Incidence, prevalence, and global burden of autism spectrum disorder from 1990 to 2019 across 204 countries

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Summary

Autism spectrum disorder (ASD) substantially contributes to the burden of mental disorders. Improved awareness and changes in diagnostic criteria of ASD may have influenced the diagnostic rates of ASD. However, while data on trends in diagnostic rates in some individual countries have been published, updated estimates of diagnostic rate trends and ASD-related disability at the global level are lacking. Here, we used the Global Burden of Diseases, Injuries, and Risk Factors Study data to address this gap, focusing on changes in prevalence, incidence, and disability-adjusted life years (DALYs) of ASD across the world. From 1990 to 2019, overall age-standardized estimates remained stable globally. Both prevalence and DALYs increased in countries with high socio-demographic index (SDI). However, the age-standardized incidence decreased in some low SDI countries, indicating a need to improve awareness. The male/female ratio decreased between 1990 and 2019, possibly accounted for by increasing clinical attention to ASD in females. Our results suggest that ASD detection in low SDI countries is suboptimal, and that ASD prevention/treatment in countries with high SDI should be improved considering the increasing prevalence of the disorder. Additionally, growing attention is being paid to ASD diagnosis in females, who might have been left behind by ASD epidemiologic and clinical research previously. ASD burden estimates are underestimated as GBD does not account for mortality in ASD.

Introduction

Neurodevelopmental disorders affect individuals' lives since very early developmental stages[1] and contribute substantially to the burden of mental disorders.[2, 3] Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders defined by persistent deficits in social communication and interaction in multiple contexts, as well as by restricted, repetitive patterns of behaviour, interests, or activities, and hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment. ASD symptoms usually begin in early life,[4] but may become more evident when social demands exceed individuals' capacities or alternative learning coping strategies, causing clinically significant impairment in functioning.[5] Data on the prevalence and socio-economic impact of ASD have been reported for a number of individual countries. For instance, a recent, large register-based cohort study in Denmark, including 6,989,627 residents, showed a prevalence of 400 per 100,000 for ASD.[6] ASD ranked 5th for males and 8th for females among mental and substance use disorders in terms of years lived with disability (YLD), and it accounted for the bulk of disability in childhood and adolescence. In contrast, the disabilities associated with schizophrenia and personality disorders were more evident in adulthood.[6] Notably, both ASD and schizophrenia were directly associated with disease-specific health loss proportion (HeLP, average proportion of health loss that individuals experience because of a specific mental or substance disorder, and additional comorbid mental and substance disorders) (77% for ASD, 89% for schizophrenia), as opposed to other disorders where comorbidities accounted for the vast majority of HeLP.[6] In the European project "Autism Spectrum Disorders In Europe (ASDEU)", the prevalence of ASD in children aged 7-9 ranged from 476 per 100,000 in South-Eastern France to 3,130 per 100,000 in Iceland.[7] In another study from India, ASD was estimated to have a prevalence of 400 per 100,000 in 2017, and in terms of disability-adjusted life years (DALYs; an index of overall disease burden), ASD ranked 7th among the mental disorders.[8] In Iran, the weighted ASD prevalence estimate for 6–18 years old subjects was as low as 63 to 160 per 100,000, in China *177 per 100,000*, lower than less recent estimates from United Arab Emirates (290 per 100,000 for 0–14 year children), and Israel (480 per 100,000 for 1–12 year children) [9–11], whilst large values were estimated in Bangladesh, 2009 (842 per 100,000) and Sri Lanka, 2009 (1,070 per 100,000), and very large values in Lebanon, 2016 (1,530 per 100,000) and South Korea, 2011 (2,640 per 100,000).[12] In the United States of America, the prevalence of ASD was estimated at 340 per 100,000 in 1996.[13]

121 Findings across numerous countries consistently showed higher prevalence and disability in males than
122 females.[6, 8, 13] In relation to time trends, different figures have been reported for individual countries, e.g.,
123 in India there was negligible age-standardized changes in ASD prevalence and DALYs from 1990-2017 (<1%
124 prevalence change, no significant DALY changes),[8] as opposed to substantial prevalence increase in Sweden
125 (250% among 0-17 years old from 2001 (420 per 100,000) to 2011 (1,440 per 100,000), and specifically 700%
126 increase in children/adolescents without intellectual disability).[14]
127 Regarding global estimates, in 2010, there were around 52 million estimated cases of ASD worldwide
128 (prevalence of 760 per 100,000, 58 DALYs per 100,000).[15] Furthermore, the global prevalence of ASD in
129 children <5 years old, across countries, has been estimated at 723 per 100,000 in 2016.[16, 17]
130 While data on prevalence, prevalence trends, and ASD-related disability have been published for individual
131 countries or globally, an updated and detailed analysis of ASD prevalence, prevalence trends over the past
132 decades, incidence and disability worldwide across the lifespan, is currently lacking.[15, 16] Additionally,
133 there is a need to better understand ASD prevalence and disability according to sex, country, and socio-
134 demographic index (SDI).
135 The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 offers a unique opportunity to
136 estimate the prevalence and disability of over 360 conditions[18] including ASD, across over 204 countries
137 and territories (with first administrative level disaggregation for 22 countries), with over 3·5 billion estimates
138 of health and health system measures from 281,586 different sources, available separately per sex and age
139 group, measured on common standardized indicators[19], from 1990 to 2019. Drawing on the GBD 2019, the
140 aim of this study was to provide the most comprehensive report to date on ASD global prevalence and disability
141 across the past 30 years.
142 Assessing trends in diagnostic rates is particularly relevant in the light of concerns on the possible impact on
143 administrative prevalence and incidence driven by changes in nosographic systems. For instance, changes in
144 the diagnostic criteria of ASD from the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV to
145 DSM-5 have led to a decrease of 13-20% in its estimated prevalence within the same dataset.[20, 21] Some
146 experts suggest the DSM-5 criteria are more stringent than DSM-IV,[22] and some children meeting the
147 criteria under the DSM-IV-TR pervasive developmental disorder (PDD) will not meet DSM-5 ASD criteria
148 but might meet the social communication disorder (SCD). Individuals with significant language deficits, high

149 overall levels of functioning, low levels to no restrictive repetitive behaviors, and individuals who barely meet
150 PDD-not otherwise specified (NOS) criteria are at greatest risk for such shifting.[20, 21] However, increased
151 awareness on ASD or exposure to potential environmental risk factors – such as pollutants/pesticides (even if
152 their role is no clear yet),[23] may have contributed to the higher administrative prevalence of the disorder, at
153 least in some countries. Therefore, a comprehensive assessment of ASD prevalence and disability at the global
154 level over the past decades is needed to estimate if and to what extent these potential factors have led to actual
155 differences over time and across regions. Based on the available literature, we hypothesized that differences
156 of prevalence and burden of ASD across countries exist, and that these differences are influenced by SDI.
157 Understanding the geographic and socioeconomic variation in the disease burden of ASD can inform national
158 and regional healthcare policies contributing to appropriate allocation of public resources.
159

160 **Methods**

161 **Data source**

162 The GBD 2019 Results Database is publicly available through the Global Burden of Disease Collaborative
163 Network website (http://ghdx.healthdata.org). In GBD 2019, ASD is defined based on DSM (III, III-R, IV, IV-
164 TR, 5), ICD (9, 10), Chinese Classification of Mental Disorders (CCMD), or diagnosed by a clinician using
165 established tools. Additional information on the methodology is available in the supplementary methods in the
166 appendix (Tables S1-S4, Figures S1-S8).[18]
167 GBD 2019 estimates provide information about incidence, prevalence, mortality, years of life lost (YLLs),
168 YLDs, and DALYs related to 369 diseases and injuries.[18] Data are provided for 204 countries and territories,
169 grouped into 21 regions and seven super-regions, and extracted from censuses, household surveys, civil
170 registration and vital statistics, disease registries, health service use, air pollution monitors, satellite imaging,
171 disease notifications, and other sources. GBD collects data from a total of 86,249 sources, including 19,354
172 sources reporting deaths, 31,499 sources reporting incidence, 19,773 sources reporting prevalence, and 26,631
173 sources reporting other metrics. Diseases and injuries analyzed by the GBD are organized into four levels of
174 hierarchy from Level 1 to Level 4. Level 1 includes three broad causes for death and disability (i.e.,
175 communicable, maternal, and nutritional diseases; non-communicable diseases; and injuries). With increasing

