

BRAIN COMMUNICATIONS

The health burden of non-communicable neurological disorders in the USA between 1990 and 2017

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In this observational study, using the Global Burden of Disease and Risk Factors Study, we aimed to (i) report the magnitude of health loss due to non-communicable neurological disorders in the USA in 2017 by sex, age, years and States and (ii) to identify non-communicable neurological disorders attributable environmental, metabolic and behavioural risk factors. We provide estimates of the burden of non-communicable neurological disorders by reporting disability-adjusted life-years and their trends from 1990 to 2017 by age and sex in the USA. The non-communicable neurological disorders include migraines, tension-type headaches, multiple sclerosis, Alzheimer's disease and other dementias, Parkinson's disease, epilepsy, motor neuron diseases and other neurological disorders. In 2017, the global burdens of non-communicable neurological disorders were 1444.41 per 100 000, compared to the USA burden of 1574.0. Migraine was the leading age-standardized disability-adjusted life-years 704.7 per 100 000, with Alzheimer's disease and other dementias (41.8.7), and epilepsy (123.8) taking the second and third places, respectively. Between 1990 and 2017, the age-standardized disability-adjusted life-years rates for aggregate non-communicable neurological disorders relative to all cause increased by 3.42%. More specifically, this value for motor neuron diseases, Parkinson's disease and multiple sclerosis increase by 20.9%, 4.0%, 2.47%, 3.0% and 1.65%, respectively. In 2017, the age-standardized disability-adjusted life-years rates for the aggregate non-communicable neurological disorders was significantly higher in females than the males (1843.5 versus 1297.3 per 100 000), respectively. The age-standardized disability-adjusted life-years rates for migraine were the largest in both females (968.8) and males were (432.5) compared to other individual non-communicable neurological disorders. In the same year, the leading non-communicable neurological disorders age-standardized disability-adjusted life-years rates among children ≤ 9 was epilepsy (216.4 per 100 000). Among the adults aged 35–60 years, it was migraine (5792.0 per 100 000), and among the aged 65 and above was Alzheimer's disease and other dementias (78 800.1 per 100 000). High body mass index, smoking, high fasting plasma glucous and alcohol use were the attributable age-standardized disability-adjusted life-years risks for aggregate and individual non-communicable neurological disorders. Despite efforts to decrease the burden of non-communicable neurological disorders in the USA, they continue to burden the health of the population. Children are most vulnerable to epilepsy-related health burden, adolescents and young adults to migraine, and elderly to Alzheimer's disease and other dementias and epilepsy. In all, the most vulnerable populations to non-communicable neurological disorders are females, young adults and the elderly.

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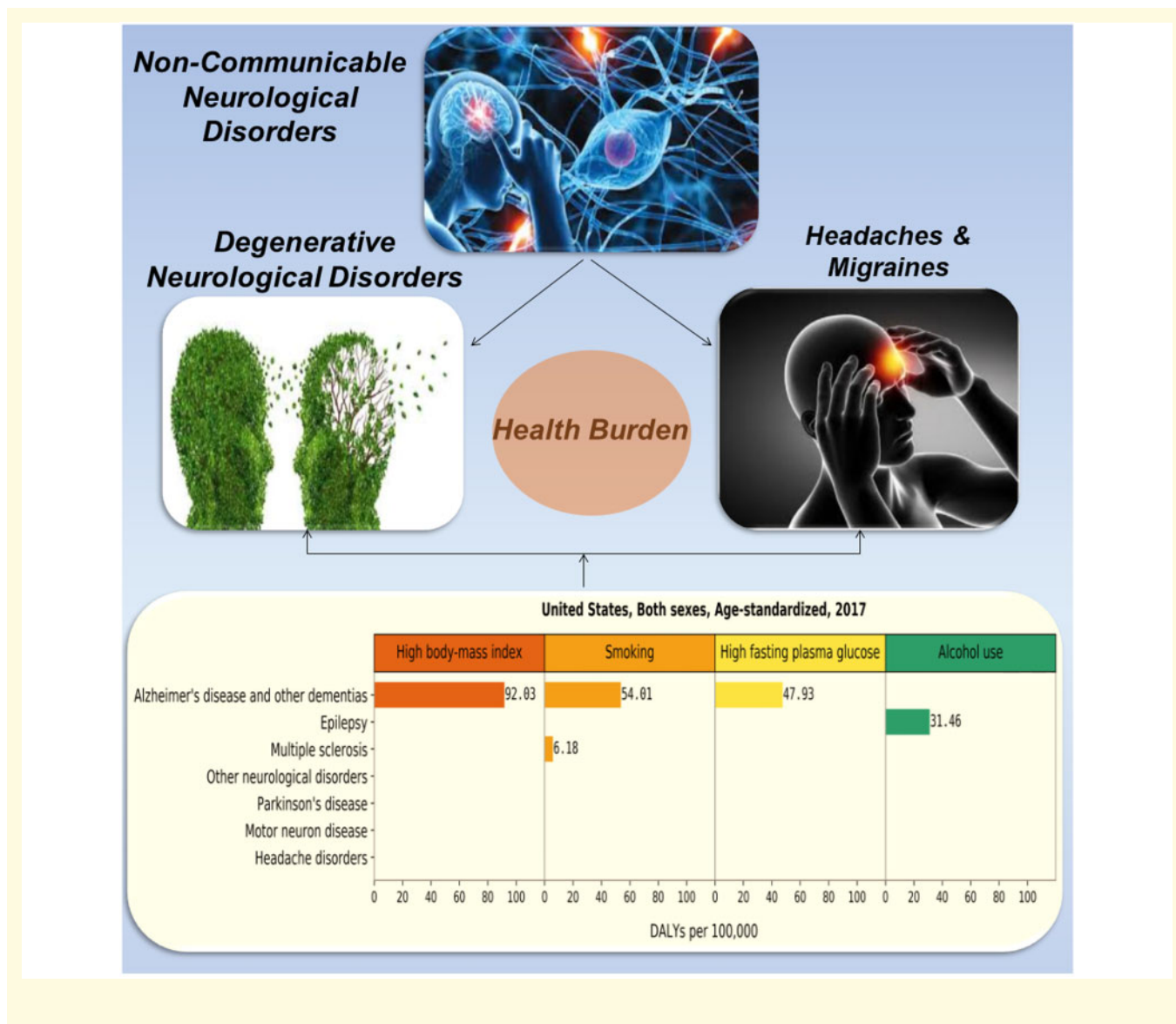
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Abbreviations: BMI = body mass index; DALYs = disability-adjusted life-years; FPG = fasting plasma glucose; GBD = Global Burden of Disease and Risk Factors Study; NCNDs = non-communicable neurological disorders



