


Incidence, prevalence and disability associated with neurological disorders in Italy between 1990 and 2019: an analysis based on the Global Burden of Disease Study 2019

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Abstract

Background Neurological conditions are highly prevalent and disabling, in particular in the elderly. The Italian population has witnessed sharp ageing and we can thus expect a rising trend in the incidence, prevalence and disability of these conditions.

Methods We relied on the Global Burden of Disease 2019 study to extract Italian data on incidence, prevalence and years lived with a disability (YLDs) referred to a broad set of neurological disorders including, brain and nervous system cancers, stroke, encephalitis, meningitis, tetanus, traumatic brain injury, and spinal cord injury. We assessed changes between 1990 and 2019 in counts and age-standardized rates.

Results The most prevalent conditions were tension-type headache, migraine, and dementias, whereas the most disabling were migraine, dementias and traumatic brain injury. YLDs associated with neurological conditions increased by 22.5%, but decreased by 2.3% in age-standardized rates. The overall increase in prevalence and YLDs counts was stronger for non-communicable diseases with onset in old age compared to young to adult-age onset ones. The same trends were in the opposite direction when age-standardized rates were taken into account.

Conclusions The increase in YLDs associated with neurological conditions is mostly due to population ageing and growth: nevertheless, lived disability and, as a consequence, impact on health systems has increased. Actions are needed to improve outcome and mitigate disability associated with neurological conditions, spanning among diagnosis, treatment, care pathways and workplace interventions.

Keywords Disability · Migraine · Stroke · Dementia · Multiple sclerosis · Motor neuron disease

Introduction

The Global Burden of Disease (GBD) study aims to provide reliable information on global trends in the health status of populations and changes in the disease burden, measured by the disability-adjusted life years (DALYs), a metric which includes fatal outcomes, i.e. years of life lost (YLLs), and non-fatal health outcomes, i.e. years lived with disability (YLDs) [1]. The measurement of both YLLs and YLDs is of key relevance in the modern scenario of health outcomes,

as the increase of populations disability is paradoxically a consequence of reduced premature deaths, but it also reflects the failure of health systems in maintaining high standards of health care. This is particularly true for non-communicable diseases (NCDs): based on 2019 estimates, NCDs account for 64% of all-cause DALYs and 80% of all-cause YLDs (see <http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/25456ecb137f47b60482ce47135fd8a8>). Over the 1990–2019 period, the share of NCDs over all-cause estimates have increased by 45% for DALYs and by 69% for YLDs (see <http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/1d45ef2f987f97ce8ec27e199b5ea9a2>).

In a publication on the burden of neurological disorders in which GBD 2016 estimates were used [2], the group of

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neurological disease as defined by GBD—i.e. Alzheimer’s disease and other dementias, epilepsy, migraine, motor neuron diseases (MND), multiple sclerosis (MS), Parkinson’s disease (PD), and tension-type headache (TTH)—was complemented by other conditions that, although not included in the standard set of neurological diseases, have a clear impact on the central or peripheral nervous systems. These include two NCDs, namely stroke and brain and nervous system cancers, three communicable neurological diseases, namely encephalitis, meningitis, and tetanus, and two injuries, namely traumatic brain injury (TBI) and spinal cord injury (SCI). Taken as a whole, this broad group of neurological conditions accounted for 11.6% of all-cause DALYs in 2016 [2]. The authors of this manuscript evidenced a consistently increasing trend for number of prevalent cases and disability, in addition to burden, for the selected neurological diseases, and hypothesized that the same indices are reasonably expected to further on increase in reason of population ageing and growth: however, no direct information was referred to YLDs associated with neurological disease by country. In addition, two recent publications addressed the burden of neurological and brain disorders in European countries, relying on GBD 2017 estimates. The first addressed the same set of neurological disorders used in the global-level GBD 2016 publication [2] and showed that neurological disorders accounted for 13.5% of all-cause DALYs and ranked third after cancers and cardiovascular diseases [3]. The second paper focused on brain disorders, i.e. the same set of enlarged neurological conditions (with the exclusion of SCI) together with mental health and substance abuse disorders: results showed that brain disorders ranked first among all NCDs in terms of prevalence (79.1%), YLDs (34.5%) and DALYs (26.9%) [4]. The common conclusion of these studies is that the burden of neurological and brain disorders is increasing, at global and European levels, and that a relevant part of such increase is driven by population ageing. The information reported by the three aforementioned manuscripts [2–4] largely refers to DALYs, with less attention to disability (i.e. YLDs), an index that reflects what happens to people while they live with a disease, which is of importance for public health purposes in ageing populations.

Italy has the largest proportion of elderly population among European countries, with 21.4% of citizens being ≥ 65 , and 6.4% ≥ 80 years [5], and these rates are expected to rise in the forthcoming years. Such trend is due to reduced fertility, which will lead to a top-heavy age structure [6, 7], and to the ongoing reduction of mortality at all ages, which will make Italians’ lives longer: at present, Italy is in the top 10 countries globally for life and healthy life expectancy [8]. Nonetheless, the increase in life expectancy has relevant consequences at the societal level, in terms of increased old age dependency ratio (i.e. the number of

people aged 65+ compared to those aged 15–64 [5]), and of the prevalence of chronic conditions that are typical of the old age, the so-called compression of morbidity.

Some neurological conditions, e.g. PD, stroke and dementias, are among those that are typical of old age: it is, therefore, likely that prevalence and disability associated with neurological diseases in Italy have increased in the past decades. Indeed, the recently published study on the global burden of neurological conditions has shown that DALY counts of neurological diseases in Italy have increased by approximately 10% between 1990 and 2016 in Italy [2]. Moreover, neurological disorders are associated with extensive care, including emergency room access, inpatient and outpatient care, surgery, rehabilitation, long term and palliative care. In fact, 37.0% to 43.6% of DALYs attributable to neurological disorders are due to YLDs [3, 4] with important differences among diseases: the burden of headache disorders, is in fact represented by YLDs only, whereas for conditions such as brain and nervous system cancers or MND, less than 5% of DALYs are attributable to YLDs.

As the prevalence of neurological disorders is expected to rise due to population ageing, understanding the trend of disability associated with these diseases in the past decades is of paramount importance to inform policy making and enable cost-effective health-care planning and strategic resource allocation for the Italian health system. The aims of this article are, therefore, the following: to describe the incidence, prevalence and YLDs associated with a broad group of neurological disorders in Italy, and their variation between 1990 and 2019; to address the trends for those NCDs with typical onset in young to adult age (e.g. headache disorders) and for those with typical onset in old age (e.g. Alzheimer’s disease and other dementias), as well as for neurological injuries and for communicable neurological diseases; to compare estimates referred to Italy to those of other Western Europe countries.

Methods

The Institute for Health Metrics and Evaluation (IHME) produces annual updates of the GBD study, including temporal and geographic trends since 1990. Each update incorporates new data and methodological improvements to provide policy makers with the most up-to-date information for health care planning and resource allocation. In this analysis, we relied on the GBD 2019 round estimates (available at <http://ghdx.healthdata.org/gbd-results-tool>) referred to Italy, and to the years 2019 and 1990. The Italian population comprised 60.6 million in 2019, with a life expectancy at birth of 83.1 years (ranking third at European level) and 71.0 years of healthy life expectancy years (ranking sixth at European level) [8].

The GBD taxonomy lists causes in a four-level scheme, from generic to narrow categories. For example, Migraine is a level 4 condition (code B.5.6.1), and it is included among “Headache disorders” (level 3, code B.5.6). In turn, headache disorders are among “Neurological disorders” (level 2, code B.5), which are “Non-communicable diseases” (level 1, code B). In this analysis, we have aggregated the estimates for 14 diseases and injuries outcomes that are generally cared for by neurological services. This broad group of neurological conditions included both level 3 and level 4 conditions as presented in the GBD, specifically as follows:

- a) A set of level 3 NCDs, namely Alzheimer’s disease and other dementias, brain and nervous system cancers, epilepsy, MND, MS, PD and stroke, as well as two level-4 ones, namely migraine and TTH.
- b) Three level-3 communicable diseases whose sequelae affect the nervous system, namely meningitis, encephalitis and tetanus.
- c) Two neurological injuries, namely TBI and SCI, that were taken from the “injury by nature” categories at level 1 (where they were identified as head and spinal injuries).

On the contrary, we did not include the residual category “Other neurological disorders”, in which the remaining neurological diseases were included. The most common are expected to be ataxias, Huntington’s disease, dystonia, sleep disorders, neuropathies, myasthenia gravis, myopathies, muscle dystrophy, cerebral palsies, but many others, often rare, are included. For such disorders, estimates are not precise and poorly informative, with incidence and prevalence information often being not reported from original studies due to poor quality of estimates [2, 3]. Non-fatal outcomes for the individual disorders included in this residual category need to be approximated by assuming the same YLDs/YLLs ratios estimated for the main fatal neurological disorders, which can be a precise approach for those conditions associated to relevant mortality (e.g. Huntington’s disease), but not for those associated to little or no mortality (e.g. myasthenia gravis). For the residual category, the most precise estimate is for mortality, which is based on vital registration, but that it is not of interest for our study.