176 granularity, Level 2 includes 22 different causes, Level 3 encompasses 174 different causes, and Level 4
177 provides the most specific estimates related to 301 specific causes.[18]
178
179 **Measures**
180 We extracted prevalence, incidence, and DALYs with their uncertainty interval (95%UI, 2·5 and 97·5
181 percentiles)[18] for ASD, globally, and by region, income group, and sex, from 1990 to 2019. Each estimate
182 is presented both as raw measure and as age-standardized rate (appendix Table S5-10).
183 DALY, an index of overall disease burden, is defined as the sum of YLLs and YLDs. One DALY represents
184 the loss of equivalent one year of full health.[24] YLL is an indicator of premature mortality, which is based
185 on a maximum observed life expectancy as a reference. It is calculated by multiplying the number of deaths
186 due to a condition and standard life expectancy at the age of death. YLD reflects the burden of illness on quality
187 of life, and is based on standardized disability weights for each health state. It is calculated by multiplying the
188 number of incident cases in the population, the "disability" weight of the specific condition, and the average
189 duration of the case until remission or death. Hence, death is a key outcome to estimate disability.
190 Estimates are provided according to SDI, which is determined by income per capita, educational attainment,
191 and total fertility rate in women <25 years old.[18] SDI categories are low (<0·46), low-middle (0·46-0·61),
192 middle (0·61-0·69), high-middle (0·69-0·80), high (>0·80). SDI of 204 GBD countries and territories are
193 provided in appendix Table S11. SDI centrality and dispersion measures as well SDI levels across countries
194 are reported in appendix Figure S8.
195
196 **Statistical analyses**
197 GBD assembles clinical informatic data including hospital data, ambulatory (including general practitioner)
198 visits, and health insurance claims. For each GBD causes (diseases), ratios of non-primary to primary diagnosis
199 rate, and ratios of outpatient to inpatient care are extracted from several regions.[18] The log of the ratios are
200 modelled by age and sex using MR-BRT (Meta-Regression-Bayesian Regularised Trimmed), the Bayesian
201 meta-regression tool.[18]

GBD uses three main modelling strategies including Cause of Death Ensemble model (CODEm), Spatiotemporal Gaussian process regression, and DisMod-MR 2.1 to generate estimates of each measure of interest by age, sex, location, and year.[18] Details of each model are provided in Supplementary methods.

Results

Prevalence, incidence, and DALYs estimates for every five years from 1990-2019 are reported in Table 1. Since in GBD YLL is zero in ASD, YLDs and DALYs values are identical. The same estimates for each year from 1990 to 2019 are also reported (appendix Table S5). GBD 2019 estimated that in 2019, over 28 million people were affected by ASD globally, corresponding to an age-standardized prevalence of ASD of 0·37%, or 369·39 per 100,000 (95%UI=305·95-441·19). Incident cases were 603,790 globally, corresponding to an age-standardized incidence of 9·32 (95%UI=7·75-11·12) per 100,000. In terms of change from 1990 to 2019, the raw number of individuals with ASD increased approximately from an estimate of 20 million (95%UI=16·9-24·2) to over 28 million (95%UI=23·5-33·8), corresponding to a relative increase of 39·3% in terms of the global prevalence of ASD (appendix Table S5). However, corresponding changes in age-standardized prevalence were negligible at the global level. Similarly, changes in both raw and age-standardized incidence estimates were also negligible at the global level.

In 2019, ASD was associated with 4,306,615 DALYs globally, corresponding to an age-standardized estimate of 56·26 DALYs per 100,000 (95%UI=36·82-81·52). As for prevalence, raw DALYs largely increased by 38·66%, but the change in age-standardized DALYs was negligible.

However, ASD was associated with different prevalence and disability figures in specific countries. Estimates were also different across countries according to different SDI strata (Table 2). As shown in Figure 1, age-standardized prevalence and DALYs of ASD were particularly high in countries with high SDI. In 2019, in 40 high SDI countries, the ASD age-standardized prevalence was 579·32 per 100,000 (95%UI=485·3-684·53), corresponding to an increase of 7·36% since 1990. Similarly, in high SDI countries, age-standardized incidence rate was 14·55 per 100,000 (95%UI=12·26-17·12), corresponding to a 9·02% increase from 1990. In 33 low SDI countries, the ASD prevalence remained overall stable, while in 2019 age-standardized incidence was 8·37 per 100,000 (95%UI=6·91-10), corresponding to an 8·57% decrease from 1990. Age-standardized

229 DALYs increased by 7·23% from 1990-2019 in high SDI countries (in 2019 88·19 per 100,000, 95%UI=57·85-
230 126·31), while age-standardized DALYs remained substantially unchanged in low SDI countries.
231 Geographical variability of ASD prevalence and disability is shown in appendix Figure S3-4. The largest
232 increase in age-standardized DALY occurred in the GBD high-income super-region, mainly from 2005 to
233 2010. Estimates of prevalence, incidence, and DALYs by GBD region in 1990 and 2019 are reported in
234 appendix Table S6. The largest age-standardized prevalence increase from 1990-2019 occurred in North
235 America (high income) (21·62%, 95%UI=18·81-24·34), with a homogeneous trend in incidence (20·87%
236 increase, 95%UI=18·1-23·61), and DALYs (21·21% increase, 95%UI=18·17-24·38). In 2019, the highest age-
237 standardized prevalence and DALYs were found in high-income Asia Pacific, high-income North America,
238 and Western Europe (appendix Figure S5-6). Across 204 GBD countries and territories, SDI and age-
239 standardized DALYs were significantly correlated (appendix Figure S7). For instance, Somalia and
240 Afghanistan had low SDI and DALYs (SDI=0·081, DALYs=57·45 per 100,000 for Somalia, SDI=0·343,
241 DALYs=43·4 per 100,000 for Afghanistan) of ASD. The UK had the highest age-standardized DALYs (112·29
242 per 100,000) among the high SDI counties (0·843). Interestingly, Taiwan showed the lowest DALYs (33·31
243 per 100,000) although it has a high SDI (0·868). Prevalence, incidence, and DALYs in 1990 and 2019 for each
244 GBD country are reported in appendix Table S10.
245 Both prevalence and DALYs remained >3 times higher in males than females during the last 30 years, but the
246 male to female ratio (both number ratio, and age-standardized rate ratio) progressively decreased from 1990
247 to 2019 (Figure 2, appendix Figure S1). Yearly figures in males and females are reported in appendix Table
248 S9. Prevalence, incidence, and DALYs in 2019 across GBD regions for males and females separately are
249 available in appendix Table S7.
250 The male to female ratio of ASD prevalence and DALYs was stable across age groups as well, with the number
251 ratio decreasing in older age groups due to longer life-expectancy for women, but with the age-standardized
252 rate ratio increasing, due to more undiagnosed women than men earlier in the observation period (Figure 3,
253 appendix Figure S2). Prevalence, incidence, and DALYs across age groups for males and females separately
254 in 2019 are available in appendix Table S8.
255

Discussion

To our knowledge, this is the first study estimating prevalence, prevalence rates trends and disability related to ASD worldwide over the past three decades.