Introduction

Neurological disorders (NDs) are heterogeneous diseases that affect the body's autonomic, peripheral and central nervous system. There are over 600 NDs affecting a range of neonatal to elderly and may be categorized by the system they affect (Janca *et al.*, 2006). These NDs may be classified as communicable (able to be transmitted to one sufferer to another) or non-communicable

(not directly transmissible) (Bruzzon *et al.*, 2009). Non-communicable neurological disorders (NCNDs), including among others Alzheimer's disease and other dementia (ADOD), Parkinson's disease, epilepsy, as well as migraines and tension headaches, are prevalent in high-income countries (GBD 2015 Neurological Disorders Collaborator Group, 2017). In the USA, NCNDs affect 14% of the American population and are expected to 'triple by 2050' (Saadi *et al.*, 2017). It is estimated that

the economic burden of NCNDs in the USA is \$800 billion annually (Gooch *et al.*, 2017).

As indicated by previous studies, susceptibility to certain NCNDs varies by age and sex (Amatniek *et al.*, 2010; Vina and Ana, 2010; Peterlin *et al.*, 2011). For example, migraines are more prevalent in females than in males (Peterlin *et al.*, 2011). Multiple sclerosis showed early onset in women than men, and peak at the age of 30 (Harbo *et al.*, 2014). Alzheimer's disease and other dementia have early onset as early as 30–65 years of age and more prevalent in women than men (Vina and Ana, 2010). Research in Parkinson's disease shows male–female differences in the age and presentation of Parkinson's disease, where women diagnosed with this condition are on average 2.1 years older than men (53.4 versus 51.3), and are more likely to experience tremor as the initial symptom than rigidity (Haaxma, *et al.*, 2007; Miller and Cronin-Golomb, 2010).

In addition to sex and age, environmental, metabolic and behavioural risk factors may also increase susceptibility to NCNDs (Ahmed *et al.*, 2016). The environmental risk factors that pose a threat are inorganic and organic hazards, exposure to toxic metals (aluminium, copper), pesticides (organo-chlorine and organophosphate insecticides), industrial chemicals (flame retardants) and air pollutants (particulate matter). The long-term exposure to these environmental risk factors has revealed alterations in the pathways associated with ADOD and may account for 30% of ADOD risk factors (Yegambaram *et al.*, 2015). High body mass index (BMI) and high fasting plasma glucose (FPG) are both metabolic risk factors found in ADOD. A 3.10-fold increase of ADOD is shown when comparing individuals with normal BMI (18.5–24.9) to obese individuals (BMI > 30) (Whitmer *et al.*, 2007). This increase is related to the accumulation of β -amyloid protein in ADOD (Barron *et al.*, 2013). Drugs are behavioural risk factors that alter neuronal function, their transmitters and eventually neuronal circuits (Neiman *et al.*, 2000). Alcohol is known to trigger seizures and induce epilepsy; however, the mechanism by which alcohol prompts seizures is unknown (Gordon and Devinsky, 2001). Smoking also serves as an additional behavioural risk factor for multiple sclerosis. Those who smoke have 1.5 higher chances of developing multiple sclerosis (Belbasis *et al.*, 2015).

In the current study, we aimed: (i) to describe the trend of NCNDs related health burden in the USA from 1990 to 2017, (ii) to report the magnitude of health loss due to NCNDs in the USA in 2017 by sex and age and (iii) to identify NCNDs risk factors in the USA. The results of this study will inform interventions to target segments of the population that are most impacted by the burden of NCNDs. Funding agencies and policymakers can also benefit from the findings of this study in allocating appropriate funds and developing a policy plan to reduce the physical, mental, social and economic burden of NCNDs in the US population.

Materials and methods

Study dataset and data source

The source of data for the current study is the Global Burden of Disease Study (GBD). GBD's study goal is to comprehensively and globally quantify and estimate premature deaths, deaths, disability and burden of disease due to disease, injuries and risk factors on annual bases. These population estimates span the period between 1990 and 2017 (Institute for Health Metrics and Evaluation, IHME <https://vizhub.healthdata.org/gbd-compare/>). GBD produces estimates by collecting evidence from various fatal and non-fatal data sources. The fatal data, which are used to estimate years of life lost, include vital registrations, verbal autopsies, surveillance data, hospital records, census/surveys and population-based cancer registries (GBD Neurological Disorders Collaborator Group, 2017, 2019). The fatal data are analysed with the Cause of Death Ensemble Model (CODEm) tool (Feigin *et al.*, 2019). The non-fatal data are used to calculate years of life lived with disability and are collected by reviewing scientific literature, population surveys, hospital outpatient data, surveillance data, disease registries and others (GBD Neurological Disorders Collaborator Group, 2017).

The causes of disease or injury in the GBD Study are classified into four levels. The first level includes three main groups; communicable, maternal, and neonatal conditions and nutritional deficiencies all in one group, non-communicable disease in the second group, and injuries in the third group. With the advance of levels from 1 to 4, the number of diseases and injuries (i.e. sub-causes) in each main group increases. Level 4 has the most detailed number of sub-causes (Lopez *et al.*, 2006). NCNDs belong to the second group (i.e. non-communicable disease), and at Level 4, it contains nine sub-causes, including migraines, tension-type headaches, multiple sclerosis, ADOD, Parkinson's, epilepsy, motor neuron, and other NDs. We used these sub-causes for the current study. Additionally, GBD Study uses 23 age categories that range from 0–6 days to 95+ and 84 risk factors, all listed under three general areas of environmental/occupational, behavioural and metabolic risk factors (Salomon *et al.*, 2015; Institute for Health Metrics and Evaluation, IHME, 2017). For a risk to be included in this list, there should be sufficient empirical evidence for a causal relationship between the risk and the disease outcome (Institute for Health Metrics and Evaluation, IHME <http://www.healthdata.org/gbd/about>).