YLDs are estimated as the product of prevalence of individual consequences of diseases (or sequelae) multiplied by their corresponding disability weights, which quantify the relative severity of sequelae as a number between 0 (representing full health) and 1 (representing death) [9]. These estimates are based on systematic reviews of published and unpublished documents, survey microdata, administrative records of health encounters, registries, and disease surveillance systems that are catalogued in the Global Health Data Exchange website (<http://ghdx.healthdata.org>). For each

condition, disability weights are calculated through a series of severity splits—typically defining sequelae as asymptomatic, mild, moderate, and severe—as described in the main GBD 2019 paper [1]. Such a distinction is of great importance in consideration of the broad severity spectrum of some conditions. For example, disability weights associated with meningitis vary between 0.01 (95% uncertainty interval, UI 0.004–0.019), which identifies mild hearing loss as a result of meningitis, and 0.542 (95% UI 0.37–0.702), which identifies severe motor plus cognitive impairments. Asymptomatic MS disability weights are set to zero, whereas those of severe MS, which identifies patients with slurred speech and difficulty swallowing, weak arms and hands, very limited and stiff leg movement, loss of vision in both eyes and urinary incontinence, are 0.719 (95% UI 0.534–0.858).

To identify the NCDs with typical onset in young to adult age vs. old age we relied on the 2019 incidence rates for Italy, using both the 5-years groups, and the five main age categories (below 5 years, 5–14, 15–49, 50–69, and 70+). For the purpose of this study, we defined conditions with typical onset in young to adult age those for which the peak of incidence rate was observed before 50 years of age and conditions with typical onset in old age those for which, on the contrary, the peak of incidence rate was observed after 70 years of age (see Supplementary Figs. 1–9).

For each condition and year, counts and age-standardized rates (the latter both for males and females) for incidence, prevalence, and YLDs, and their relative 95% UIs are presented, as well as the change in counts and in age-standardized rates between 1990 and 2019. We also extracted, for comparison, the age-standardized rates for the group of Western Europe countries as defined by the GBD, to address whether estimates for Italy are significantly different from those of other countries: estimates are considered different if the 95% UI referred to Italy do not overlap with that referred to Western Europe countries. Western Europe countries include: Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom (<http://ghdx.healthdata.org/countries>).

Changes over the period were also analysed at the group level, i.e. young to adult-age onset NCDs, older age onset NCDs, neurological injuries, and communicable neurological diseases.

Results

All-cause prevalence for neurological disorders in 2019 in Italy (60.6 million citizens) accounted for 58.2 million cases and 8.96 million YLDs.

Our classification of NCDs in young to adult and old-age typical onset enabled to allocate migraine, TTH, MS and epilepsy to the first group; Alzheimer's disease and other dementias, brain and nervous system cancers, MND, PD and stroke were on the contrary allocated to the second.

Table 1 shows incidence, prevalence, and YLDs, both as counts and age-standardized rates, for selected neurological conditions referred to 1990 and 2019, as well as the change between 1990 and 2019. The most prevalent conditions in 2019 were migraine and TTH, with 12.5 and 23.2 million prevalent cases (28.5 million cases when combined), and an increase of 8.2% and 12.8% compared to 1990. The prevalent cases of Alzheimer's disease and other dementias were 1.37 million in 2019, more than doubled compared to 1990; stroke and TBI had estimates of 770 and 650 thousand prevalent cases. The same diseases were also leading causes for incidence. With regard to disability, migraine was the leading condition both in terms of YLD counts and age-standardized rates, followed by dementias, stroke, and TBI. TBI had fewer YLD counts than stroke and Alzheimer's disease and other dementias, but higher age-standardized YLD rates. YLDs due to migraine (almost 470,000, i.e. 754/100,000 age-standardized YLD rates) were higher than the sum of the YLDs associated with the remaining neurological disorders. Migraine in fact accounted for 5.2% of all-cause YLD counts for Italy (8.96 million YLDs) and 7.0% of age-standardized YLD rates (10 747/100,000). Headache disorders combined accounted for almost 519,000 YLDs (828/100,000 age-standardized rates), which correspond to 5.8% of all-cause YLDs and 7.7% of all-cause age-standardized YLD rates.

Table 2 shows age-standardized rates for incidence, prevalence, and YLDs by sex for selected neurological conditions. Most of the differences are connected to incidence, with females showing higher rates for migraine and MS, whereas males showed higher incidence rates for MND, PD and TBI. With regard to prevalence, differences were found for migraine and MS, with females showing higher rates, and for both neurological injuries, with males showing higher rates. Finally, with regard to YLDs, higher age-standardized rates were observed in males only for TBI. It has to be noticed that a large gender difference exists for migraine-related YLDs with, however, large UIs.

Changes over time provide additional information (Tables 1, 2 and Fig. 1). With regard to incidence, a consistent decrease both for counts and age-standardized rates was observed for stroke, meningitis, tetanus and TBI, whereas a consistent increase both for counts and age-standardized rates was observed for TTH, MS, dementias and MND. For other conditions, the trend was not uniform: for encephalitis and PD, the trend was increasing when counts were taken into account, and decreasing in terms of age-standardized rates; the opposite was observed for migraine.

As for prevalence, a consistent decrease both for counts and age-standardized rates was observed for meningitis and tetanus, whereas a consistent increase both for counts and age-standardized rates was observed for migraine, TTH, MS and MND. For other disorders, the trend was not uniform: for PD, stroke, TBI and SCI the trend was increasing when counts were taken into account, and decreasing in age-standardized rates; for dementias and brain and nervous system cancers the trend was increasing for counts and stable in age-standardized rates; finally, for encephalitis, the trend was decreasing in age-standardized rates, and stable in counts.

With regard to YLDs, a consistent decrease both for counts and age-standardized rates was observed for meningitis and tetanus, whereas a consistent increase both for counts and age-standardized rates was observed for MS and MND. For PD, stroke, TBI and SCI the trend was increasing when counts were taken into account, and decreasing in age-standardized rates; for migraine, TTH and dementias and brain and nervous system cancers the trend was increasing when counts were taken into account, and stable in age-standardized rates; finally, for encephalitis, the trend was decreasing in age-standardized rates, and stable in counts.

Table 3 shows that, between 1990 and 2019, young to adult-age onset NCDs underwent a consistent increase for incidence, prevalence and YLDs, which denotes the joint effect of increasing trends and demographic change. The opposite can instead be seen for communicable neurological diseases. Old-age onset NCDs underwent the largest increase over the period in terms of counts, likely driven by the dramatic increase in dementias and MND, but such an effect was not paralleled by age-standardized rates, which denotes that the observed increase is due to population ageing together with population growth. Finally, a decrease was shown for the incidence of neurological injuries, whereas the increase observed in prevalence and YLD counts is due to the effect of changes in demographic composition. Taken as a whole, incidence and prevalence of selected neurological conditions increased both in counts and in age-standardized rates, whereas YLDs increased only in counts.

Young to adult-age onset NCDs were the most incident and prevalent neurological diseases, both in terms of counts and age-standardized rates, with little or no variations between 1990 and 2019 (see Supplementary Figs. 10 and 11). Figure 2 shows the share of young to adult-onset NCDs with regard to YLD counts and rates in 1990 and 2019: in terms of counts, a reduction of the share of young to adult-age onset NCDs and an increase of old-age onset NCDs can be seen; the opposite is observed when age-standardized YLD rates are taken into account.

