)	79.49	103.40	0.9 (0.9;1.0)
Goiás	2.33	3.30	1.1 (1.1;1.2)	2.19	2.84	0.9 (0.9;1.0)	103.55	128.83	0.8 (0.7;0.8)	87.75	94.90	0.3 (0.2;0.3)
Maranhão	1.30	2.59	2.4 (2.3;2.5)	0.98	2.01	2.5 (2.4;2.7)	64.35	106.40	1.7 (1.6;1.9)	47.75	73.27	1.5 (1.5;1.6)
Mato Grosso	1.34	2.37	2.0 (1.9;2.1)	1.50	2.39	1.6 (1.5;1.7)	60.34	87.43	1.4 (1.3;1.5)	61.23	77.22	0.8 (0.7;0.9)
Mato Grosso do Sul	1.81	2.88	1.6 (1.5;1.7)	1.82	2.55	1.2 (1.1;1.3)	79.78	114.67	1.3 (1.2;1.4)	72.46	87.84	0.7 (0.7;0.8)
Minas Gerais	2.35	3.53	1.4 (1.3;1.4)	2.06	3.09	1.4 (1.3;1.5)	108.44	133.83	0.7 (0.6;0.7)	83.70	102.37	0.7 (0.7;0.7)
Pará	1.21	2.18	2.1 (2.0;2.2)	1.09	1.58	1.3 (1.2;1.3)	55.41	83.99	1.5 (1.4;1.5)	45.69	53.74	0.5 (0.5;0.6)
Paraíba	1.67	2.93	1.9 (1.9;2.0)	1.72	2.55	1.4 (1.3;1.4)	73.95	113.30	1.5 (1.4;1.5)	69.07	81.29	0.6 (0.6;0.6)
Paraná	1.98	3.40	1.9 (1.8;1.9)	1.84	2.90	1.6 (1.6;1.7)	88.31	131.76	1.4 (1.3;1.5)	74.11	98.38	1.0 (1.0;1.1)
Pernambuco	1.40	2.90	2.6 (2.5;2.7)	1.49	2.60	2.0 (1.9;2.1)	66.15	117.73	2.0 (1.9;2.2)	64.88	89.12	1.1 (1.0;1.2)
Piauí	1.41	2.30	1.7 (1.6;1.8)	1.36	1.99	1.4 (1.3;1.4)	62.04	87.39	1.2 (1.1;1.3)	54.06	66.21	0.7 (0.7;0.8)
Rio de Janeiro	2.48	3.54	1.2 (1.2;1.3)	2.32	3.09	1.0 (0.9;1.1)	113.71	138.02	0.7 (0.6;0.8)	96.64	104.71	0.3 (0.2;0.3)
Rio Grande do Norte	1.71	3.04	1.9 (1.9;2.0)	1.73	2.78	1.7 (1.6;1.7)	75.05	118.06	1.5 (1.5;1.6)	69.22	92.17	1.0 (0.9;1.0)
Rio Grande do Sul	2.35	3.77	1.6 (1.5;1.7)	2.12	3.02	1.2 (1.1;1.3)	101.59	137.57	1.1 (1.0;1.1)	79.83	95.01	0.6 (0.5;0.7)
Rondônia	1.55	2.43	1.7 (1.6;1.9)	1.36	1.98	1.3 (1.2;1.4)	69.74	94.24	1.1 (1.1;1.2)	56.80	64.74	0.5 (0.4;0.6)
Roraima	1.78	2.54	1.3 (1.2;1.4)	1.76	2.70	1.5 (1.5;1.6)	78.11	98.97	0.8 (0.8;0.9)	72.18	94.21	1.0 (0.9;1.0)
Santa Catarina	2.26	3.60	1.6 (1.5;1.7)	2.16	3.13	1.3 (1.3;1.4)	96.19	127.98	1.0 (0.9;1.0)	82.26	97.32	0.6 (0.5;0.6)
São Paulo	2.65	3.87	1.3 (1.2;1.4)	2.49	3.50	1.2 (1.1;1.2)	119.27	141.86	0.6 (0.5;0.7)	97.64	111.11	0.4 (0.4;0.5)