Statistical analysis

GBD study uses DisMod-MR 2.1, a Bayesian meta-regression tool, to analyse non-fatal data (Feigin *et al.*, 2019). For the current study, we provide estimates of the burden of NCNDs as measured by disability-adjusted

life-years (DALYs) and their trends from 1990 to 2017 by age and sex in the USA. The term DALYs refers to the sum of years lost due to premature death and years lived with disability (GBD Collaborator *et al.*, 2016). For all estimates, GBD reports the 95% uncertainty intervals (UIs), which are calculated by the IHME staff. The lower and upper bounds of the UI are determined based on the 25th and 975th values of the ordered 1000th values. Significance of differences is established if 975 or more of the ordered 1000 values of difference were on either side of zero (GBD Neurological Disorders Collaborator Group, 2017).

Data availability

Data available using the following URL: <https://vizhub.healthdata.org/gbd-compare/> and <http://ghdx.healthdata.org/gbd-results-tool>.

Results

NCNDs in the USA

In 2017, NCNDs ranked 6th among the top 10 leading non-communicable causes of DALYs in the USA (Supplementary Fig. 1), similar to the global estimate (Supplementary Fig. 2). A ranking that did not shift from 1990, and contributed to 6.7 million (UI 8.1–5.6 million) DALYs, up from 4.9 million in 1990 (Table 1).

In 1990, migraine was the largest contributor to DALYs (1.86 million). However, ADOD was the largest contributor to total DALYs (2.40 million) in 2017.

Between 1990 and 2017, the aggregate NCNDs age-standardized DALY rates increased by 3.42%, and of separate NCNDs, epilepsy had the largest increase in DALY rates (5.46%). Migraine ranked 1st both in 1990 and 2017, accounting for 694.1 (UI 443.6–1008.1) and 704.78 (UI 445.99–1020.5) age-standardized DALY rates, respectively. This followed by ADOD, epilepsy and tension headache (Table 1).

As illustrated in Table 2, in 2017, aggregate NCNDs contributed to 6.74% of total DALYs up from 5.68% in 1990. ADOD was the largest contributor accounting for 2.54% of total DALYs. In 1990, migraines accounted for the largest proportion (2.35%) of DALYs relative to total DALYs. Between 1990 and 2017, the proportion of DALYs due to the aggregate NCNDs relative to DALYs from all other causes increased by 18.5%. The largest increase in the proportions was evident in Parkinson's disease (58.5%), followed by motor neuron disease (55.3%), multiple sclerosis and ADOD.

NCNDs related DALYs by sex

In 2017, 2.6 million males (UI 2.19–3.10 million) and 4.17 million females (3.40–5.02 million) were estimated to have NCNDs. Across the aggregate of eight NCNDs, the age-standardized DALY rates were higher for females [1843.4 (UI 1410.3–2330.8)] than males [1297.3; (UI: 1064.9–1581.5)]. When examined separately, migraine and ADOD were the leading NDs for females, responsible for 1.66 million (1.07–2.37 million), and 1.60 million (1.52–1.69 million) DALYs, respectively. For males, the leading NCNDs were ADOD followed by migraine accounting for 9.43 million (8.93

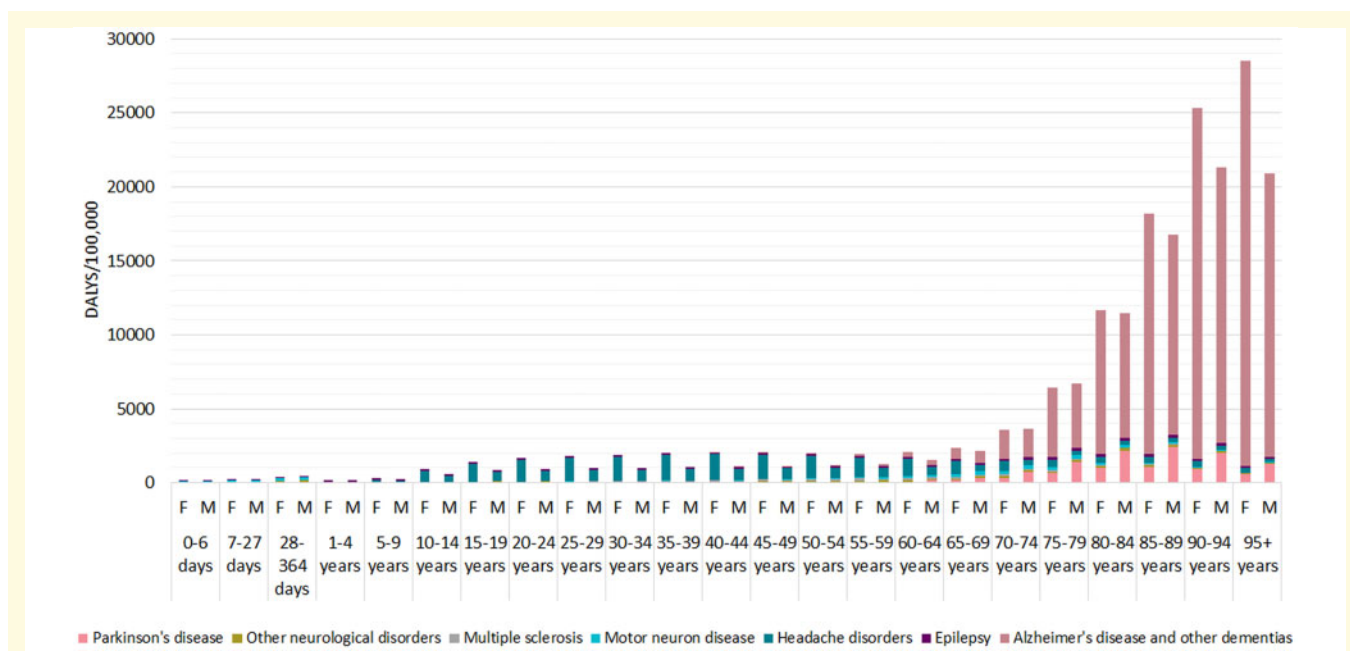


Figure 1 Age-standardized DALY rates for separate NCNDs by age and sex in the USA, 2017.