Compared to the group of Western Europe countries as a whole, the most striking results were observed for age-standardized rate variations in the period 1990–2019. Compared to the other countries, Italy showed a

Table 1 Incidence, prevalence and years lived with a disability for selected neurological conditions in Italy, years 1990–2019, both sexes, counts and age-standardized rates and percentage change over time

			Counts			Age-standardised rates		
			1990	2019	Change	1990	2019	Change
Young to adult-age onset NCDs	Migraine	Incidence	761,737 (674,936 to 851,301)	693,328 (617,048 to 775,956)	−9.0% (−12.2 to −5.6%)	1467.6 (1297.0 to 1638.4)	1528.4 (1354.4 to 1709.3)	4.1% (1.8 to 6.7%)
		Prevalence	11,539,567 (10,071,697 to 13,244,875)	12,488,060 (10,866,465 to 14,382,675)	8.2% (2.9 to 13.8%)	18,823.3 (16,533.3 to 21,645.5)	20,337.7 (17,724.7 to 23,405.8)	7.5% (4.2 to 11.3%)
		YLDs	428,442 (60,294 to 999,838)	467,569 (69,422 to 1,085,192)	9.1% (2.3 to 17.0%)	699.0 (91.6 to 1 644.2)	754.0 (91.3 to 1 781.7)	7.7% (−1.0 to 12.8%)
	TTH	Incidence	6,924,922 (6,148,754 to 7,750,792)	7 399 179 (6 578 880 to 8 283 797)	6.8% (2.6 to 11.2%)	11,507.6 (10,191.2 to 12,864.6)	11,850.2 (10,463.6 to 13,286.3)	3.0% (0.4 to 5.6%)
		Prevalence	20,647,795 (18,432,606 to 22,872,626)	23,287 870 (20,931,617 to 25,813,025)	12.8% (8.4 to 17.0%)	33,199.0 (29,462.1 to 36,915.0)	35,514.3 (31,460.2 to 39,340.7)	7.0% (4.3 to 9.5%)
		YLDs	45,799 (12,898 to 163,750)	52,235 (14,845 to 188,815)	14.1% (3.3 to 21.7%)	71.0 (19.2 to 258.3)	73.9 (19.5 to 279.8)	4.1% (−4.5 to 9.3%)
	MS	Incidence	1292 (1109 to 1487)	1 424 (1 204 to 1 658)	10.2% (4.3 to 17.0%)	2.2 (1.9 to 2.6)	2.8 (2.4 to 3.3)	26.3% (23.0 to 30.5%)
		Prevalence	45114 (38270 to 52987)	73,486 (61,962 to 86,509)	62.9% (57.8 to 68.5%)	64.0 (54.2 to 75.4)	85.6 (71.7 to 102.2)	33.8% (30.7 to 38.4%)
		YLDs	11353 (7910 to 15044)	18,268 (12,816 to 24,227)	60.9% (53.5 to 69.2%)	16.2 (11.2 to 21.5)	21.7 (15.2 to 29.0)	33.8% (27.1 to 40.9%)
Epilepsy	Incidence	19 761 (12 835 to 26 832)	21,357 (13,553 to 28,891)	8.1% (−16.1 to 40.3%)	39.6 (24.9 to 54.7)	39.0 (24.1 to 55.1)	−1.5% (−24.0 to 25.4%)	
	Prevalence	170,232 (113,351 to 222,536)	190,510 (124,111 to 254,479)	11.9% (−12.8% to 43.3%)	292.7 (196.0 to 387.1)	277.0 (178.5 to 377.8)	−5.4% (−26.1 to 21.4%)	
	YLDs	41,518 (21,624 to 67,948)	40,423 (20,851 to 70,180)	−2.6% (−32.5 to 43.0%)	72.8 (37.9 to 121.0)	61.3 (31.1 to 105.9)	−15.8% (−42.4 to 24.8%)	

Table 1 (continued)

		Counts			Age-standardised rates			
		1990	2019	Change	1990	2019	Change	
Old-age onset NCDs	Alzheimer's disease and other dementias	Incidence	90,748 (74,769 to 106,630)	186,108 (156,694 to 214,287)	105.1% (95.8 to 117.0%)	100.9 (84.5 to 115.8)	103.7 (88.1 to 119.3)	2.8% (0.6 to 6.1%)
		Prevalence	649,189 (540,788 to 760,512)	1,369,006 (1,148,213 to 1,604,011)	110.9% (101.6 to 121.9%)	735.5 (615.3 to 845.5)	742.1 (627.4 to 862.2)	0.9% (-1.7 to 4.2%)
		YLDs	93,692 (65,580 to 126,413)	204,584 (141,692 to 276,418)	118.4% (107.5 to 130.5%)	106.5 (75.0 to 142.4)	108.7 (75.7 to 146.8)	2.0% (-0.7 to 5.5%)
Brain and nervous system cancers		Incidence	4471 (3699 to 5137)	6056 (3886 to 7645)	35.5% (-15.9 to 67.6%)	6.3 (5.2 to 7.3)	6.1 (4.1 to 7.6)	-2.9% (-38.7 to 19.7%)
		Prevalence	11 439 (9 342 to 13 375)	18,878 (12,213 to 24,506)	65.0% (4.5 to 115.7%)	19.0 (15.5 to 22.6)	23.6 (15.7 to 29.9)	24.5% (-23.0 to 61.7%)
		YLDs	1572 (1068 to 2104)	2339 (1388 to 3458)	52.7% (-4.9 to 93.7%)	2.3 (1.6 to 3.1)	2.6 (1.5 to 3.7)	11.5% (-29.3 to 41.0%)
MND		Incidence	979 (909 to 1052)	1901 (1798 to 1999)	94.2% (88.1 to 100.5%)	1.3 (1.2 to 1.4)	1.5 (1.4 to 1.6)	26.1% (22.2 to 30.6%)
		Prevalence	4119 (3525 to 7805)	7785 (6656 to 8996)	89.0% (77.6 to 102.6%)	5.6 (4.5 to 6.5)	7.6 (6.6 to 8.8)	36.5% (30.1 to 44.5%)
		YLDs	875 (597 to 1163)	1 655 (1 127 to 2 192)	89.0% (77.6 to 102.6%)	1.2 (0.8 to 1.6)	1.6 (1.1 to 2.1)	36.5% (30.1 to 44.5%)
PD		Incidence	16,426 (13,478 to 19,446)	22,405 (18,345 to 26,681)	36.4% (26.7 to 47.7%)	17.6 (14.7 to 20.7)	14.9 (12.4 to 17.6)	-15.4% (-19.5 to -11.3%)
		Prevalence	154,609 (127,896 to 184,618)	207,097 (168,366 to 251,061)	33.9% (25.6 to 42.9%)	166.1 (138.1 to 197.4)	131.4 (107.9 to 156.8)	-20.9% (-25.0 to -16.7%)
		YLDs	21,546 (14,762 to 29,515)	28,840 (19,618 to 39,472)	33.9% (24.5 to 42.7%)	23.2 (15.9 to 31.6)	18.6 (12.6 to 25.5)	-19.8% (-24.3 to -15.1%)
Stroke		Incidence	106,934 (90,775 to 128,136)	94,074 (83,223 to 106,720)	-12.0% (-18.9 to -5.5%)	124.4 (107.3 to 146.8)	68.9 (61.5 to 76.8)	-44.6% (-48.4 to -41.2%)
		Prevalence	732,828 (655,372 to 826,087)	772,098 (698,726 to 873,841)	5.3% (0.5 to 11.3%)	869.0 (780.9 to 968.4)	632.9 (569.2 to 703.1)	-27.2% (-30.2 to -23.9%)
		YLDs	109,993 (79,321 to 141,103)	121,126 (87,312 to 155,582)	10.1% (4.4 to 16.8%)	130.2 (94.1 to 165.3)	95.9 (68.8 to 122.0)	-26.3% (-29.5 to -23.0%)

Table 1 (continued)