We found that both raw prevalence and disability related to ASD have increased over the last 30 years globally (1990-2019), but that the corresponding age-standardized figures have remained overall stable globally. The lack of material change in global age-standardized estimates can be misleading. In fact, the age-standardized prevalence and disability related to ASD increased in high SDI countries, while it remained stable or decreased in low SDI countries. The increase in raw numbers is a combination of the increased age-standardized estimates in high SDI countries and the number of total population in low SDI countries, whose age-standardized estimates are stable (Table 2). Over the past three decades, relatively more females were diagnosed with ASD, despite the challenges in diagnosing ASD among high-functioning females due to camouflage or co-occurring internalized symptoms.[25] Yet, males remained around three times more likely to receive an ASD diagnosis globally in 2019. The increase in the global raw prevalence of ASD is consistent with findings previously published at a local level, across different high SDI countries. For instance, in Japan, the cumulative incidence of ASD has been rising from 2009 to 2016 nationwide.[26] In Denmark, the ASD incidence has also increased both in youth and adults.[27]

There are at least two possible factors concomitantly contributing to such trends. First, certain risk factors for ASD[28] might have increased over time, resulting in increased rates of ASD. For example, in a recent umbrella review pooling evidence from 46 meta-analyses of observational studies, reporting on 67 factors putatively associated with 544,212 cases of ASD, credibility of evidence was graded as convincing for maternal age ≥35 years old (31% increased risk), maternal chronic hypertension (48% increased odds), maternal gestational hypertension (37% increased odds), and maternal overweight before or during pregnancy (28% increased odds).[2, 29] Interestingly, among these risk factors, there is evidence of increased global rates in advanced maternal age from the UK,[30] China,[31] South Korea,[32] and Greece.[33] Also, a report from GBD 2019 showed that hypertensive disorders during pregnancy have increased by almost 11% from 1990 to 2019, from a raw incidence of 162·96 per 100,000 in 1990 to 180·76 per 100,000 in 2019.[34] Also, the highest figures of maternal hypertensive disorders emerged for older maternal age groups.[34] Even maternal obesity has increased over the last decades. For instance, in the UK, from 1990 to 2004, maternal obesity increased

284 from 9,900 per 100,000 to 16,000 per 100,000, and up to a projected 22,000 per 100,000 in 2010 if the upward
285 trend would persist.[35] Similar figures emerged according to nationally representative samples including
286 619,323 births between 1989 and 2007, again from the UK, describing an increase in first trimester maternal
287 obesity prevalence from 7,600 per 100,000 to 15,600 per 100,000.[35] Similarly, in US, the proportion of
288 women aged 20-39 years with BMI more than 30 kg/m^2 increased from less than 10,000 per 100,000 to 31,800
289 per 100,000 between 1970s and 2011.[36] Obesity has doubled in the US from 2000 to 2018.[37]
290 Second, the increase in the prevalence and related burden of ASD might be due to increased screening and
291 diagnostic capacity in high SDI countries. ASD diagnostic attention has extended into adulthood,[27] and
292 persons previously misdiagnosed with psychosis ortual disability or personality disorders now receive an ASD
293 diagnosis.[38] Also, services offering support and early detection of ASD might have expanded over previous
294 years in high SDI countries, with subsequently improved capacity of early diagnosis.[26, 27] In 2006, the
295 American Academy of Pediatrics recommended screening all children for ASD during routine paediatrician
296 visits at 18 and 24 months of age, which parallels the main increase of age-standardized DALY in the GBD
297 high-income super region from 2005-2010.[39] Also, the hypothesis of increased prevalence due to increased
298 screening and diagnostic capacity has been confirmed by some initial reports showing increased service use of
299 children with ASD in recent years.[17, 40, 41] Additionally, data from the ASDEU [42] study in Italy show
300 that ASD prevalence estimate increased from 799 per 100,000 to 1,150 per 100,000 depending on source of
301 data, with real-world registries underestimating prevalence as opposed to studies based on ad-hoc screening
302 tools.[42, 43] ASDEU data also showed that ASD prevalence estimation was sensitive to the effects of local
303 clinical practices and investment in diagnostic training of local teams. For instance, in France, the use of the
304 national classification of psychiatric disorders historically led to a more restrictive use of ASD diagnosis. In
305 contrast, the increasing trend observed in South-Western France was likely related to the investment of
306 specialized teams, even though the prevalence of ASD in South-Eastern France was still overall low due to a
307 paucity of early diagnosis and specific management structures of ASD. In Iceland, the number of teams that
308 formally diagnose ASD has increased since 2010, in which contributed to particularly high prevalence
309 compared to the other countries. [44]

310 In some high-income countries, a range of benefits are provided to families with children with a formal
311 diagnosis of ASD, which is likely to raise the detection of ASD. For instance, in UK, many children with
312 ASD are qualified for disability living allowance (DLA), claiming carer's allowance or child tax credit. [45]

313 On the other hand, some high SDI countries, especially Taiwan, showed lower prevalence and disease
314 burden compared to high-income Western countries. These low estimates are likely due to several reasons;
315 (1) most studies in Asia only included special school population, overlooking the mainstream school
316 population; (2) most studies in China have not used contemporary screening and diagnostic methods.[46]
317 Taiwan had even lower disease burden of ASD compared to China, likely due to the lack of standardized
318 methods for estimating the prevalence of ASD. Indeed, in a systematic review, Hong Kong and Taiwan
319 showed a more than 200-fold difference among reports from multiple registry systems, and there must be
320 substantial methodological differences to result in such a huge variation. [47]

321 However, globally, ASD is still inadequately addressed by current mental health services and organizations.
322 For instance, in the United States of America, less than half of mental health facilities provide specific
323 behavioural treatments, and only around one-third of these facilities accept new cases with ASD.[48]
324 Geographical insights from global reports of risk factors for ASD are also valuable in interpreting changes in
325 ASD figures in low SDI. For instance, if certain risk factors for ASD have increased, it would be surprising
326 not to see a corresponding increase in ASD, unless major improvements have been implemented in other
327 aspects of ASD prevention, which is reasonably unlikely in low SDI countries. Hence, since maternal
328 hypertensive disorders have largely increased in low SDI countries,[34] the low prevalence ASD figures in
329 low SDI countries might be interpreted as a lack of proper screening and diagnostic services for ASD.
330 This study has some limitations. First, GBD 2019 estimates were based on mathematical models, and where
331 evidence was not available, data were imputed. Further efforts are required to reflect all disease burden. In
332 our study, deaths and YLLs could not be estimated for ASD in spite of the known premature mortality
333 associated with medical comorbidities.[49] Indeed, among mental disorders listed in the 2019 GBD study,
334 deaths and YLLs were only calculated for anorexia nervosa and bulimia nervosa, as these were the only
335 mental disorders considered by the GBD group as directly underlying causes of death. For mental disorders
336 for which the cause of death is another disease or injury, such as suicide, YLLs and deaths was not