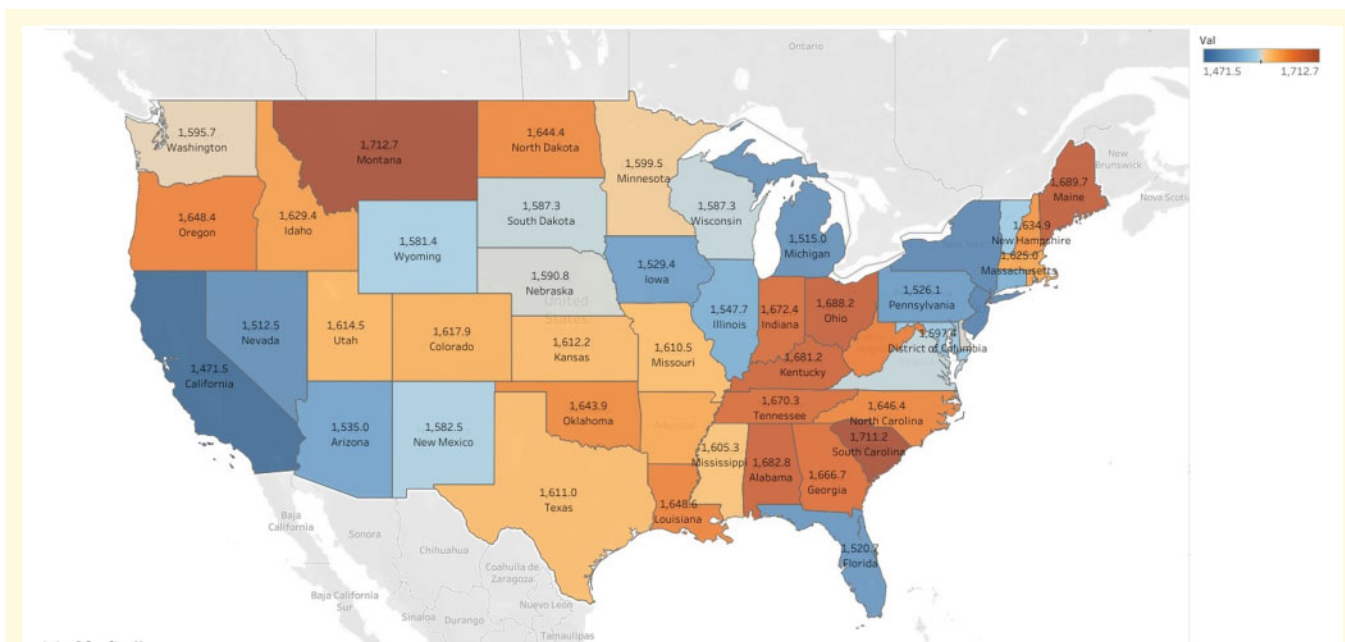


Figure 2 Age-standardized DALY rates (100 000) for NCNDs for both sexes in the USA, 2017.

Table 1 NCNDs age-standardized DALY ranks, all ages DALY numbers, age-standardized DALY rates, and age-standardized DALYs percent change for both sexes in the USA, 1990 and 2017

NCNDs	1990 Rank	1990 DALYs in million	1990 DALY per 100 000	2017 Rank	2017 DALYs in millions	2017 DALY per 100 000	1990–2017 Rate % change
Aggregate NCNDs	5	4.49 (3.61–5.50)	1521.9 1200.4–1897.3	6	6.77 (5.64–8.13)	1574.0 (1246.8–1956.2)	3.42
Migraine	1	1.86 (1.19–2.69)	694.1 443.6–1008.1	1	2.40 (1.53–3.44)	704.7 445.9–1020.5	1.53
ADOD ^a	2	1.47 (1.39–1.57)	413.6 389.2–439.0	2	2.55 (2.42–2.67)	418.7 398.7–439.0	1.24
Epilepsy	3	0.30 (0.20–0.44)	117.4 76.9–172.6	3	0.41 (0.25–0.62)	123.8 75.1–187.4	5.46
Tension-type headache	4	0.26 (0.14–0.41)	96.4 54.4–154.3	4	0.34 (0.19–0.55)	96.5 96.5–154.8	0.00
Parkinson's disease	6	0.20 (0.18–0.23)	58.1 53.4–67.8	5	0.41 (0.34–0.44)	72.5 61.1–78.0	2.47
Other NDs	5	0.16 (0.15–0.18)	66.2 58.7–75.4	6	0.24 (0.20–0.28)	67.4 56.3–82.5	1.83
Multiple sclerosis	7	0.11 (0.09–0.13)	40.4 33.7–47.6	7	0.20 (0.16–0.23)	47.1 39.2–54.6	1.65
Motor neuron disease	8	0.09 (0.96–0.12)	35.5 34.2–36.7	8	0.19 (0.18–0.20)	42.9 40.6–44.7	20.9

^a Alzheimer's disease and other dementias.

million–9.92 million) and 7.38 million (4.62–1.10 million) DALYs, respectively. In both 1990 and 2017, there was a higher age-standardized DALY rates in females than males for ADOD, migraine, multiple sclerosis and tension headache (Table 3). Whereas the burden of Parkinson's disease, epilepsy, motor neuron diseases and other NDs (i.e. NDs that are not explicitly estimated) was higher in males (Table 3).