			Counts			Age-standardised rates		
			1990	2019	Change	1990	2019	Change
Communicable diseases	Encephalitis	Incidence	3591 (3083 to 4078)	4 272 (3 793 to 4 737)	19.0% (11.2 to 27.6%)	6.5 (5.5 to 7.6)	6.1 (5.3 to 6.8)	-7.0% (-12.0 to -1.9%)
		Prevalence	9677 (7423 to 12,044)	9977 (7632 to 12,211)	3.1% (-1.3 to 7.6%)	15.0 (11.7 to 18.6)	12.5 (9.8 to 15.2)	-17.0% (-20.0 to -13.7%)
		YLDs	1033 (721 to 1393)	1035 (721 to 1384)	0.2% (-4.0 to 4.4%)	1.7 (1.2 to 2.2)	1.4 (1.0 to 1.9)	-16.5% (-19.8 to -13.4%)
	Meningitis	Incidence	6 677 (5 156 to 8 393)	2962 (2439 to 3522)	-55.6% (-63.0 to -47.3%)	16.5 (12.3 to 21.4)	5.5 (4.5 to 6.6)	-66.8% (-71.6 to -60.3%)
		Prevalence	30,029 (24,656 to 36,444)	9031 (7879 to 10,375)	-69.9% (-73.1 to -66.6%)	50.8 (41.8 to 61.6)	12.3 (10.6 to 14.3)	-75.9% (-78.2 to -73.4%)
		YLDs	2826 (1917 to 3865)	829 (578 to 1 095)	-70.7% (-73.2 to -68.1%)	5.0 (3.4 to 6.9)	1.2 (0.8 to 1.6)	-75.7% (-77.7 to -73.8%)
	Tetanus	Incidence	379 (308 to 466)	115 (82 to 165)	-69.6% (-77.0 to -57.7%)	0.4 (0.4 to 0.5)	0.1 (0.1 to 0.1)	-83.4% (-87.3 to -76.8%)
		Prevalence	23 (18 to 29)	8 (6 to 11)	-64.5% (-71.8 to -53.5%)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	-74.9% (-80.7 to -67.9%)
		YLDs	3 (2 to 4)	1 (1 to 1)	-68.9% (-76.0 to -57.3%)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	-82.2% (-85.9 to -75.8%)
Neurological injuries	TBI	Incidence	311,925 (264,451 to 373,544)	293,426 (244,319 to 355,929)	-5.9% (-11.2 to -0.3%)	490.5 (418.3 to 581.4)	377.1 (319.2 to 450.6)	-18.3% (-20.0 to -16.5%)
		Prevalence	594,610 (561,364 to 626,824)	652,766 (614,279 to 691,707)	9.8% (7.9 to 12.1%)	808.3 (764.1 to 825.5)	657.0 (621.5 to 694.4)	-23.1% (-26.1 to -20.0%)
		YLDs	86,061 (60,155 to 116,787)	93 736 (66 044 to 126 346)	8.9% (6.8 to 11.5%)	117.9 (82.4 to 159.6)	96.3 (67.5 to 130.6)	-18.7% (-20.0 to -17.3%)
	SCI	Incidence	6984 (5309 to 9235)	7144 (5,225 to 9725)	1.9% (-4.8 to 8.8%)	10.2 (8.0 to 12.9)	7.8 (6.1 to 9.8)	-10.7% (-13.9 to -6.8%)
		Prevalence	152,759 (143,157 to 165,237)	167,203 (155,913 to 180,891)	9.5% (6.6 to 13.0%)	218.3 (204.3 to 235.2)	192.6 (179.3 to 207.6)	-23.6% (-26.2 to -20.9%)
		YLDs	40,412 (28,984 to 52,258)	44,023 (31,605 to 56,655)	8.9% (5.2 to 12.9%)	58.6 (41.6 to 76.2)	52.3 (37.5 to 67.6)	-11.8% (-14.3 to -8.9%)

NCDs non-communicable diseases, *YLDs* years lived with a disability, *MND* motor neuron disease, *MS* multiple sclerosis, *PD* Parkinson's disease, *SCI* spinal cord injury, *TBI* traumatic brain injury, *TTH* tension-type headache

significantly higher increase in incidence rates of dementias and MND, a higher increase in prevalence rates for migraine, TTH, MS and MND, and a higher increase in YLD rates of MND. Italy showed a significantly higher decrease in incidence rates for PD, stroke, encephalitis, meningitis and TBI, and a significantly higher decrease in prevalence and YLD rates of PD, encephalitis, meningitis,

TBI and SCI. Please refer to Supplementary Table 1 for full details on the Italy–Western Europe Countries comparison.

Table 2 Incidence, prevalence and years lived with a disability for selected neurological conditions in Italy, years 1990–2019, separately for males and females, age-standardized rates, and percentage change over time

			Males			Females		
			1990	2019	Change	1990	2019	Change
Young to adult–age onset NCDs	Migraine	Incidence	1010.2 (880.5 to 1136.2)	1066.8 (930.2 to 1201.5)	5.6% (2.1 to 9.5%)	1935.8 (1715.0 to 2157.6)	2011.9 (1778.9 to 2251.1)	3.9% (0.8 to 7.0%)
		Prevalence	12,574.5 (10,884.4 to 14,677.0)	13,491.2 (11,607.8 to 15,761.4)	7.3% (2.6 to 12.4%)	25,196.2 (22,026.4 to 28,716.3)	27,289.6 (23,667.3 to 31,259.0)	8.3% (3.7 to 13.2%)
		YLDs	458.7 (59.6 to 1 057.9)	492.0 (59.0 to 1 132.0)	7.2% (−0.7 to 13.6%)	938.0 (122.3 to 2 212.2)	1019.9 (122.5 to 2499.1)	8.7% (−1.8 to 15.0%)
	TTH	Incidence	11,198.4 (9885.7 to 12,550.5)	11,621.7 (10,247.6 to 13,031.6)	3.8% (0.1 to 7.4%)	11,793.8 (10,432.5 to 13,174.2)	12,070.4 (10,663.9 to 13,1565.6)	2.3% (−1.0 to 6.0%)
		Prevalence	32,340.7 (28,669.2 to 36,103.4)	35,617.1 (31,429.0 to 39,651.2)	10.1% (5.8 to 14.2%)	33,982.6 (30,255.1 to 37,767.3)	35,378.0 (31,485.9 to 39,176.7)	4.1% (1.2 to 7.3%)
		YLDs	57.7 (12.4 to 238.3)	61.5 (12.7 to 264.4)	6.6% (−5.3 to 13.2%)	83.8 (25.8 to 280.0)	86.2 (26.1 to 296.2)	2.9% (−5.5 to 8.2%)
	MS	Incidence	1.7 (1.4 to 2.0)	2.1 (1.8 to 2.4)	22.5% (18.5 to 27.3%)	2.8 (2.4 to 3.2)	3.6 (3.1 to 4.2)	29.4% (25.8 to 33.9%)
		Prevalence	46.2 (38.7 to 54.2)	61.2 (50.8 to 73.1)	32.6% (27.9 to 38.0%)	80.4 (68.1 to 94.8)	109.1 (91.6 to 129.9)	35.7% (32.1 to 40.6%)
		YLDs	12.0 (8.3 to 16.1)	15.8 (10.9 to 21.1)	31.4% (21.3 to 41.6%)	20.2 (14.1 to 26.7)	27.5 (19.1 to 36.8)	36.2% (28.1 to 44.7%)
Epilepsy	Incidence	43.0 (27.3 to 59.5)	41.0 (25.7 to 58.2)	−4.6% (−26.72 to 22.4%)	36.2 (22.4 to 50.2)	37.1 (23.0 to 52.4)	2.3% (−20.9 to 30.9%)	
	Prevalence	308.6 (205.1 to 408.1)	278.8 (179.4 to 380.1)	−9.7% (−29.9 to 15.5%)	278.1 (183.7 to 369.2)	276.0 (176.7 to 375.8)	−0.8% (−23.1 to 27.5%)	
	YLDs	77.3 (40.6 to 128.1)	62.1 (31.5 to 108.0)	−19.7% (−45.4 to 19.5%)	68.6 (35.6 to 112.6)	60.7 (30.7 to 104.8)	−11.6% (−39.3 to 29.0%)	

Table 2 (continued)

			Males			Females		
			1990	2019	Change	1990	2019	Change
Old-age onset NCDs	Alzheimer's disease and other dementias	Incidence	84.1 (69.4 to 97.5)	88.4 (74.2 to 102.4)	5.1% (2.3 to 9.6%)	110.7 (93.4 to 126.9)	114.7 (97.9 to 131.6)	3.6% (1.2 to 7.0%)
		Prevalence	596.7 (493.3 to 697.9)	612.5 (513.3 to 715.9)	2.6% (-0.6 to 7.1%)	807.7 (681.8 to 936.7)	825.3 (699.8 to 954.7)	2.2% (-0.5 to 5.5%)
		YLDs	8.6 (60.6 to 116.6)	89.7 (62.3 to 121.3)	3.6% (0.1 to 8.3%)	116.7 (82.4 to 156.3)	120.7 (84.7 to 162.8)	3.4% (0.4 to -7.0%)
	Brain and nervous system cancers	Incidence	7.1 (5.3 to 8.1)	7.1 (4.6 to 9.4)	0.3% (-42.2 to 31.5%)	5.6 (4.2 to 7.0)	5.2 (2.8 to 7.0)	-7.4% (-44.4 to 28.7%)
		Prevalence	18.9 (14.1 to 22.3)	25.4 (16.5 to 34.2)	34.0% (-23.9 to 84.5%)	19.3 (14.1 to 25.1)	22.2 (12.1 to 31.4)	15.0% (-33.5 to 77.6%)
		YLDs	2.5 (1.7 to 3.4)	2.9 (1.6 to 4.4)	16.7% (-32.9 to 57.8%)	2.1 (1.4 to 3.0)	2.2 (1.1 to 3.4)	4.9% (-37.6 to 52.8%)
MND		Incidence	1.5 (1.4 to 1.6)	2.0 (1.8 to 2.1)	27.9% (23.9 to 32.4%)	1.2 (1.1 to 1.3)	1.4 (1.3 to 1.5)	23.0% (18.4 to 27.9%)
		Prevalence	6.2 (5.4 to 7.2)	8.5 (7.3 to 9.9)	36.6% (29.7 to 45.1%)	5.0 (4.3 to 5.9)	6.8 (5.9 to 7.9)	35.1% (27.6 to 43.6%)
		YLDs	1.3 (0.9 to 1.8)	1.8 (1.2 to 2.4)	36.6% (29.7 to 45.1%)	1.1 (0.7 to 1.4)	1.4 (1.0 to 1.9)	35.1% (27.6 to 43.6%)
PD		Incidence	21.1 (17.5 to 24.9)	18.6 (15.4 to 21.9)	-12.2% (-16.6 to -7.8%)	15.7 (13.0 to 18.5)	12.3 (10.1 to 14.5)	-22.0% (-27.5 to -16.6%)
		Prevalence	176.5 (145.5 to 210.4)	150.9 (123.3 to 180.3)	-14.5% (-18.5 to -10.7%)	160.4 (132.3 to 190.9)	116.5 (95.2 to 139.1)	-27.4% (-32.7 to -22.1%)
		YLDs	24.7 (16.9 to 34.0)	21.4 (14.5 to 29.4)	-13.5% (-17.9 to -8.6%)	22.3 (15.3 to 30.5)	16.4 (11.3 to 22.6)	-26.5% (-32.7 to -20.3)
Stroke		Incidence	130.4 (112.4 to 153.9)	69.7 (62.7 to 77.7)	-46.5% (-50.6 to -43.0%)	119.0 (102.1 to 141.1)	67.8 (60.4 to 76.1)	-43.0% (-47.0 to -39.4%)
		Prevalence	840.0 (750.0 to 947.2)	593.4 (532.2 to 662.8)	-29.4% (-32.5 to -26.0%)	896.0 (807.5 to 995.3)	668.8 (602.2 to 742.2)	-25.3% (-29.0 to -21.2%)
		YLDs	119.8 (86.8 to 153.0)	85.7 (60.8 to 109.6)	-28.5% (-31.9 to -24.9%)	138.6 (100.0 to 175.7)	104.8 (75.7 to 133.8)	-24.4% (-28.1 to -20.5%)