337 considered to fully reflect all premature mortality. A method in order to estimate the proportion of premature
338 deaths from those indirect causes is not yet available for current estimation of YLLs.[50] While GBD 2019
339 provides the most comprehensive and updated sources of estimates of burden of diseases to date, burden
340 estimates arelikely underestimated.
341 Second, while raw prevalence, incidence, and burden of ASD have increased in the last 30 years, global age-
342 standardized estimates did not, which can be a misleading results if finer grained results split by SDI group
343 are not considered. Also, as the vast majority of cases of ASD have onset in childhood, the age-standardized
344 estimates of ASD are less relevant than when disorders affecting older strata of the population are under
345 investigation.[51, 52]
346 Third, as suggested by others,[52] the DSM/ICD algorithms for ASD are only guiding principles in order to
347 organize available information from different data sources and informants. Such algorithms are crucial since
348 caseness based on 'scoring above/below threshold' results are also insufficient.[52] Hence prevalence and
349 incidence estimates might have been influenced by the ASD definition criteria across different sources and the
350 change of criteria from DSM-IV to DSM-5.
351 Also, we do not report prevalence, incidence and burden of ASD by intellectual disability levels, despite the
352 previous report that YLDs of intellectual disability levels constitutes DALY of ASD.[18] Lastly, multiple
353 studies have shown that the presence of co-occurring problems of ASD including ADHD, could diminish the
354 performance of diagnostic algorithms of ASD.[53–57] GBD 2019 took the disability weights for the sequela
355 of ASD for intellectual disability into account, but methods to make dependent comorbidity corrections
356 computationally feasible are still under development.[18] Current GBD database provides the prevalence,
357 incidence, and YLDs of ASD according to six intellectual disability levels; ASD with no, borderline, mild,
358 moderate, and profound intellectual disability. Among 167 input sources, only 19 studies that reported
359 information on the IQ level were used in the meta-analysis to calculate the severity splits by intellectual
360 disability.[18] In the upcoming studies, those sequelae can also be taken into account with more input data and
361 modified classification criteria since DSM-5 classifies intellectual disability into four levels.[5]
362 Alongside its limitations, there are also strengths of the current study. In epidemiological studies of ASD, there
363 is no uniform approach to case definition across published studies. For example, surveys of large national
364 registrations or administrative databases usually result in a downward bias, and surveys that rely on parent

report in a household survey often overestimate prevalence.[52] One of the strengths of the GBD 2019 is that its estimates with known biases were adjusted or crosswalked for alternative definitions. For instance, estimates of autism rather than of ASD, general population surveys without additional case finding, record report, and review of record notes, were adjusted (appendix Table S2, Table S4).[18]

Additionally, consistent with previous epidemiological surveys of ASD,[52] there were very few studies from low SDI countries as classified by the World Bank 2020. GBD 2019 also utilized data inputs for ASD from 34 countries. However, GBD 2019 used an integrated modelling approach to estimate not only the epidemiological parameters for regions with available data, but also for the countries and territories, as well as regions in which sufficient data were not available.[18]

In summary, results of the present study show that raw ASD prevalence and related burden have increased over the last 30 years in high SDI countries, without concomitant large improvement of management strategies for the disorder (even though there has been progress over the last 30 years), which led to increased disability. In low SDI countries, suboptimal detection strategies likely led to an absence of increase or even a decreased prevalence. Insufficient prevention strategies as well as changes in health services organizations in high (and possibly also in low) SDI countries likely contributed to the increased incidence of ASD. Overall, results of this study call for more resources to be allocated to detect ASD in low SDI countries and to prevent ASD in high SDI countries, as well as to decrease illness burden of ASD globally. ASD burden estimates in GBD are likely underestimated.

Acknowledgments

Not applicable

Authors' contributions

All authors contributed and approved the study's protocol. MS created the first draft of the manuscript. MS, DY and SL analysed data. MS, JS, and SC provided overall guidance. All authors read, edited, and approved the final version of the manuscript.

392 **Conflict of interest statements**

393 MS received honoraria/has been consultant for Angelini, Lundbeck. CUC has been a consultant and/or advisor
394 to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Damitsa,
395 Gedeon Richter, Hikma, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-
396 ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka,
397 Pfizer, Recordati, Rovi, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva,
398 and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring
399 Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He
400 received royalties from UpToDate and is also a stock option holder of LB Pharma.

401

402 **Data sharing**

403 Data are publicly available at the Institute for Health Metrics and Evaluation (IHME) website
404 (http://www.ghdx.healthdata.org/gbd-results-tool).

405

406 **Ethics committee approval**

407 We followed the standard procedure recommended to register additional publication from GBD2019 project
408 after publication of capstone paper.[18] Our study was also approved by the Institutional Review Board at
409 Yonsei University Health System for the data use.

410

411

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561

562 **Figure Legends**

563 **Figure 1(a). Age-standardized prevalence rates (per 100 000) by location, both sexes combined, 2019 (b).**
564 **Age-standardized DALY rates (per 100 000) by location, both sexes combined, 2019**
565 DALY=disability-adjusted life-year
566
567 **Figure *2.* Trends from 1990 to 2019 *(a)* in number and age-standardized prevalence rates *(b)* in male to**
568 **female (M/F) prevalence ratio of ASD at the global level.**
569 Error bars indicate the 95% uncertainty level (UI) for prevalent cases. Shading indicates the 95% UI for the
570 age-standardized prevalence rate. ASD= autism spectrum disorder.
571
572 **Figure 3. Age patterns by sex in 2019 of (a) the total prevalent cases and age-specific prevalence rate (b)**
573 **male to female (M/F) prevalence ratio of ASD at the global level.**
574 Error bars indicate the 95% uncertainty level (UI) for prevalent cases. Shading indicates the 95% UI for the
575 age-standardized prevalence rate. ASD= autism spectrum disorder
576

577 **Table Legends**

578 **Table 1. Global prevalence, Incidence, and DALYs attributable to ASD, by year (age-standardized**
579 **rate per 100000)**

580 Data in parentheses are 95% uncertainty intervals (UI). ASD=autism spectrum disorder, DALY=disability-
581 adjusted life-year.

582

583 **Table 2. Prevalence, Incidence, and DALYs of ASD in counts and age-standardized rates for both sexes**
584 **combined in 1990 and 2019, with percentage change between 1990 and 2019 by SDI**

585 Data in parentheses are 95% uncertainty intervals (UI). ASD=autism spectrum disorder, SDI=socio-
586 demographic index, DALY=disability-adjusted life-year.

587

Table 1. Global prevalence, Incidence, and DALYs attributable to ASD, by year (age-standardized rate per 100000)

	Prevalence	Incidence	DALYs
1990	372·85 (309·07, 444·87)	9·17 (7·62, 10·92)	56·69 (37·01, 82·21)
1995	371·47 (307·85, 443·26)	9·18 (7·63, 10·94)	56·51 (36·9, 82·09)
2000	370 (306·49, 441·51)	9·21 (7·65, 10·97)	56·3 (36·75, 81·67)
2005	368·41 (305·12, 439·59)	9·2 (7·64, 10·96)	56·08 (36·67, 81·38)
2010	371·08 (307·6, 442·85)	9·3 (7·73, 11·09)	56·52 (36·98, 82·05)
2015	369·75 (306·24, 441·47)	9·32 (7·75, 11·11)	56·33 (36·81, 81·65)
2019	369·39 (305·95, 441·19)	9·32 (7·75, 11·12)	56·26 (36·82, 81·52)
Percent change between 1990 and 2019	-0·93 (-1·29, -0·61)	1·71 (1·37, 2·04)	-0·76 (-1·36, -0·16)