The age-standardized rate of DALYs for aggregate NCNDs increased by 4.05% and 3.57% in males and females, respectively, from 1990 to 2017 (Table 3). During this time, the percent change in DALY numbers and age-standardized rates for females increased across separate NCNDs. For males, except for other NDs that decreased by 4.79%, the DALY numbers and age-standardized rates of separate NCNDs increased. The highest

Table 2 Percent of total DALYs and rank of all age DALYs due to NCNDs for both sexes, in the USA, 1990 and 2017

NCNDs	1990 DALYs proportion relative to DALYs from all causes	1990 % Rank	2017 DALYs proportion relative to DALYs from all causes	2017 % Rank	1990–2017 Proportion % change
Aggregate NCNDs	5.68% (4.93–6.55%)	5	6.74% (5.98–7.6%)	5	18.5
ADOD ^a	1.88% (1.74–2.02%)	2	2.54% (2.33–2.76%)	1	35.5
Migraine	2.35% (1.61–3.20%)	1	2.38% (1.65–3.23%)	2	1.4
Epilepsy	0.38% (0.26–0.55%)	3	0.41% (0.26–0.61%)	3	7.3
Parkinson's disease	0.26% (0.23–0.31%)	5	0.41% (0.34–0.45%)	4	58.5
Tension-type headache	0.33% (0.20–0.50%)	4	0.35% (0.21–0.52%)	5	4.9
Other NDs	0.21% (0.19–0.24%)	6	0.24% (0.20–0.28%)	6	12.8
Multiple sclerosis	0.15% (0.13–0.17%)	7	0.20% (0.17–0.22%)	7	38.6
Motor neuron disease	0.13% (0.11–0.14%)	8	0.20% (0.17–0.22%)	8	56.3

^aAlzheimer's disease and other dementias.

Table 3 NCNDs related DALY counts, age-standardized rates and percent change for male and female in the USA, 1990, 2017

	Male						Female					
	1990		2017		Percent change		1990		2017		Percent change	
	Number	Rate 100 000	Number	Rate	Number	Rate 100 000	Number	Rate 100 000	Number	Rate 100 000	Number	Rate 100 000
Global	28 695 611.1	1312.3	46 258 788.7	1275.1	61.0	−3.00	40 248 881.8	1670.9	64 907 538.6	1606.9	61.00	−4.00
NCNDs	1 612 027.4	1246.8	2 601 385.2	1297.3	61.3	4.05	2 878 102.3	1780.0	4 177 905.2	1843.4	45.16	3.57
Motor neuron disease	54 672.1	41.8	113 233.8	51.4	107.1	23.02	45 231.0	30.1	85 782.8	35.0	89.65	16.60
ADOD ^a	482 495.8	377.9	943 268.4	385.3	95.5	1.95	994 851.4	429.7	1 609 481.9	439.0	61.78	2.18
Parkinson's disease	108 734.4	80.4	255 446.8	104.1	134.9	29.39	95 185.0	44.0	156374.3	48.3	64.28	9.80
Epilepsy	151 278.8	121.0	203 769.0	124.6	34.7	2.92	152 690.0	114.0	212 174.6	123.1	38.96	7.94
Multiple sclerosis	38 104.6	28.1	66 147.5	31.2	73.5	11.13	77 389.7	52.0	137 862.6	62.4	78.14	19.90
Migraine	567 995.1	432.5	738 062.6	439.3	29.9	1.57	1 292 043.9	949.8	1 666 257.9	968.8	28.96	2.00
Tension-type headache	111 537.5	85.1	150 348.8	85.2	34.8	0.18	149 834.1	107.2	199 302.3	107.5	33.02	0.33
Other NDs	97 208.9	79.7	131 108.1	75.9	34.8	−4.79	70 876.9	53.0	110 668.4	59.0	56.14	11.2

^aAlzheimer's disease and other dementias.

percent change increase for females was in multiple sclerosis (19.9%), motor neuron disease (16.3%) and other NDs (11.2%), respectively. For males, they were in Parkinson's disease (29.3%), motor neuron diseases (23.0%) and multiple sclerosis (11.1%). Altogether, females were more impacted by the burden of the NCNDs as an aggregate or when examined separately.

NCNDs related DALYs by age

In 2017, children between the ages of 5 and 9 years experienced the largest age-standardized DALY rates due to

epilepsy [118.3 (UI 63.29–194.50)], raising 14% from 103.6 (UI 57.1–171.0) in 1990, burdening 24 136.4 (UI 12 911.0–3968.4) children in this age category. In the same year, age-standardized DALY rates due to migraines were highest in people aged 35 years to 39 years [1274.2 (UI 825.6–1833.1)] followed by people aged 40–44 years [1261.9 (UI 828.5–1784.7)] causing 461 930.5 (UI 374 012.1–671 380.5) number of DALYs. ADOD age-standardized DALYs rates rapidly increased after age 65 years and became the dominant NCND burden for individuals between the ages of 65 and 95+ years, accounting for 74 787.64 (UI 70 407.78–79 585.73) DALY rates

(Supplementary Table 1) and 2.4 million (UI 1.73–1.96) total DALYs. Yet, the increase in the age-standardized DALY rates of epilepsy in the 65–69 years group from 147.1 (UI 84.5–231.8) to 208.7 (UI 114.9–333.7) in the 85–89 years age group is noticeable.

In 2017, migraine was the leading cause of NCND in females and males between the ages 35 and 44, contributing to 3149 (UI 2016.3–4546.4), and 1372.6 (UI 846.9–2100.5) DALYs per 100 000, respectively. The sharp increase in the age-standardized DALYs for ADOD was also evident in both sexes after age 65 (Fig. 1).

NCNDs related DALYs by the states

In 2017, across the 50 States, NCNDs related age-standardized DALY rates differences were negligible. Nevertheless, the State with the largest aggregate NCNDs age-standardized DALYs was Montana [1712.7 (UI 1369.2–2137.0)], and the State with lowest DALYs was California [1471.5 (UI 1141.7–1884.9)] (Fig. 2 and Supplementary Table 2). Moreover, the age-standardized DALY rates for migraine, ADOD, epilepsy and tension headache ranked 1st, 2nd, 3rd and 4th, respectively, across the States (Fig. 3). In 2017, the States with the largest age-standardized DALY rates for migraine were District of Columbia [725.5 (UI 461.8–1050.8)], followed by North Carolina and Georgia. South Carolina was the State with the largest age-standardized DALY rates for ADOD [544.9 (UI 496.9–598.1)], followed by Georgia and Alabama. Michigan [151.8 (UI 70.1–287.8)] had the largest age-standardized DALY rates for epilepsy, followed by West Virginia and Louisiana. District of Columbia, Minnesota and Mississippi had the largest rates of tension-type headache (Table 4).

Across all the States, the DALYs (per 100 000) ranking of migraine and ADOD in females were first and second

(Supplementary Fig. 3). However, in males, with some exceptions, in the majority of the States, ADOD ranked first, and migraine ranked second in males (Supplementary Fig. 4).