Table 2 (continued)

			Males			Females		
			1990	2019	Change	1990	2019	Change
Communicable diseases	Encephalitis	Incidence	6.8 (5.8 to 7.9)	6.4 (5.6 to 7.2)	-5.7% (-11.3 to -0.1%)	6.3 (5.3 to 7.3)	5.8 (5.0 to 6.5)	-7.9% (-12.7 to -2.5%)
		Prevalence	15.0 (11.5 to 18.6)	12.6 (9.8 to 15.3)	-16.3% (-19.6 to -12.8%)	15.0 (11.8 to 18.6)	12.4 (9.8 to 15.1)	-17.6% (-20.5 to -14.5%)
		YLDs	1.5 (1.1 to 2.1)	1.3 (0.9 to 1.8)	-13.4% (-16.9 to -9.9%)	1.8 (1.2 to 2.4)	1.4 (1.0 to 2.0)	-18.9% (-22.5 to -15.6%)
	Meningitis	Incidence	18.0 (13.4 to 23.4)	5.9 (4.8 to 7.1)	-67.2% (-72.1 to -60.6%)	15.0 (11.1 to 19.4)	5.1 (4.1 to 6.1)	-66.2% (-70.9 to -59.7%)
		Prevalence	53.8 (44.2 to 65.7)	12.9 (11.2 to 15.0)	-76.1% (-78.6 to -73.5%)	47.8 (39.6 to 58.1)	11.6 (10.1 to 13.5)	-75.6% (-77.8 to -73.2%)
		YLDs	5.0 (3.4 to 6.8)	1.2 (0.9 to 1.6)	-75.2% (-77.4 to -73.2%)	5.1 (3.4 to 7.0)	1.2 (0.8 to 1.6)	-76.1% (-78.2 to -74.2%)
	Tetanus	Incidence	0.3 (0.2 to 0.5)	0.1 (0.0 to 0.1)	-79.4% (-86.5 to -54.1%)	0.5 (0.4 to 0.6)	0.1 (0.1 to 0.1)	-85.1% (-89.0 to -79.8%)
		Prevalence	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	-69.9% (-78.6 to -46.0%)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	-7.0% (-82.8 to -70.6%)
		YLDs	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	-78.1% (-82.2 to -53.2%)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	-83.8% (-87.9 to -78.4%)
Neurological injuries	TBI	Incidence	599.7 (514.1 to 705.4)	494.3 (420.9 to 589.5)	-13.7% (-15.5 to -11.7%)	362.7 (302.9 to 440.4)	251.6 (208.8 to 306.7)	-25.8% (-28.0 to -23.5%)
		Prevalence	1 027.3 (970.9 to 1 089.6)	884.7 (834.6 to 937.2)	-17.6% (-20.4 to -14.5%)	584.6 (548.2 to 618.3)	430.6 (403.5 to 457.3)	-30.6% (-34.4 to -27.0%)
		YLDs	151.1 (105.5 to 204.9)	130.4 (90.9 to 177.7)	-13.9% (-15.3 to -12.2%)	84.1 (59.1 to 113.9)	62.3 (43.7 to 84.4)	-26.3% (-27.8 to -24.6%)
	SCI	Incidence	10.7 (8.7 to 13.2)	8.9 (7.2 to 11.0)	-6.1% (-10.5 to -1.2%)	9.0 (6.7 to 12.0)	6.4 (4.8 to 8.4)	-17.1% (-21.3 to -12.1%)
		Prevalence	259.2 (241.8 to 280.5)	241.3 (224.3 to 261.8)	-16.6% (-19.4 to -14.0%)	175.1 (163.7 to 189.4)	143.3 (132.9 to 155.0)	-29.0% (-2.1 to -25.9%)
		YLDs	70.8 (50.3 to 91.9)	66.8 (47.4 to 86.1)	-6.9% (-9.8 to -3.5%)	45.9 (32.4 to 59.5)	38.0 (26.8 to 49.6)	-18.2% (-21.1 to -14.9%)

NCDs non-communicable diseases, *YLDs* years lived with a disability, *MND* motor neuron disease, *MS* multiple sclerosis, *PD* Parkinson's disease, *SCI* spinal cord injury, *TBI* traumatic brain injury, *TTH* tension-type headache

Discussion

This study pointed out five main results. First, the most common incident and prevalent neurological diseases are headache disorders. Second, there has been a dramatic increase in the counts and age-standardized rates of incidence and

prevalence of some conditions with typical onset in old age, in particular for Alzheimer disease and other dementias, brain and nervous system cancers and MND. In contrast, for PD the increase was limited to counts whereas a decrease in age-standardized rates was observed, meaning that the variation over time was associated with population

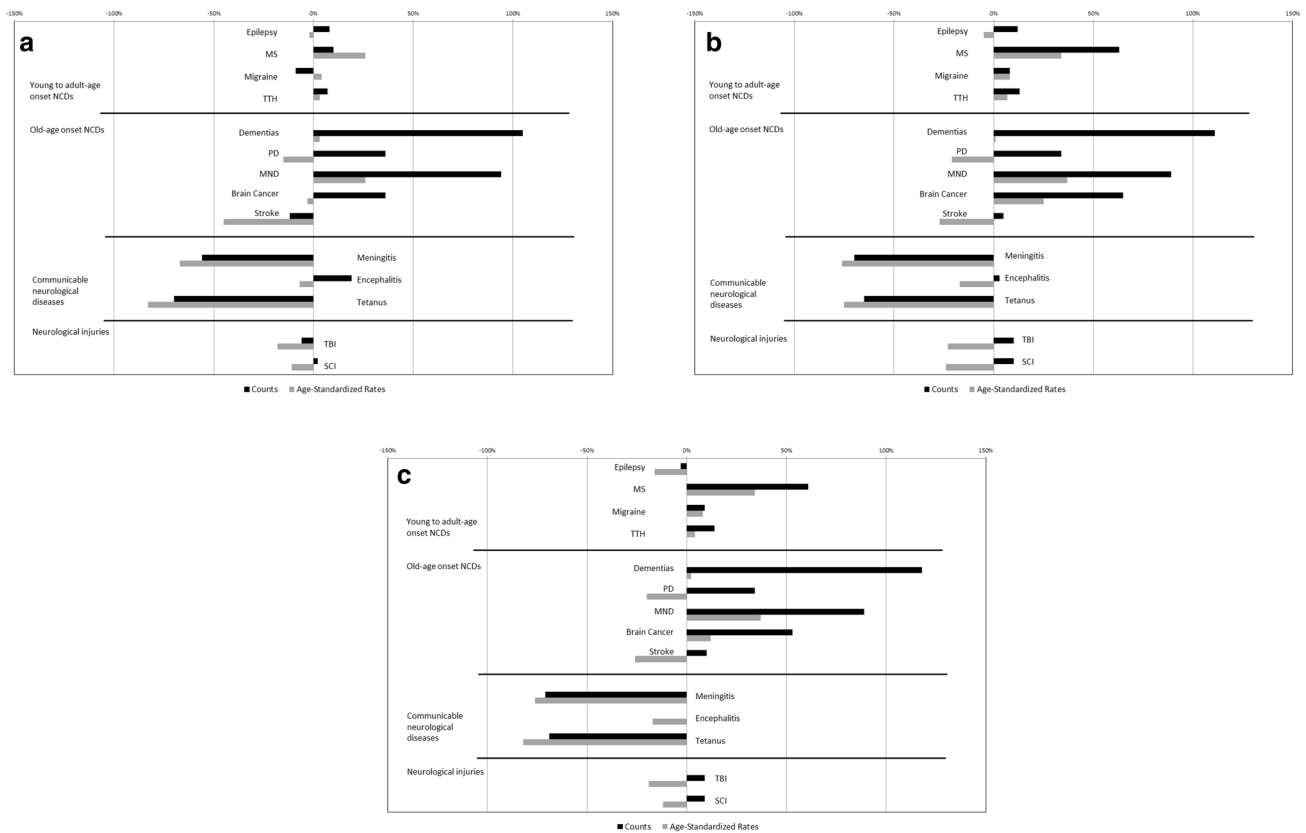


Fig. 1 Percentage change between 1990 and 2019 in Italy for incidence, prevalence and YLDs associated to neurological conditions by sub-groups, counts and age-standardized rates. **A** Incidence, **B** Prevalence, **C** YLDs, *NCDs* non-communicable diseases, *YLDs* years lived