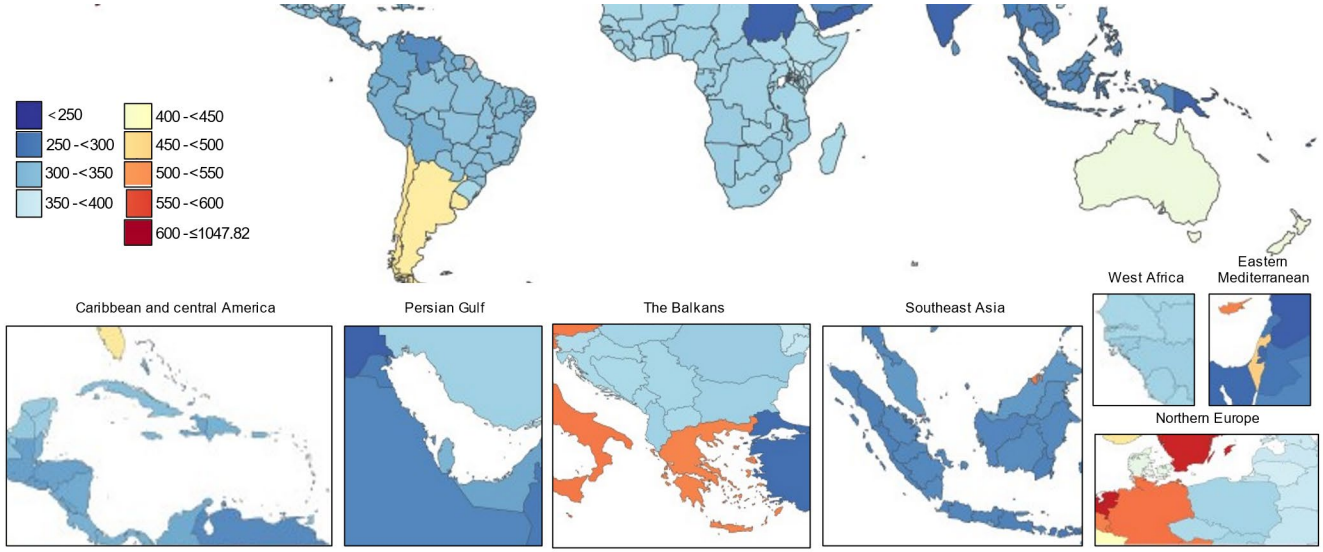
Data in parentheses are 95% uncertainty intervals. ASD=autism spectrum disorder, DALY=disability-adjusted life-year.

588

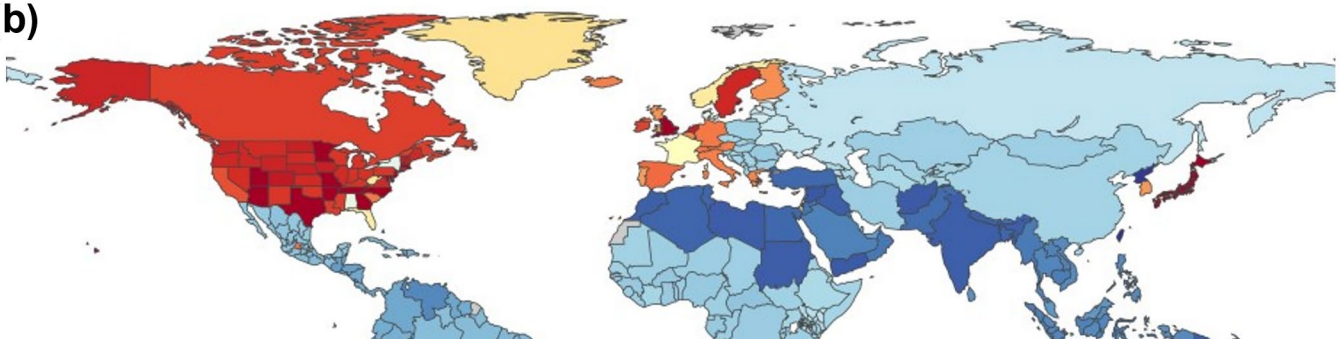
Table 2. Prevalence, Incidence, and DALYs of ASD in counts and age-standardize rates for both sexes combined in 1990 and 2019, with percentage change between 1990 and 2019 by SDI

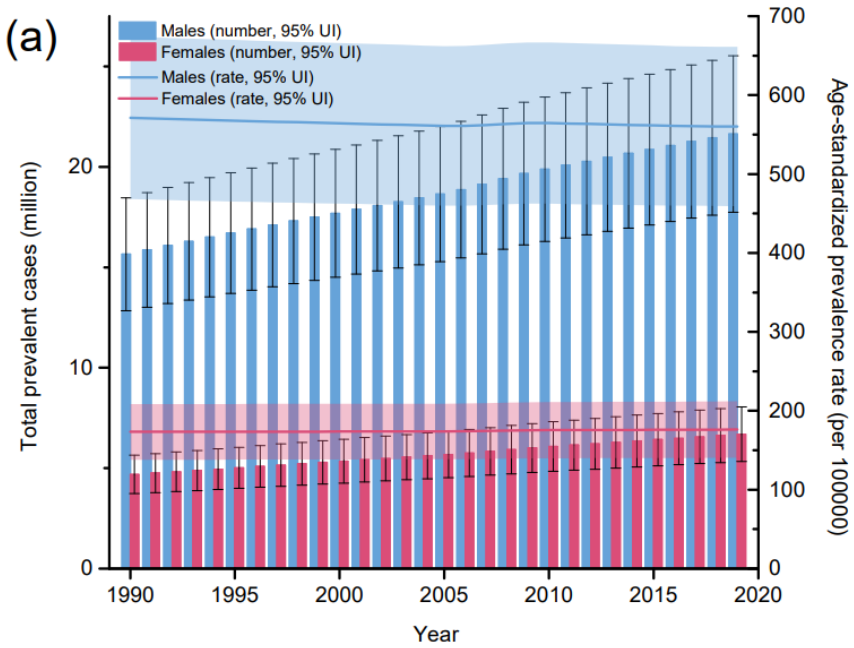
	1990		2019		Change in age-standardized rates 1990 vs 2019 (%)
	Counts	Age-standardized Rate (per 100k)	Counts	Age-standardized Rate (per 100k)	
Prevalence					
High SDI	4319310·91 (3613075·85, 5102134·39)	539·6 (451·69, 638·43)	5484191.81 (4587040.6, 6520432.4)	579.32 (485.3, 684.53)	7.36 (6.32, 8.44)
High-middle SDI	4665416·45 (3863288·72, 5575606·19)	404·58 (334·91, 483·25)	5520270.68 (4566935.66, 6619212.44)	405.43 (335.95, 485.02)	0.21 (-0.13, 0.58)
Middle SDI	5698915·84 (4667746·23, 6901112·08)	319·69 (262·68, 387·21)	7566751.79 (6220223.87, 9144157.82)	321.44 (264.5, 388.03)	0.55 (-0.13, 1.2)
Low-middle SDI	3710773·55 (3057599·06, 4450284·58)	311·5 (257·2, 373·87)	5612896.33 (4621358.88, 6739732.39)	312.82 (258.23, 375.69)	0.42 (0.19, 0.71)
Low SDI	1931430·44 (1592707, 2329439·65)	340·49 (280·16, 408·27)	4125396.41 (3401889.87, 4965501.49)	342.19 (281.4, 410.17)	0.5 (0.34, 0.67)
Incidence					
High SDI	75696·18 (63921·23, 89058·3)	13·34 (11·27, 15·7)	72188.89 (60836.09, 84978.74)	14.55 (12.26, 17.12)	9.02 (7.85, 10.18)
High-middle SDI	100983·35 (83515·13, 120116·77)	10·17 (8·41, 12·1)	77478.68 (64215.47, 92331.77)	10.26 (8.5, 12.22)	0.86 (0.48, 1.3)
Middle SDI	173883·21 (143430·56, 208736·99)	8·41 (6·94, 10·1)	139285.52 (114749.5, 167031.97)	8.11 (6.69, 9.73)	-3.57 (-4.4, -2.78)
Low-middle SDI	148418·01 (122088·01, 177305·72)	8·17 (6·72, 9·76)	137108.79 (112678.55, 163454.94)	8.07 (6.63, 9.62)	-1.25 (-1.59, -0.91)
Low SDI	103576·67 (85506·15, 123644·4)	9·16 (7·56, 10·93)	151148.38 (124810.59, 180570.67)	8.37 (6.91, 10)	-8.57 (-8.97, -8.22)
DALYs					
High SDI	654788·46 (429488·92, 932431·28)	82·24 (53·77, 117·37)	822966.75 (541875.32, 1175034.03)	88.19 (57.85, 126.31)	7.23 (5.77, 8.62)
High-middle SDI	713058·64 (465214.03, 1032596.51)	61·81 (40·34, 89·52)	838198.35 (546345.01, 1211677.09)	62.11 (40.45, 89.8)	0.48 (-0.65, 1.63)
Middle SDI	875926·92 (569680.49, 1284765·37)	48·84 (31·84, 71·55)	1155444.35 (754950.52, 1679972.43)	49.2 (32.13, 71.58)	0.74 (-0.38, 1.94)
Low-middle SDI	566660·58 (372962·49, 827870·71)	47·17 (31·01, 68·47)	856770.97 (561754.28, 1245320.05)	47.6 (31.17, 69.08)	0.91 (-0.4, 2.14)
Low SDI	293882·69 (191832·25, 427362·15)	51·31 (33·63, 74·49)	630884.75 (414558.98, 917939.77)	51.87 (34.07, 75.17)	1.08 (-0.18, 2.28)