DALYs attributed risks for NCNDs

Of the 84 risks quantified in GBD 2017, high BMI [92.03 (UI 40.4–159.2)], smoking [55.4 (UI 28.4–81.5)], high FPG [47.9 (UI 11.8–101.2)] and alcohol use [31.4 (UI 17.5–51.1)] were the attributable age-standardized DALY risks for aggregate NCNDs (Table 5) and (Supplementary Fig. 5). In 2017, high BMI [556 906.7 (UI 24 579.7–966 510.9)], smoking [313 080.9 (UI 156 446.8–470 030.6)] and high FPG [289 994.5 (UI 67 283.5–613 875.2)] contributed the largest number of DALYs for ADOD, respectively. This followed by alcohol use [113 250.7 (UI 61 973.7–184 139.9)] as the only attributable DALYs risk for epilepsy and smoking [26 766.5 (UI 180 715.7–35 636.0)] for multiple sclerosis (Table 5).

From 1990 to 2017, there was an increase in the proportion of age-standardized DALY rates for ADOD attributable to high BMI (31%) and high FPG (42%), while the proportion of ADOD attributable risk to smoking decreased 58%. DALY rates for epilepsy attributable to smoking increased 6.0%, while this rate for multiple sclerosis attributable to alcohol decreased by 19% (Table 5).

South Carolina had the highest age-standardized DALY rates for ADOD attributable to high BMI [115.4 (UI 201.1–48.9)]. District of Columbia had the highest DALY rates for ADOD attributable to smoking [66.5 (UI 105.7–31.6)]. South Carolina had the highest DALY rates for ADOD attributable to high FPG [65.6 (UI 139.6–15.5)]. Michigan was the State with the highest DALYs for epilepsy attributable to alcohol [41.0 (UI 85.5–15.6)], and the State with the highest DALYs for multiple

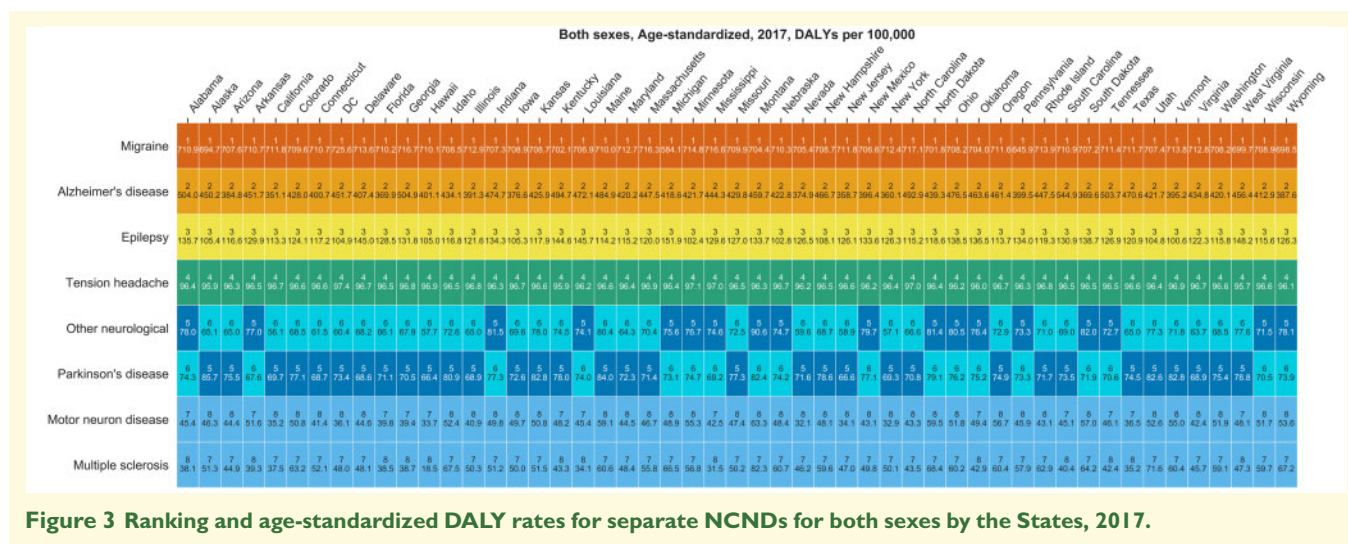


Figure 3 Ranking and age-standardized DALY rates for separate NCNDs for both sexes by the States, 2017.

Table 4 States with the largest age-standardized DALY rates due to migraine, ADOD, epilepsy and tension, headache, for both sexes, 2017

States	NCNDs	Rates (95% UI)
District of Columbia	Migraine	725.5 (461.8–1050.8)
North Carolina	Migraine	717.0 (455.1–1039.3)
Georgia	Migraine	716.7 (455.9–1032.7)
South Carolina	Alzheimer's disease and other dementias	544.9 (496.9–598.1)
Georgia	Alzheimer's disease and other dementias	504.9 (460.8–552.5)
Alabama	Alzheimer's disease and other dementias	503.9 (457.3–549.8)
Michigan	Epilepsy	151.8 (70.1–287.8)
West Virginia	Epilepsy	148.1 (54.8–311.3)
Louisiana	Epilepsy	145.7 (60.8–278.8)
District of Columbia	Tension-type headache	97.4 (54.3–156.6)
Minnesota	Tension-type headache	97.0 (54.7–155.1)
Mississippi	Tension-type headache	97.0 (54.7–154.0)

Table 5 Attributable all age DALY numbers, age-standardized DALY rates (per 100 000) and age-standardized DALYs percent change risks for ADOD, multiple sclerosis and epilepsy for both sexes in the USA, 1990 and 2017

NCNDs	Aggregate NCNDs Age-standardized rate				Alzheimer's disease and other dementias			Epilepsy	Multiple sclerosis
	High BMI Number/ rate	Smoking Number/ rate	High FPG Number/ rate	Alcohol Number/ rate	High BMI Number/ rate	Smoking Number/ rate	High FPG Number/ rate	Smoking Number/ rate	Alcohol Number/ rate
1990	240 450.6/69.7	439 380.1/124.3	120 738.5/33.6	82 189.2/29.6	248 450.6/9.7	461 764.8/129.4	120 738.5/33.6	82 189.2/29.6	21 664.9/7.6
2017	556 906.7/92.0	313 564.1/55.4	289 945.4/47.9	113 250.7/31.4	55 690.7/92.1	313 080.9/51.1	289 945.4/47.9	113 250.7/31.4	26 766.5/6.1
	1990/2017% change				1990/2017% change			1990/2017% change	
	124.1%/31.9%	-28.6%/-55.3%	140.1%/42.6%	37.7%/6.1%	124.1/31.9%	-32.2/-58.2%	140.1/42.6%	37.7/6.1%	23.5/-19%

sclerosis attributable to smoking was Montana [11.4 (UI 17.3–6.5)] (Supplementary Table 3).