ageing and growth, and with a control on environmental risk factors. Third, most of the disability associated with neurological conditions is due to migraine: YLDs associated with migraine were higher than the sum of YLDs associated with the remaining conditions, and accounted for 7% of all-cause age-standardized YLDs for Italy. Fourth, sex differences were mostly observed for incidence and prevalence. Females showed higher incidence and prevalence for migraine and MS, whereas males showed higher incidence for MND, PD and TBI, and a higher prevalence for TBI and SCI. Fifth, and most relevant, YLDs associated with neurological diseases increased by 22.5% between 1990 and 2019. Among conditions with typical onset in the young to adult age the increase was by 10.0%, and for those with typical onset in old age by 57.4%. However, the increase in YLDs was due to a clear epidemiological change mostly for young to adult-onset conditions, for which age-standardized YLD rates increased by 5.0%, whereas for old-age onset disease the variation herein observed was mostly an effect of population ageing and growth as age-standardized YLD rates decreased by 13.7%. We cannot, however, exclude the possible effect played by the inclusion of less severe disease

with a disability, *MND* motor neuron disease, *MS* multiple sclerosis, *PD* Parkinson's disease, *SCI* spinal cord injury, *TBI* traumatic brain injury, *TTH* tension-type headache

forms: this is, for example, the case of clinically isolated syndromes within MS. A consistent increase in both YLD counts and age-standardized rates was observed only for MS (+60.9% and +33.8%) and for MND (+89% and +36.5%).

Young to adult-age onset NCDs

In Italy, headache disorders, and migraine in particular, were the leading incident, prevalent and disabling conditions. In 2019, they represented 49% of all-cause morbidity and accounted for 5.8% of YLDs, with migraine alone being responsible for 5.2% of all-cause YLDs. Such a finding is most likely due to the changing structure of the Italian population, which is undergoing a consistent ageing process, and where middle-aged people constitute the largest group. Unfortunately, migraine incidence and prevalence rates increased, and disability remained stable over time, despite the availability of a broad set of effective compounds for both the acute treatment [10] and prophylaxis [11–14]. It has to be considered that the estimates referred to 2019 still do not account for the effect of monoclonal antibodies for migraine prophylaxis, which have been approved in Italy on

Table 3 Change between 1990 and 2019 for prevalence, incidence and YLDs associated to neurological conditions in Italy by group in counts and age-standardized rates

		Age-standardized rates								
Counts		Young to adult- age onset NCDs	Old-age onset NCDs	Neurological injuries	Communicable diseases	All				
		Young to adult- age onset NCDs	Old-age onset NCDs	Neurological injuries	Communicable diseases	All				
Incidence										
1990	7,707,712 (6,939,499 to 8,555,449)	219,557 (196,760 to 246,567)	318,909 (271,246 to 380,391)	10,648 (8986 to 12,431)	8,256,825 (7,477,164 to 9,109,050)	13,017.0 (11,679.5 to 14,414.0)	250.6 (228.1 to 277.6)	500.6 (429.0 to 592.7)	23.5 (19.1 to 28.5)	13,791.7 (12,422.1 to 15,145.4)
2019	8,115,288 (7,296,914 to 8,986,042)	310,545 (280,665 to 339,830)	300,540 (250,968 to 363,563)	7349 (6669 to 8095)	8,733,722 (7,908,181 to 9,603,751)	13,420.4 (12,052.7 to 14,863.8)	195.3 (178.2 to 211.6)	384.9 (326.9 to 459.1)	11.6 (10.4 to 13.0)	14,012.2 (12,654.9 to 15,457.8)
Change	5.3% (1.5 to 9.2%)	41.6% (31.9 to 9.4%)	-5.8% (-11.1 to -0.1%)	-30.7% (-38.7 to -22.5%)	5.8% (2.2 to 9.4%)	3.1% (0.8 to 5.3%)	-22.0% (-26.0 to -18.4%)	-23.1% (-26.1 to -20.1%)	-50.2% (-56.4 to -43.3%)	1.6% (-0.6 to 3.7%)
Prevalence										
1990	32,402,708 (29,594,987 to 35,193,536)	1,552,283 (1,409,416 to 1,639,210)	747,370 (706,276 to 788,018)	39,730 (33,913 to 47,149)	34,742,090 (31,923,175 to 37,542,380)	52,479.0 (47,774.0 to 57,084.3)	1795.2 (1643.7 to 1948.9)	1026.7 (973.7 to 1084.4)	65.8 (56.0 to 78.4)	55,366.6 (50,705.4 to 59,994.4)
2019	36,039,926 (33,072,492 to 39,030,457)	2,374,864 (2,127,650 to 2,639,689)	819,968 (773,097 to 867,675)	19,016 (16,346 to 21,807)	39,253,775 (36,297,623 to 42,175,956)	56,214.6 (51,286.1 to 61,081.0)	1537.6 (1 402.0 to 1 677.9)	849.6 (804.8 to 898.7)	24.7 (21.4 to 28.3)	58,626.5 (53,712.0 to 63,512.2)
Change	11.2% (7.9 to 14.4%)	53.0% (46.4 to 59.9%)	9.7% (7.9 to 11.9%)	-52.0% (-58.0 to -46.1%)	13.0% (9.8 to 16.0%)	7.1% (5.0 to 9.1%)	-14.3% (-16.7 to -11.9%)	-17.2% (-18.6 to -15.7%)	-62.3% (-66.6 to -58.1%)	5.9% (3.9 to 7.8%)
YLDs										
1990	527,294 (148,437 to 1,100,029)	227,678 (167,478 to 290,616)	126,472 (91,358 to 166,867)	3862 (2669 to 5138)	885,124 (487,601 to 1,513,017)	860.0 (232.8 to 1808.7)	263.4 (193.7 to 335.7)	176.4 (127.4 to 232.5)	6.7 (4.6 to 9.0)	13046.5 (668.2 to 2316.3)
2019	578,495 (162,446 to 1,217,794)	358,605 (260,663 to 462,172)	137,759 (99,629 to 182,356)	1865 (1318 to 2453)	1,076,724 (622,962 to 1,772,153)	911.0 (222.6 to 1964.7)	227.4 (165.7 to 291.9)	148.6 (108.1 to 196.5)	2.6 (1.8 to 3.4)	1289.6 (596.8 to 2364.5)
Change	10.0% (3.3 to 17.3%)	57.4% (50.3 to 65.3%)	8.9% (6.8 to 11.5%)	-51.6% (-56.2 to -47.5%)	22.5% (15.5 to 31.8%)	5.0% (-5.5 to 11.2%)	-13.7% (-16.2 to -10.8%)	-15.8% (-17.4 to -13.9%)	-61.0% (-64.7 to -57.7%)	-2.3% (-11.8 to 4.3%)