Table 3. Age-standardized Years Lived with Disability (YLDs) and Age-standardized Years of Life Lost (YLLs) per 100,000 and Average Annual Percent Change (AAPC) by sex, according to Federative unit and Brazil, 1990-2019

	YLD						YLL					
	Male			Female			Male			Female		
	Years		AAPC	Years		AAPC	Years		AAPC	Years		AAPC
Federative unit	**1990**	**2019**	**(95%CI)**	**1990**	**2019**	**(95%CI)**	**1990**	**2019**	**(95%CI)**	**1990**	**2019**	**(95%CI)**
Sergipe	1.30	2.36	2.1 (1.9;2.2)	1.55	2.28	1.3 (1.3;1.4)	59.18	92.36	1.5 (1.4;1.6)	65.23	76.91	0.6 (0.5;0.6)
Tocantins	1.46	3.04	2.6 (2.5;2.7)	1.08	1.78	1.7 (1.6;1.8)	63.04	119.56	2.3 (2.2;2.3)	43.02	57.74	1.0 (1.0;1.0)
Brazil	**2.08**	**3.37**	**1.7 (1.7;1.8)**	**1.99**	**2.93**	**1.3 (1.3;1.4)**	**94.11**	**127.82**	**1.1 (1.0;1.1)**	**80.37**	**96.27**	**0.6 (0.6;0.6)**

Source: GHDx[19].

AAPC: Average Annual Percent Change; CI: Confidence Interval; YLDs: Years Lived with Disability; YLLs: Years of Life Lost.

Table 4. Age-standardized of measures per 100,000 and Average Annual Percent Change (AAPC) by sex, according to Socio-Demographic Index (SDI) quintiles, 1990-2019

	Male			Female		
SDI quintiles	**1990**	**2019**	**AAPC (95%IC)**	**1990**	**2019**	**AAPC (95%IC)**
			Incidence			
Low	2.8	5.4	2.2 (2.1;2.3)	2.3	4.1	1.9 (1.9;2.2)
Low Middle	3.2	5.9	2.2 (2.1;2.2)	3.3	4.6	1.2 (1.1;1.3)
Middle	3.5	5.7	1.8 (1.7;1.8)	3.2	4.5	1.2 (1.1;1.2)
High Middle	4.7	6.8	1.3 (1.2;1.4)	4.0	5.7	1.2 (1.2;1.3)
High	5.2	7.6	1.3 (1.2;1.4)	4.6	6.2	1.1 (1.0;1.1)
			Prevalence			
Low	5.2	11.9	2.9 (2.8;3.0)	4.8	10.4	2.7 (2.6;2.9)
Low Middle	6.1	12.7	2.6 (2.5;2.7)	6.8	11.3	1.8 (1.7;1.8)
Middle	6.5	12.7	2.3 (2.2;2.4)	6.7	11.3	1.8 (1.7;1.9)
High Middle	9.0	15.1	1.8 (1.7;1.9)	8.5	14.5	1.9 (1.8;1.9)
High	10.1	17.0	1.8 (1.8;1.9)	10.0	16.0	1.6 (1.6;1.7)
			Mortality			
Low	2.7	4.6	1.8 (1.8;2.0)	2.1	3.3	1.6 (1.5;1.8)
Low Middle	2.9	5.0	2.0 (1.9;2.0)	2.9	3.7	0.9 (0.8;0.9)
Middle	3.1	4.8	1.6 (1.5;1.6)	2.8	3.6	0.9 (0.8;0.9)
High Middle	4.2	5.6	1.1 (1;1.2.0)	3.4	4.5	0.9 (0.9;1.0)
High	4.7	6.3	1.1 (1;1.2.0)	3.9	4.9	0.8 (0.8;0.8)
			DALY			
Low	63.5	109.7	1.9 (1.8;2.0)	51.3	78.1	1.5 (1.4;1.6)
Low Middle	69.9	119.5	1.9 (1.8;2.0)	68.3	86.7	0.8 (0.8;0.9)
Middle	75.4	113.4	1.5 (1.4;1.5)	66.6	82.1	0.8 (0.7;0.8)
High Middle	102.4	130.9	0.8 (0.8;0.9)	82.2	102.0	0.7 (0.7;0.8)
High	113.4	142.7	0.8 (0.7;0.9)	94.1	109.2	0.5 (0.5;0.5)
			YLL			
Low	62.2	107.0	1.9 (1.8;2.0)	50.1	75.8	1.5 (1.4;1.6)
Low Middle	68.4	116.7	1.9 (1.8;2.0)	66.7	84.3	0.8 (0.7;0.9)
Middle	73.8	110.5	1.4 (1.4;1.5)	65.0	79.7	0.7 (0.7;0.8)