Discussion

In this article, we aimed to present a comprehensive assessment of the US status and trends in the burden of NCNDs. We found that by contributing to nearly 7 million and nearly 7% of the GBDs, NCNDs were the sixth leading cause of DALY rates in 2017. These estimates have remained nearly stable since 1990 (GBD Neurological Disorders Collaborator Group, 2017; Roth et al., 2018) and confirm that high-income countries are mostly burdened with NCNDs (GBD Neurological Disorders Collaborator Group, 2019). The absolute number of aggregate NCNDs and their age-standardized rates increased by 18.5% and 3.4%, respectively, between 1990 and 2017. The increase in the absolute numbers of DALYs is expected with the population growth and aging. Also, the longer one lives, the longer one is exposed to the behavioural, environmental and metabolic risk factors (GBD 2017 Risk Factor Collaborators, 2018).

Of the individual NCNDs, migraine, followed by ADOD, epilepsy and tension headache, were the top four

contributors of DALY rates between 1990 and 2017. Parkinson's disease DALY rate moved up from the sixth leading NCNDs in 1990 to the fifth in 2017. Of the NCNDs in this study, the largest contributor of all age DALYs were ADOD (2.54%), migraine (2.38%), followed by epilepsy, and Parkinson's disease, both equally contributing to 0.41% of total DALYs. These findings are consistent with previous findings of GBD, and other national and international studies (Lipton et al., 2001; GBD Neurological Disorders Collaborator Group, 2017; Burch et al., 2018; GBD 2016 Headache Collaborators, 2018) suggesting interventions and quality of medical care aimed at reducing the burden of NCNDs have not been effective enough.

NCNDs related DALYs by sex

For the aggregate NDs, the burdens were significantly higher in females than in males, with female to male ratio of 1.4 and 1.6, respectively. A higher prevalence of migraines in females compared to males has been reported before (Lipton et al., 2001; Burch et al., 2018). Of individual NCNDs, females were primarily burdened by migraines and ADOD. However, men's health was compromised primarily by ADOD, migraine and Parkinson's diseases, similar to previous findings from

other western countries (Stovner *et al.*, 2007; Miller and Cronin-Golomb, 2010; Vukovic *et al.*, 2010; Hirsch *et al.*, 2016; GBD Neurological Disorders Collaborator Group, 2017; Vetvik and MacGregor, 2017). With the exception of other neurological diseases, both females and males experienced an increase in the burden of NCNDs between 1990 and 2017; however, females experienced slightly more increase. The increase with time in the burden of neurological diseases may be explained by the change and improvement of the diagnostic criteria and procedure for suspect cases, and the longer survival of the affected individuals (Dubois *et al.*, 2014; Wijnen *et al.*, 2018; Pinkhardt *et al.*, 2019; Pinto *et al.*, 2019). It is also likely that the decrease in other NDs is the result of the improvement in early detection of the more common neurological cases (Petersen *et al.*, 2001; Iranzo *et al.*, 2006). Among the females, multiple sclerosis, motor neuron diseases and other NDs presented the largest percent increase in DALY rates between 1990 and 2017. In males, Parkinson's disease, motor neuron diseases and multiple sclerosis were the top three NCNDs with the highest percent of change in DALY rates between 1990 and 2017. These findings suggest the need for further research to understand risk factors related to sex differences in NCNDs. For example, while sex hormones, genetic variations, exposure to and response to stress, and pain have been some of the proposed determining factors for variations in migraine risk in sexes (Peterlin *et al.*, 2011) there is also evidence to support that males are underdiagnosed (Vetvik and MacGregor, 2017).

NCNDs related DALYs by age

In 2017, epilepsy was particularly burdensome in children aged 5–9 years. Paediatric epilepsy is a common chronic ND and an important contributor to childhood disability (Aaberg *et al.*, 2017; Lekoubou *et al.*, 2018). Minimizing the burden of childhood epilepsy requires careful implementation and evaluation of home healthcare, outpatient and therapeutic interventions (Kassebaum *et al.*, 2017). The noticeable second peak in the burden of epilepsy in older individual in our findings supports multiple reports that with the increase of aging population it is likely that older people develop new-onset epilepsy (Faught *et al.*, 2012; Choi *et al.*, 2017; Sen *et al.*, 2018; GBD Neurological Disorders Collaborator Group, 2019). In one report, the annual incidence of epilepsy in adults over the age of 65 from 85.9 per 100 000 was reported to be more than 135 per 100 000 in those over the age of 80 (Ziso *et al.*, 2017). With the continuing aging population, the treatment of epilepsy in older individuals amid their comorbid conditions may require the familiarity of the neurologist with the treatment complexity of this disorder to inform their therapeutic decision making better (Sen *et al.*, 2018).

Migraine and tension headaches were highly burdensome for adolescents and young adults, especially the 35- and 44-years old individuals, similar to previous population-based epidemiological studies (Lipton *et al.*, 2001; Burch *et al.*, 2018; Philipp *et al.*, 2019; Hagen *et al.*, 2020). Daily stress due to school work, and lack of adequate sleep, among other factors, precipitate the burdens of these disorders in school-age children and the adult population (Visudtibhan *et al.*, 2010; Houle *et al.*, 2012; Pellegrino *et al.*, 2018). We found similar results for both females and males with small variations. Females experienced the burden of migraine and tension headaches for a slightly longer period, i.e., until 44 years. For males, the pick age of experiencing these burdens ends at 39 years. Overall, the burden of migraine in the adults, ADOD, and new-onset epilepsy in older adults burden the health of the working population, and with the aging of the population could become among the most costly ailments in the USA.