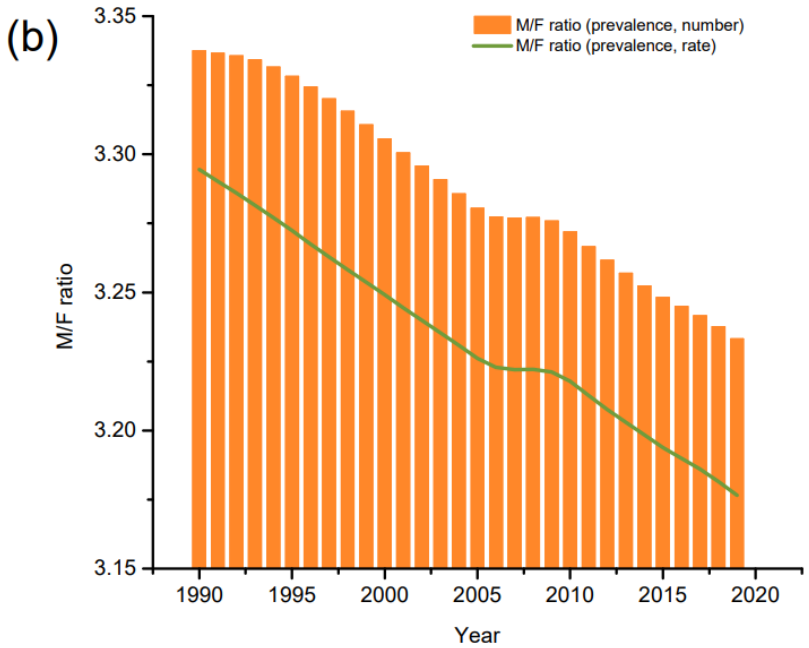
Data in parentheses are 95% uncertainty intervals (UI). ASD=autism spectrum disorder, SDI=socio-demographic index, DALY=disability-adjusted life-year.

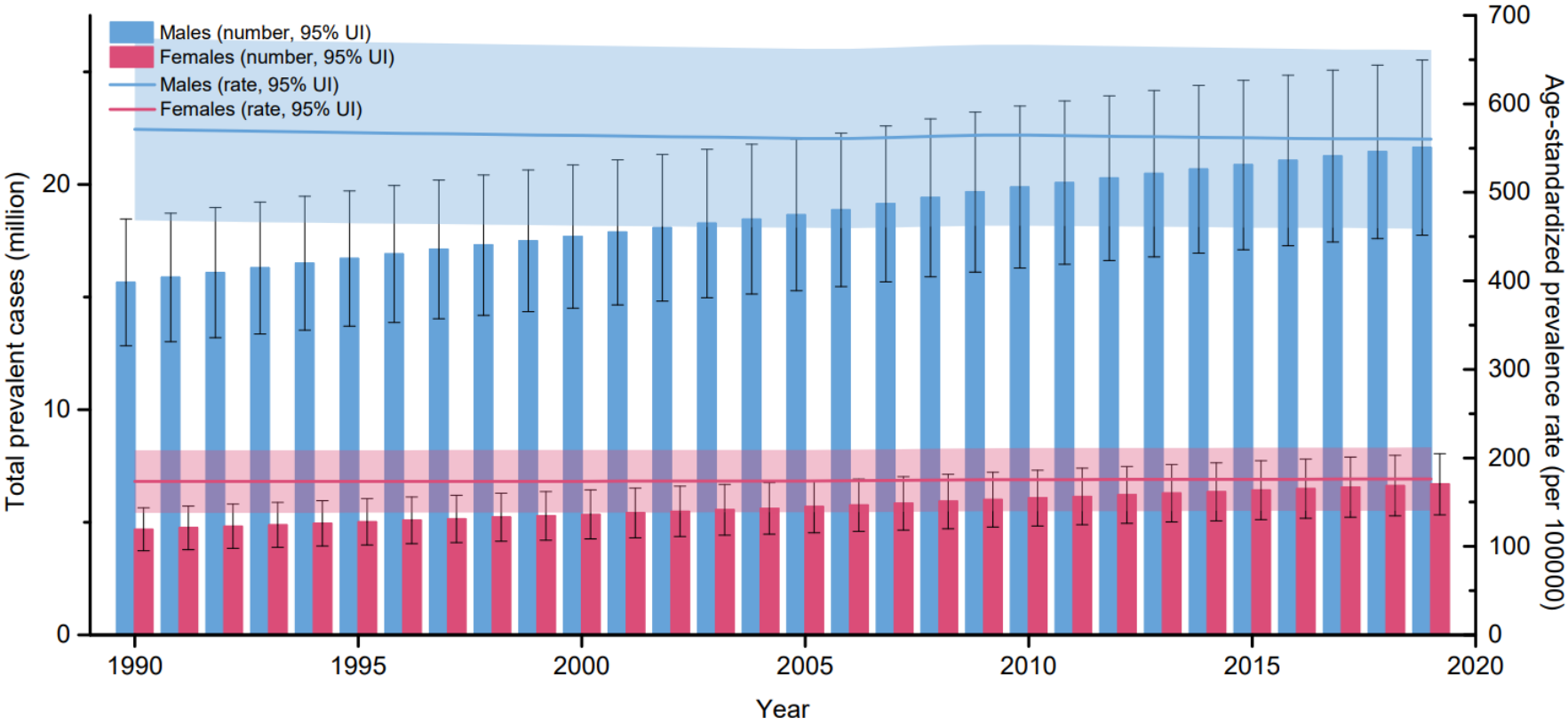

<250
250-<300
300-<350
350-<400
400-<450
450-<500
500-<550
550-<600
600-≤1047.82
Caribbean and central America
Persian Gulf
The Balkans
Southeast Asia
West Africa
Eastern Mediterranean
Northern Europe