NCDs non-communicable diseases, YLDs years lived with a disability

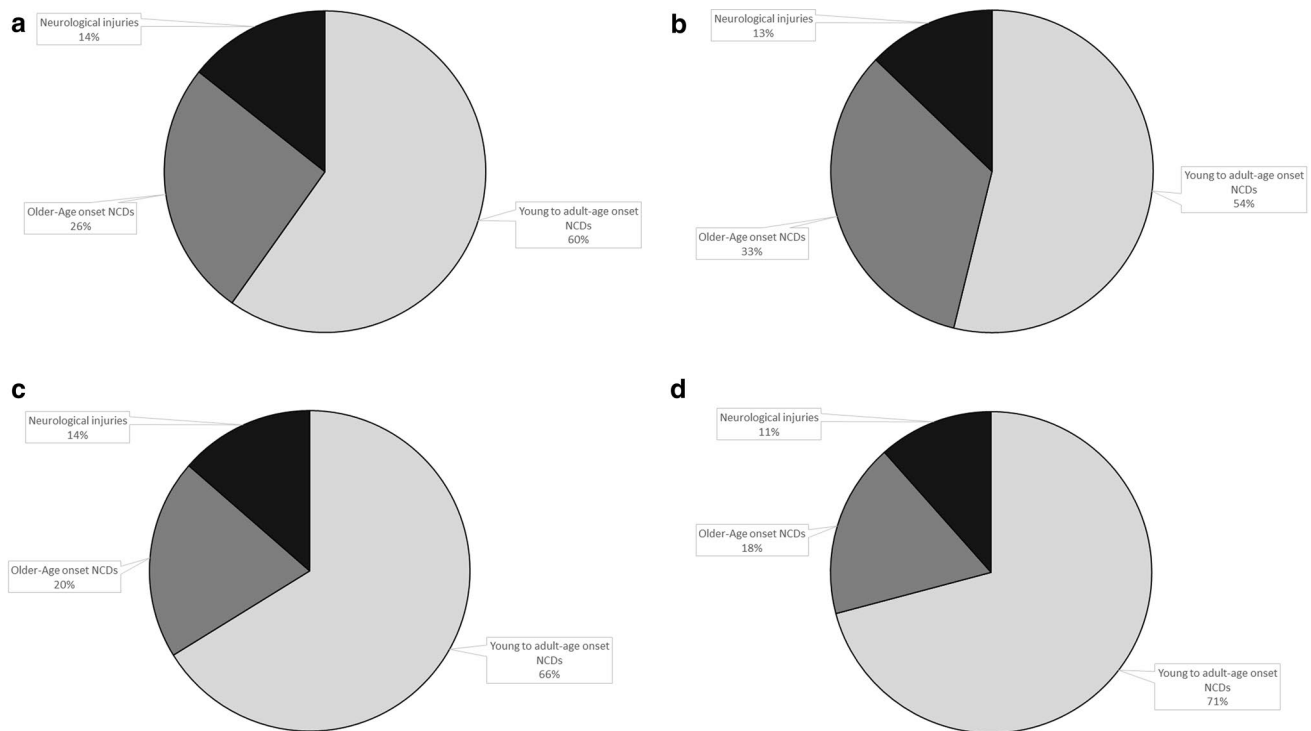


Fig. 2 Share of different disease groups on YLD counts and age-standardized rates in Italy, 1990 and 2019. **A** YLD counts in 1990; **B** YLD counts in 2019; **C** age-standardized YLD rates in 1990; **D** age-

standardized YLD rates in 2019. Counts and rates for communicable neurological conditions were not included as their share was below 0.5%

2020. Very recently, some real-life studies (or open-label phases of previous RCTs) showed that such new compounds (specifically, erenumab, fremanezumab, galcanezumab and eptinezumab) produce long-term effect on disease course and patients' reported disability [15–19]. It is likely to presume that the effect of these new therapies will be observable in future estimates.

Migraine is much more common among women, with a slightly increasing trend, and mean YLDs show a large gender difference. Such a difference has, however, to be interpreted with caution in reason of the large UI in age-standardized YLDs, which can be interpreted as an indicator of the fleeting quality of such estimates and call for specific studies on the incidence, prevalence and disability features of migraine in the Italian population. A review highlighted some elements that might explain the reasons for such high disability levels [20]: among them, the peak age of migraine prevalence among women in the third and fourth decades of life, i.e. when many women are engaged in balancing professional duties together with family and social lives, the presence of several comorbidities and the fact that headaches themselves are common comorbidities of many diseases. The picture of headache-related disability is however incomplete and complicated by the difficulty in capturing the impact of headaches on sufferers' daily lives. Such an impact is variable in relation to the frequency and duration

of attacks, and the person-level limitations with daily activities, which vary according to pain severity, accompanying symptoms and the individual's "activity profile" of different persons [21]. The lack of relevant differences in YLD rates by gender is likely associated with such activity profile and not with gender issues as traditionally shown also in other GBD publications [22]. Compared to Western Europe estimates, those for Italy show a higher increase in prevalence of both migraine and TTH. The scenario that likely explains this is referred to the modification of the Italian population structure, in which the middle-aged ones constitute the largest group and, even more likely, to the increased awareness of headache disorders. A recent study showed that 53.2% of patients attending headache centers were aware of their condition [23]. Although this figure might be considered low, it represents an improvement in awareness, in particular it is considered that data referred to 2009 showed that only 26.8% of Italian patients were aware of their condition [24].

Similar to headache disorders, YLDs due to epilepsy can be interpreted as the impact of seizures on daily living activities and the stigmatizing effects of the disease. First-line antiepileptic drugs offer good control on seizures in the majority of patients, but approximately 20% of patients suffer from drug-resistant epilepsy [25], and some of them are candidates for invasive surgical approaches [26]. The trends over time of incidence, prevalence and YLDs of epilepsy

remained substantially stable, with age-standardized rates showing a decrease, but the large UIs reflect the imprecision of estimates. The same trend was observed in the recent paper on the global burden of epilepsy [27], but the UIs of 2019 estimates are less wide than previous ones perhaps due to the larger amount of data [3, 27].

Data referred to MS show a considerable increase of all indicators both for counts and age-standardized rates, which is a result of both population ageing and growth, inclusion of more disease forms, such as clinically isolated syndromes, as well as a change in the epidemiology of MS. Such a change can be a consequence of an improved diagnostic ability—updated diagnostic criteria (i.e., 2010 revision of McDonald’s criteria [28])—along with more sophisticated neuroimaging techniques, which made it possible to include clinically isolated syndromes in the present version of MS estimates. Nonetheless, the most relevant change is the increased prevalence and YLDs associated with MS, which can be due to an increased disease duration and prolonged survival, in turn accompanied by long-term disability [29–32]. Such a result might appear controversial in consideration of the impact that new disease-modifying therapies—i.e. fingolimod, alemtuzumab, or natalizumab vs. glatiramer acetate or interferon beta—had on reduced disability progression in MS, generally defined in terms of lower hazard of conversion to secondary progressive MS, reduced relapse rates, or reduced risk of walking aid need [33, 34]. However, this is likely the main cause for increased YLDs: these relatively new therapies, in fact, by reducing conversion into secondary progressive MS, determine a prolonged survival with MS, with the effect of increasing YLDs and YLD rates. Sex differences were also found, with women expectably showing higher incidence and prevalence rates, as well as higher YLDs rates, which were however partly overlapping. Higher YLD rates might be connected to social role issues, with women showing lower employment rates than men, as well as to higher comorbidity rates [35]. Finally, with regard to the higher increase observed for Italian MS prevalence estimates contrasted to Western European ones, it is likely to suppose that the reason lies again in the modification of the Italian population structure, in which the middle aged group constitute the largest one, but also in the possibility to obtain an adequate level of care, which is well rooted in the Italian territory. In fact, as reported by a recent descriptive study, there are 236 MS centers, which included almost 45,000 patients in a national registry in 2018 [36].

Old-age onset NCDs

Incidence, prevalence and YLDs associated with Alzheimer’s disease and other dementias have more than doubled in Italy over the 1990–2019 period, but not in terms of age-standardized rates, where only for incidence a minor

increase was found, suggesting that such an increase is a consequence of population ageing. Dementias are the second cause of disability among neurological disorders, and the main driver among old-age onset neurological NCDs. The overall impact of dementias in Italy is noteworthy, mostly in reason of its demographic composition. In fact, Italy is one of the countries with the highest rate of oldest old in Europe and worldwide; compared to the other Western Europe countries, Italy had lower mortality rates both in 2019 (387.9 vs 423.7) and 1990 (642.1 vs 679.1), higher life expectancy both in 2019 (83.1 vs 82.1) and 1990 (77.2 vs 76.4) [8], resulting in a higher proportion of people susceptible to develop dementias. As dementias have no cure to date, efforts aimed to reduce the impact of such conditions on the lives of sufferers and their caregivers is, and will be, more and more of importance. Likewise, it is important to reduce the impact of those pre-dementia conditions, such as hearing loss and hypertension in adulthood, depression and diabetes in older age, which collectively account for 16.3% of the weighted population attributable fractions associated to dementias [37]. GBD 2019 estimates show that, compared to Western Europe, the age-standardized prevalence rates in Italy for hearing loss among adults are 2% higher (6 680.1 vs 6 547.1) and those of hypertension are 92% higher (17.5 vs 9.1); among the oldest old, the prevalence rates for diabetes are 6.3% higher (29 668.6 vs 27 920.9). These factors are likely to contribute to the high prevalence of dementias in Italy, and should be specifically targeted to reduce the impact of these conditions.