Table 4. Age-standardized of measures per 100,000 and Average Annual Percent Change (AAPC) by sex, according to Socio-Demographic Index (SDI) quintiles, 1990-2019

	Male			Female		
SDI quintiles	**1990**	**2019**	**AAPC (95%IC)**	**1990**	**2019**	**AAPC (95%IC)**
High Middle	100.2	127.5	0.8 (0.8;0.9)	80.2	99.0	0.7 (0.7;0.8)
High	110.9	139.0	0.8 (0.7;0.9)	91.8	105.9	0.5 (0.5;0.5)
			YLD			
Low	1.3	2.7	2.6 (2.4;2.7)	1.1	2.3	2.4 (2.3;2.7)
Low Middle	1.5	2.9	2.3 (2.2;2.3)	1.6	2.5	1.5 (1.4;1.5)
Middle	1.6	2.8	1.9 (1.9;2.0)	1.6	2.4	1.4 (1.3;1.5)
High Middle	2.2	3.3	1.5 (1.4;1.5)	2.0	3.0	1.4 (1.4;1.4)
High	2.5	3.7	1.5 (1.4;1.6)	2.3	3.3	1.2 (3.3;1.2)

Source: GHDx[19].

AAPC: Average Annual Percent Change; CI: Confidence Interval; DALYs: Disability-Adjusted Life Years; YLDs: Years Lived with Disability (YLDs); YLLs: Years of Life Lost; SDI: Socio-Demographic Index.

Discussion

Morbidity, mortality, and the burden of MM have been rising in Brazil between 1990 and 2019. In accordance with the epidemiology of MM, the highest measures were registered for male sex. Mortality increased, nevertheless, at a slower pace than incidence, corresponding to a higher rising trend of prevalence for both sexes. YLL continues to be the main component of DALY yet shows a smaller upward trend than YLD. Overall, age-standardized incidence, prevalence mortality, DALY, YLL, and YLD were greater in federative units with higher SDI, especially in those from high- and high-middle quintiles, while the poorest places showed the highest ascending trends for all the measures from 1990 to 2019.

While we found a similar pattern of MM epidemiology across the Brazilian States, we also observed differences in the magnitude of the measures of MM, which is probably related to uneven access to healthcare services facilitating diagnosis and treatment, aging, population growth, and quality of data, as indicated by other investigations[3,4,10]. Federative units with incidences above that found for Brazil – Distrito Federal, São Paulo, Rio de Janeiro, Minas Gerais, Santa Catarina, Rio Grande do Sul (for men), and Goiás (for women), coincided with those having the highest proportions of persons aged 65 years or older in 2010 and 2019[26,27] and, in most cases, with the highest level of development. Therefore, the underreporting of MM data due to poor access to early diagnosis and treatment in low-income areas in Brazil must be taken into account when interpreting these results.