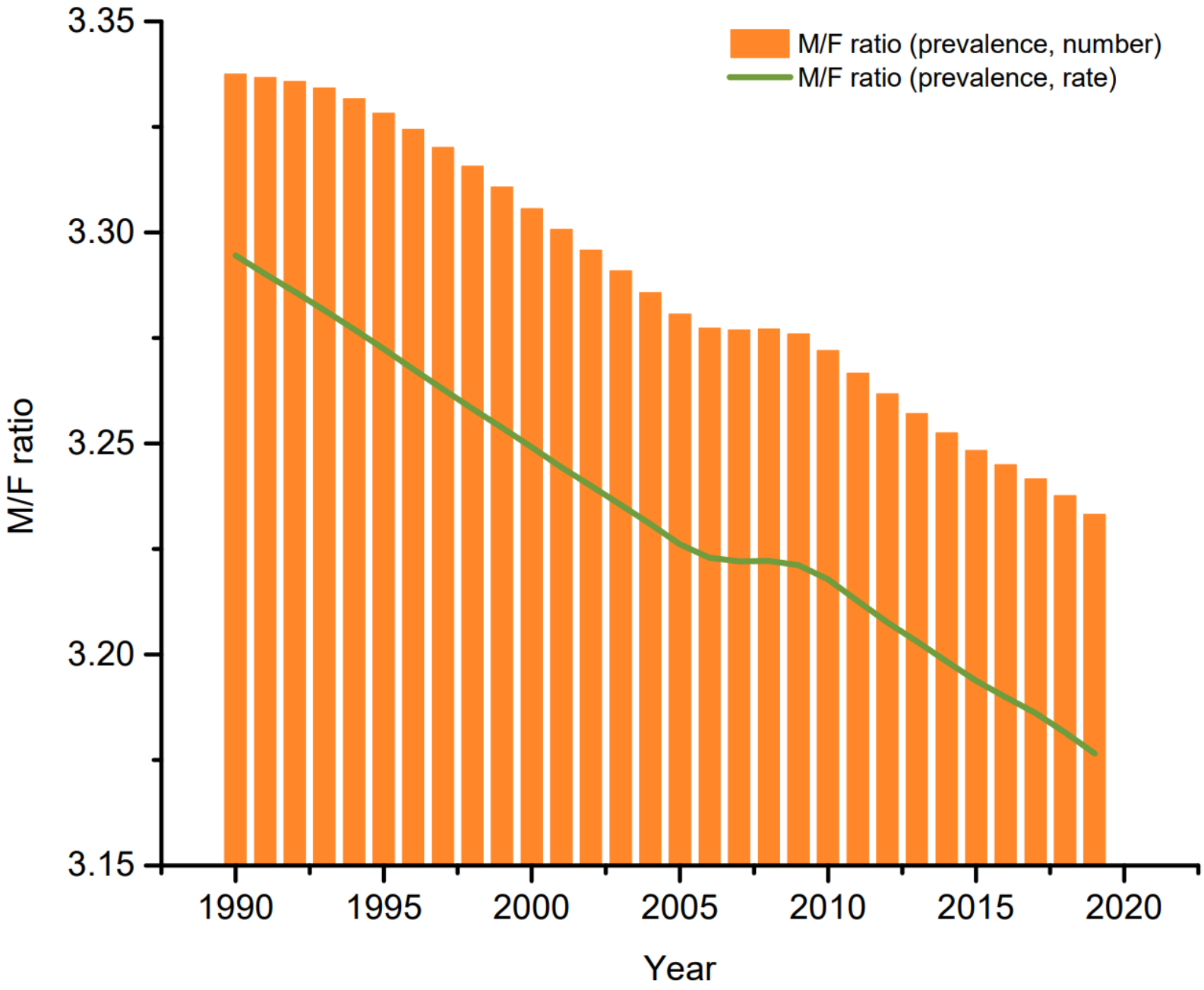
(b)