Brain and nervous system cancers and MND were responsible for the lower share of incidence, prevalence and YLDs among old-age onset NCDs. As shown in recent studies, based on previous iterations of GBD studies, the burden of these two conditions is mostly due to premature mortality at both global and European level, with only 3–5% of DALYs being attributable to YLDs [3, 4, 38, 39]. What our data add to this information is the specific increase between 1990 and 2019 in prevalence for both brain and nervous system cancers and MND and, for MND only, the increase in YLDs. A possible explanation is that enhanced disease-modifying and palliative treatments and overall management of these conditions enable patients to live longer after the diagnosis. Concerning brain and nervous system cancers, 5-year survival in Italy increased by 4.7% between 2000–2004 and 2010–2014 [40], likely due to increased survival of gliomas, which can be achieved if patients are treated in high-specialty centres [41]. About MNDs, which are mostly represented by amyotrophic lateral sclerosis and spinal muscle atrophy, increased survival is likely due to the increasing use of mechanical ventilation [42] and to the availability, in the last few years, of new therapies for spinal muscle atrophy [43]. At present, however, such new therapies have proved effectiveness mostly on paediatric populations; thus the

effect on YLDs can be hypothesized only on the younger groups of the population.

Globally, PD has been recognized as one of the most fast-growing conditions in terms of prevalence and burden [44]. This does not apply to Italy, where we found an increase in incidence, prevalence and YLDs only in counts but not in age-standardized rates, which decreased by 15–21%. Such a trend is similar to what was shown at the global level, where YLDs increased by 30.6%, but age-standardized YLD rates were stable (0.1% change, 95% UI -2.8 to 3.3%) [1]. Among the reasons for such a global-level rise, demographic (i.e. population ageing and increased life expectancy) and environmental causes (i.e. factors related to industrialization, such as exposure to pesticides, solvents or metals) have been considered as the most relevant. With regard to the Italian case, it can be hypothesized that increased incidence, prevalence and YLDs are associated with population ageing and not with industrialization, as Italy is in a radical deindustrialization phase [45].

Stroke is a leading burdensome condition. Globally, it accounts for 5.7% of all-cause DALYs and for 1.8% of all-cause YLDs [1] and much of its burden, as shown by the recent studies based on European estimates for 2017, is associated with premature mortality: in fact, YLDs accounted for approximately 20% of the total burden of neurological disorders [3, 4]. The estimates herein presented show a consistent decrease in stroke incidence, and an increase in prevalence and YLD, which are, however, associated with a decrease in age-standardized rates, which can be interpreted as the result of preventive measures. Stroke is a highly preventable disease [46], and the reduction of Italian rates, which for stroke incidence are broader compared to Western Europe countries, might be associated with better control of risk factors [47, 48].

Neurological injuries

Our results show a significant decrease in incidence, prevalence and YLD rates for TBI and SCI, with trends that were wider than in Western Europe in general. With regard to TBI, these findings are consistent with data from regional Italian studies showing a 40% decrease in incidence between 1985 and 2000 [49, 50] but are in contrast with the rising worldwide incidence. Such discrepancy could be attributed to the lack of rigorous high-quality data—in particular, the incomplete capture of mild cases which do not require extensive interventions or access to emergency setting and might therefore be not recorded—leading to an underestimation of TBI incidence [51, 52]. On the other hand, SCI estimates from this study are in line with the global estimates and the results presented in a recent Italian epidemiological study [53].

Data on prevalence and YLDs of TBI and SCI point out a significant increase in counts and a significant decrease in age-standardized rates, indicating that the number of people living with the long-term sequelae of TBI and SCI is increasing. This increase is mostly due to the increased life expectancy after the acute events, which are mostly represented by falls and road accidents [54]. Altogether, these findings provide support for the need to invest in a rigorous granular collection of data for TBI and SCI and the planning of adequate public health initiatives aimed to reduce the long-term outcomes associated with these injuries, in particular in the elderly.

Communicable neurological diseases

Concerning meningitis and tetanus, the estimates herein presented show a consistent, and robust decrease for all indicators, whereas in the case of encephalitis incidence estimates were raised, prevalence and YLDs were stable, and age-standardized rates for the three indicators showed a significant decrease. Such a result is very likely due to improved public health actions such as sanitation and vaccine coverage [55] and is consistent with previous observations [2, 45, 56] and the global shift from communicable to non-communicable disorders generally observed in high-income countries [1, 57]. It is finally noteworthy to observe that between 1990 and 2019, the reduction observed for incidence, prevalence and YLD estimates was larger in Italy compared to the rest of Western European countries particularly for meningitis and encephalitis.

Limitations

This study suffers from the general limitations of GBD studies. First, the adjustments of non-fatal outcomes to account for biases introduced by different case definitions, e.g. registries based on medical data vs. patients' reports. Second, the 95% UIs used to define the precision of the estimates are sometimes wide, reflecting the overall uncertainty of the estimates. Third, the adjustment for comorbidities, which is made under the assumption of the independent distribution of comorbid conditions. This is critical in consideration of the high number of comorbidities that people with conditions typical of older age, such as PD or dementias, may have, as well as of the fact that headache disorders are comorbid to a great amount of conditions. Fourth, the estimates herein presented are not complete as we decided to exclude from our analysis the residual category "Other neurological disease", which is aimed to address the burden of neurological disorders not explicitly attributable to the most relevant diseases. As previously stated, estimates for non-fatal outcomes of this residual category have little precision as they need to be approximated assuming the same YLDs/

YLLs ratios estimated for the main fatal neurological disorders. For some of the conditions included in the residual category, such as nerve diseases and myasthenia gravis, mortality is very low [58–60], thus leading to imprecise YLDs estimation. Should these condition be included, we would have a minimal increase in YLDs (21.1, corresponding to 1.6% of the total age-standardized YLD rates reported for our group of conditions) and a negligible one for prevalence (0.9, corresponding to 0.002% of the total age-standardized prevalence rates), whereas incidence for the residual category was set to zero. Fifth, we used an ad-hoc approach to identify conditions with typical onset in young to adult vs. old age, i.e. addressing the peak for incidence before the age of 50 or after 70, which is not a common procedure in GBD-based studies. Other studies, using a different approach, might therefore produce different results.

Conclusions

In conclusion, we reported information on incidence, prevalence and disability associated with neurological disorders in Italy relying on the GBD 2019 estimates. Our results show that headache disorders are still the most prevalent and disabling conditions, and that epidemiological patterns have changed between 1990 and 2019. In particular, our work pinpoints a worrisome rise in incidence and prevalence for conditions with typical onset in older ages, particularly dementias and PD as an effect of population ageing; for MND, on the contrary, estimates suggest a consistent increase which cannot be explained by population ageing only, but also as an effect of prolonged survival.

Taken together, YLDs associated with this broad set of neurological conditions—where stroke, brain and nervous system cancers, TBI, SCI, encephalitis, meningitis, and tetanus were added to the standard set of neurological diseases—between 1990 and 2019 increased by 22.5% in counts whereas age-standardized rates decreased by 2.3%. Hence, the increase is mostly due to population ageing and growth, with the only exceptions of MND and MS (for which classification changes and the inclusion of less severe varieties can be also implicated), and points out the increased survival for many of these conditions.

Such a scenario calls for public health actions towards improving outcomes and mitigating disability associated with neurological diseases. These actions should involve different levels of care, from early diagnosis and targeted treatment, up to rehabilitation, as well as behavioural changes, modifications to public and private environment and workplace interventions.

Acknowledgements A. Raggi, D. Sattin and S. Schiavolin are supported by a grant from the Italian Ministry of Health (Ricerca Corrente, Fondazione Istituto Neurologico C. Besta, Linea 4—Outcome Research: dagli Indicatori alle Raccomandazioni Cliniche). F.G. Magnani is supported by a grant from the Italian Ministry of Health (GR-2016-02365049). C. Toppo is supported by a grant from the European Union’s Horizon 2020 Research and Innovation Programme (Grant Agreement No. 848180). S. Mondello is supported by a grant from the Italian Ministry of Health (GR-2013-02354960).

Funding None for this article. The GBD initiative is supported by the Bill and Melinda Gates Foundation.

Availability of data and materials The data used for this publication are available on the GHDx website of the Institute for Health Metrics and Evaluation: <http://ghdx.healthdata.org/gbd-results-tool>.

Code availability Not applicable.

Declarations

Conflicts of interest E. Beghi reports grants from UCB-Pharma, SOBI, Revallesio, the American ALS Association and the Italian Ministry of Health, outside the submitted work. M. Piccininni reports being partially funded by a research grant from Novartis Pharma for a self-initiated research project on migraine remission, and being awarded a research grant from the Center for Stroke Research Berlin (private donations). The remaining authors declare no conflicts of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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