Increasing incidence trends can also be explained by improvements in MM diagnosis made over the period, despite the recognized inequalities between public and private health services concerning (timely) access to diagnosis and treatment[28]. Socio-economic disparities should have influenced MM detection among federative units, considering that the diagnosis of MM is quite complex and costly, resulting in underestimation of the disease especially in regions lacking infrastructure or having other health needs[3,17]. The detection of MGUS and SMM, which usually precede MM, and a complete diagnostic investigation of MM would rarely been performed in federative units with low SDI. Thus, the increase

in the incidence of MM observed in Brazil might not reflect a real rise in the disease, but rather an improved access to diagnosis and awareness of the disease. Another study[10] evaluated rising age-specific incidence rates, an aging population, and population growth as the main contributors to the increase in MM incidence worldwide. Similarly, all these factors should have influenced the ascending incidence of MM in Brazil, and the contribution of individual factors to new cases of myeloma should be demonstrated in future investigations.

The advances achieved in the treatment of MM in Brazil in the late 1980s brought with the ASCT and the use of thalidomide combined with the drug regimens combinations from the early 2000s, improved survival (decelerating mortality rate and YLL) and contributed to the rising trends in prevalence rates and YLD. Thalidomide has been made available nationwide without cost in public and private health care; however, the access to novel drug therapies have been unequal compared to developed countries[10,14]. Other drugs such as bortezomib, lenalidomide and monoclonal antibodies, more recently approved in Brazil, have been made accessible for only a small part of patients, who are covered by private health insurance, acquire medicine via judicialization or participate in clinical trials[29].

Moreover, despite the increase of ASCT rates for MM in Brazil (2009-2012)[8], only about 30% of patients met eligibility for the procedure[8,30]. Since ASCT criteria require healthier patients younger than 75 years[10], patients from poorer regions with limited or no access to timely diagnosis and treatment, are unlikely to be candidates.

Downward trends in mortality have been observed for countries with higher SDI[4]. Mortality rates increased by 1.3% and 0.9% per year for men and women, respectively, whereas incidence increased by 1.5% for men and 1.1% for women, suggesting some improvement in MM treatment in Brazil between 1990 and 2019. This same pattern can be found by comparing mortality and incidence according to SDI quintiles. Another study carried out in Brazil reported an ascending annual percent change of 2.5% in age-adjusted (20+ years) MM mortality for both sexes, from 1996 to 2015[30]. In line with our findings, the authors also observed higher ascending trends of age-standardized mortality (> 20 years) in the North, Northeast, and Midwest regions compared to the Southwest and South regions of Brazil[31].

We recognize the limitations of our study that was based on secondary data, which may compromise the accuracy of MM measures. Furthermore, considering the nature of the study design, the assessment of known risk factors that could have affected MM distribution (e.g. black race, high BMI and genetic factors[1,2,4]), was beyond the scope of this work. Nevertheless, our study provided an overview of the disease pattern at the population level in Brazil and its federative units. Future research should be performed to further assess the MM epidemiology in Brazil in the face of the demographic transition, the introduction of bortezomib, incorporated into SUS just after the study period, and emerging therapies, as well as the effect of the COVID-19 pandemic.

Conclusions

This study provided the first description of MM in Brazil and its 27 federative units from 1990 to 2019. Age-standardized (40+ years) incidence, prevalence, mortality, DALY, YLL, and YLD of MM showed increasing trends in Brazil over the period. Ascending trends of mortality were less pronounced than incidence (as well as YLL compared to YLD), approaching the scenario of high-income countries. In addition, federative units with higher levels of development showed the highest measures; however, poorer places had higher rising trends. Morbidity, mortality, and disease burden of MM were significantly higher in men compared to women.

Collaborators

Oliveira MM (0000-0002-0804-5145)* conceived the study, analyzed data, interpreted the results, and contributed to the writing of the study. Veloso GA (0000-0002-5348-3793)* conceived the study, contributed to the data analysis, interpreted the results. Malta DC (0000-0002-8214-5734)* conceived the study, interpreted the results, and revised the manuscript critically for important intellectual content. Curado MP (0000-0001-8172-2483)* conceived the study and revised the manuscript critically for important intellectual content. Menezes de Pádua C (0000-0001-7083-3188)* conceived the study, interpreted the results, and wrote the original draft of the study. ■

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