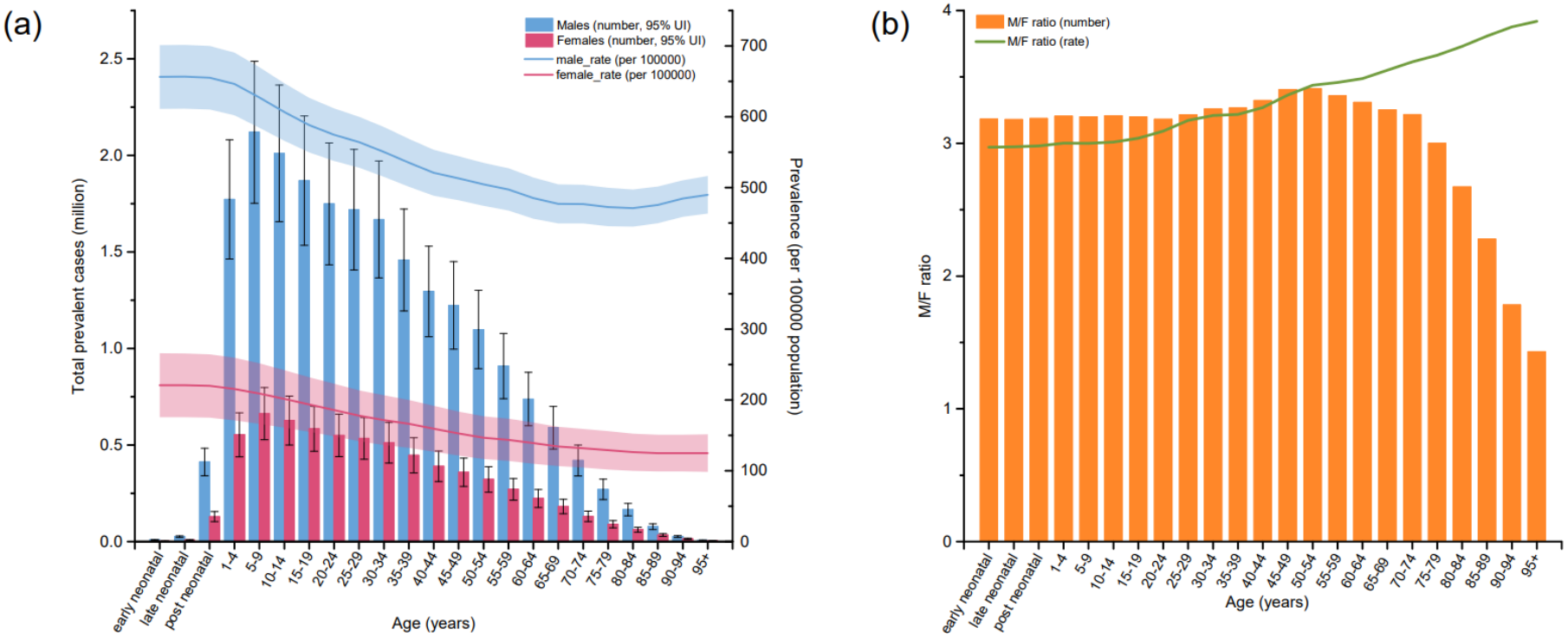


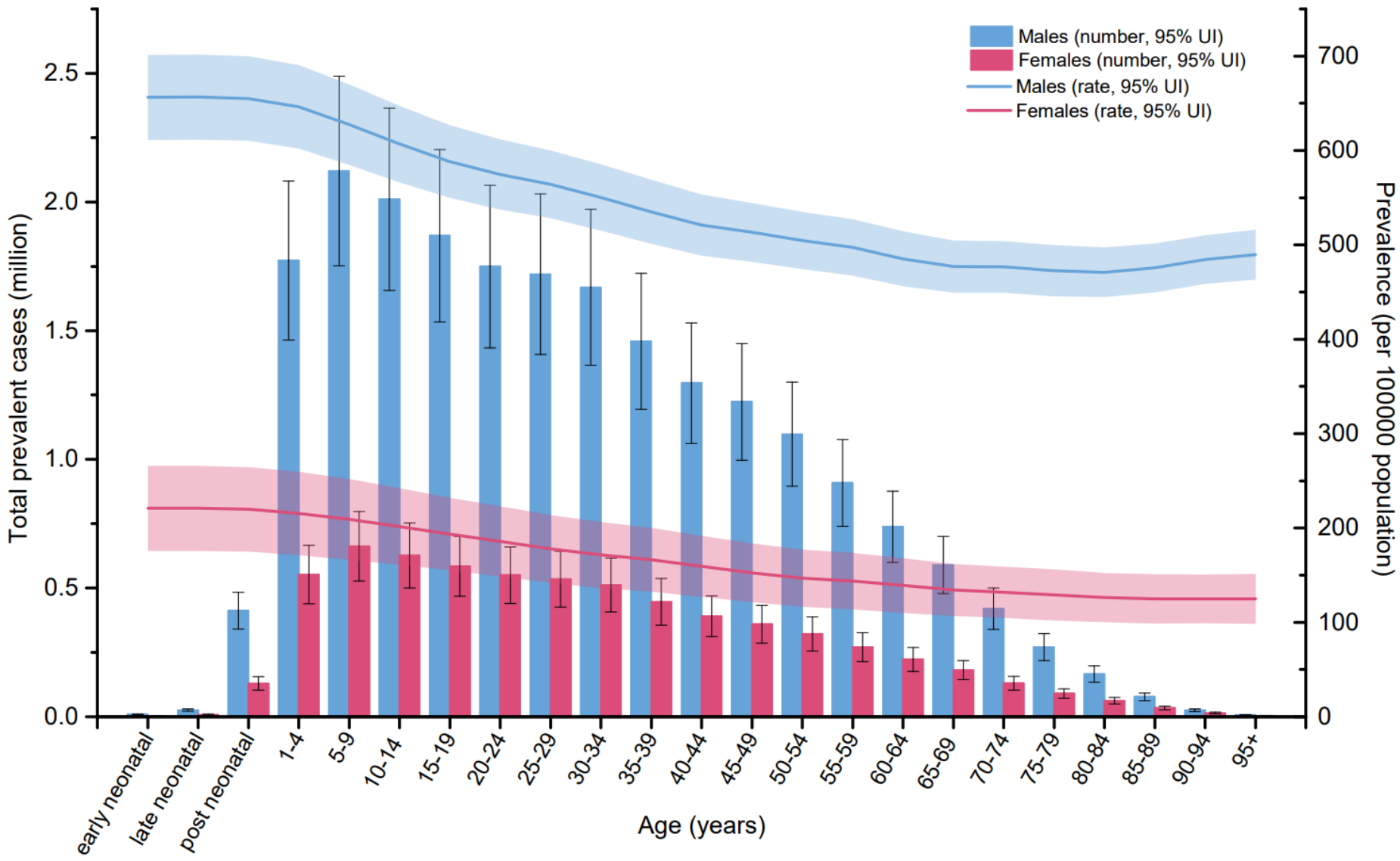

(a)
Males (number, 95% UI)
Females (number, 95% UI)
Males (rate, 95% UI)
Females (rate, 95% UI)
Total prevalent cases (million)
Age-standardized prevalence rate (per 100000)
Year
0
10
20
0
100
200
300
400
500
600
700
1990
1995
2000
2005
2010
2015
2020

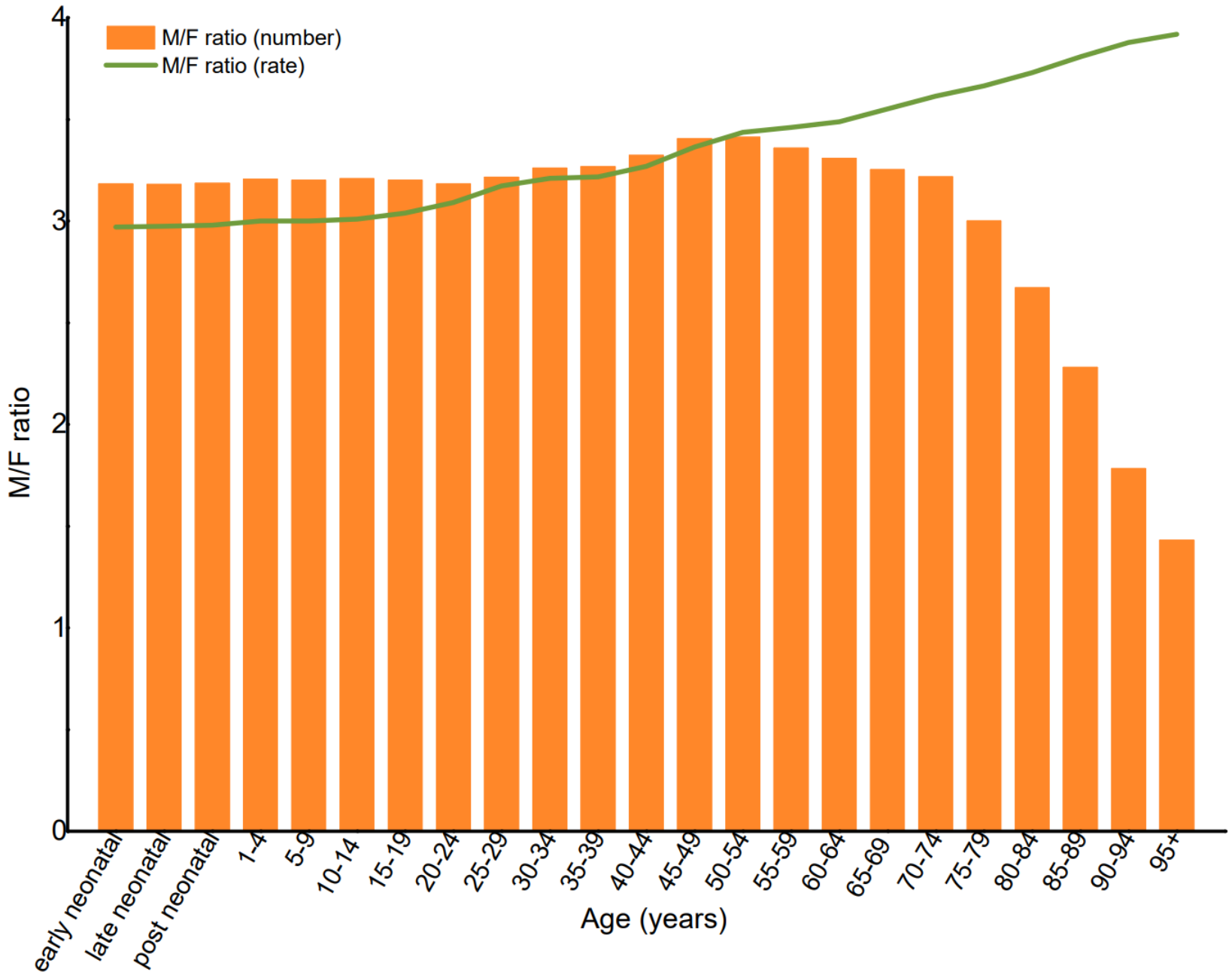

(b)
M/F ratio (prevalence, number)
M/F ratio (prevalence, rate)
M/F ratio
Year
3.15
3.20
3.25
3.30
3.35
1990
1995
2000
2005
2010
2015
2020


Males (number, 95% UI)
Females (number, 95% UI)
Males (rate, 95% UI)
Females (rate, 95% UI)
Total prevalent cases (million)
Age-standardized prevalence rate (per 100000)
Year
0
10
20
0
100
200
300
400
500
600
700
1990
1995
2000
2005
2010
2015
2020


M/F ratio (prevalence, number)
M/F ratio (prevalence, rate)
3.35
3.30
3.25
3.20
3.15
M/F ratio
1990
1995
2000
2005
2010
2015
2020
Year


(a)
Males (number, 95% UI)
Females (number, 95% UI)
male_rate (per 100000)
female_rate (per 100000)
Total prevalent cases (million)
Prevalence (per 100000 population)
Age (years)
(b)
M/F ratio (number)
M/F ratio (rate)
M/F ratio
Age (years)


Males (number, 95% UI)
Females (number, 95% UI)
Males (rate, 95% UI)
Females (rate, 95% UI)
Total prevalent cases (million)
Prevalence (per 100000 population)
Age (years)
0.0
0.5
1.0
1.5
2.0
2.5
0
100
200
300
400
500
600
700
early neonatal
late neonatal
post neonatal
1-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90-94
95+


M/F ratio (number)
M/F ratio (rate)
M/F ratio
0
1
2
3
4
early neonatal
late neonatal
post neonatal
1-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90-94
95+
Age (years)