NCNDs related DALYs by the States

In 2017, in all 50 States in the USA, migraine, Alzheimer's diseases, epilepsy and tension headache held the top four ranks in terms of DALY rates for both sexes. In females, however, in eight States, including Alaska, DC, Hawaii, Iowa, Minnesota, Nebraska, New Hampshire and Vermont tension headache ranked third leading Parkinson's disease, and in males, in seven States including DC, Maine, Minnesota, Montana, New Hampshire, Texas and Vermont Alzheimer's disease ranked first leading migraine. In both 1990 and 2017, except for five States, including Alaska, California, DC, Nevada, and New Jersey, the burden of combined NCNDs in terms of DALY rates increased in both sexes. These findings allow benchmarking State-specific NCNDs health loss. The interpretation of differences in the burden of NCNDs by States requires an understanding of the regional risk exposure as well as the role of cultural, social and economic factors influencing NCNDs related availability and accessibility to care.

DALYs attributed risks for NCNDs

Our assessment also highlights the crucial part played by the risk factors such as high BMI, smoking, high FPG and alcohol use in contributing to the burden of aggregate and individual NCNDs in both sexes in the USA. In general, these risks have been positively associated with non-communicable diseases and socioeconomic development status of the societies (GBD 2017 Risk Factor Collaborators, 2018). Of the 84 risks, we identified that high BMI, smoking, and high FPG were the contributing risk factors in increasing the burden of Alzheimer's diseases. While smoking was the contributing risk factor for increasing the burden of multiple sclerosis, and alcohol

use was the contributing risk factor for increasing the burden of epilepsy.

Previous studies have reported the association between high BMI and the risk of dementia. (Arnoldussen *et al.*, 2019; Bianchi *et al.*, 2019; Gregorio *et al.*, 2019; Nam *et al.*, 2019). A new systematic review study indicates the essential role of nutrition in the pathogenesis and evolution of neurodegenerative diseases (Bianchi *et al.*, 2019). According to this review, while high BMI and malnutrition are risk factors for the development of dementia and Parkinson's disease, Mediterranean diet, a diet rich with nutritional support and calorie-controlled diets are protective against these diseases (Bianchi *et al.*, 2019). It is also suggested that nutritional interventions may provide a better outcome for patients diagnosed with dementia (Chen *et al.*, 2019). Furthermore, the evidence for the direct and possible indirect association between tobacco and Alzheimer's disease, as well as tobacco and multiple sclerosis, is presented in previous studies (Campdelacreu, 2014; Durazzo *et al.*, 2014; Kvistad *et al.*, 2016; Moss *et al.*, 2017; Marck *et al.*, 2020; Wang *et al.*, 2019). Also, results from the lab and human research have supported the risk of long-term alcohol use in increasing the risk of epilepsy (Leach *et al.*, 2012; Welch and Derry, 2014; Fu *et al.*, 2016).

It is evident that with population aging, the cost of screening, identification and treatment of NCNDs will increase (Nag and Jelinek, 2019). Researchers have suggested the self-management approach in adopting healthy lifestyle behaviours (Nag and Jelinek 2019). However, to reduce the health burden of NCNDs requires the willingness and cooperation of the institution of medicine and public health policymakers. Our findings provide these constituents with information that could have the potential to improve the prevention of NCNDs, as well as the care of those who carry the burden of NCNDs (Orgeta *et al.*, 2019). They also can help those who are accountable for prioritizing investments in research and development for the health and social services that will be required to deal with an aging population (Prince *et al.*, 2016).

Limitations

Our results are limited since GBD estimates are influenced by the quality, time and availability of epidemiological data that supply the GBD study. Besides, the complex grouping of NCNDs sub-causes in GBD is continuously changing due to new additions of diseases. Also, the GBD study does not allow to account for the racial health disparities in the burden of NCNDs.

Also, our findings of the burden of NCNDs in the USA are underestimated since the list of NDs we used is not comprehensive and does not include infectious conditions, stroke, brain and other nervous system cancers, traumatic brain and spinal cord injuries. Indeed, a future iteration of similar study should include stroke, since the contribution of the stroke to the burden of NCNDs is

significant (GBD Neurological Disorders Collaborator Group, 2019). Also, GBD uses the global standard population, which is a much younger population compared to the USA, therefore downsizing the burden of NCNDs, which mainly occur in older adults. Additionally, in the list of risk factors in the GBD, we were unable to identify risks attributable to the burden of migraine, tension headache and motor neuron diseases. Since these neurological conditions largely burden the working segment of the population, more research is needed to identify their risk factors, to quantify their level of exposure, and to report trends in exposures and the resulting disease burden. Nevertheless, our findings reveal an increase in the burden of aggregate and separate NCNDs, which can stimulate hypothesis generation on the effects of interventions in the prevention and management of NCNDs.

Conclusions

In summary, between 1990 and 2017, the burden of NCNDs, both in terms of numbers and rates, has increased, suggesting these conditions have exceeded the effect of population growth. Also, the health burden of migraine, ADOD and epilepsy surpassed the burden of the other NCNDs during this time. In 2017, migraines and tension headaches topped the burden of NCNDs for the young adult and adult segments of the USA, while the elderly were the most vulnerable populations to ADOD and epilepsy. Additionally, females were more burdened by migraine, tension headache, ADOD and multiple sclerosis, while the burden of Parkinson's disease, epilepsy, motor neuron disease and other NDs were more common in males than females. This suggests the need for further research to understand risk factors for sex differences. Moreover, our data show modifying risk factors such as smoking and alcohol use, as well as obesity and high blood sugar, contribute to the burden of ADOD, epilepsy and multiple sclerosis. While risks attributable to smoking decreased for ADOD and multiple sclerosis, the risks attributable to obesity, high blood sugar and alcohol (except for multiple sclerosis) increased between 1990 and 2017. These findings suggest that with the aging of the US population, the burden of NCNDs will continue to impact the health of the individuals and their families, which subsequently will impose a financial burden on society. Moreover, our findings of the burden of NCNDs by sex, age and risk factors in the US inform health policymakers what risk modification strategies in a specific population could have the potential to improve the burden of NCNDs.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

The authors report no competing interests.

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