	All ages deaths (thousands)			Age-standardised death rates (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
(Continued from previous page)						
Gallbladder and bile duct disease	74·0 (63·6–93·6)	89·1 (72·1–105·0)	20·4%	1·8 (1·5–2·2)	1·3 (1·1–1·6)	−25·5
Pancreatitis	51·6 (37·7–64·6)	76·6 (57·4–95·5)	48·5%	1·2 (0·9–1·5)	1·2 (0·9–1·4)	−6·0
Other digestive diseases	247·9 (194·2–296·2)	378·1 (301·6–500·4)	52·5%	5·9 (4·6–7·0)	5·7 (4·5–7·5)	−3·1
Neurological disorders	594·5 (468·3–703·0)	1273·8 (980·9–1466·9)	114·3%	13·7 (10·8–16·1)	18·8 (14·5–21·8)	37·8
Alzheimer's disease and other dementias	141·2 (110·8–208·5)	485·7 (307·8–590·5)	244·0%	3·6 (2·8–5·4)	7·1 (4·5–8·6)	95·4
Parkinson's disease	53·5 (42·4–70·1)	111·1 (81·2–138·6)	107·7%	1·4 (1·1–1·8)	1·7 (1·2–2·1)	20·8
Epilepsy	130·2 (86·4–167·7)	177·6 (119·7–222·3)	36·4%	2·6 (1·8–3·1)	2·6 (1·7–3·2)	1·0
Multiple sclerosis	15·4 (11·4–18·8)	18·2 (14·1–21·8)	17·8%	0·4 (0·3–0·4)	0·3 (0·2–0·3)	−25·0
Other neurological disorders	254·2 (154·1–343·1)	481·1 (317·9–690·7)	89·3%	5·7 (3·5–7·7)	7·2 (4·8–10·4)	25·9
Mental and behavioural disorders	138·1 (95·2–188·0)	231·9 (176·3–329·1)	68·0%	3·2 (2·2–4·3)	3·5 (2·6–4·9)	9·3
Schizophrenia	20·0 (13·1–24·6)	19·8 (16·6–25·0)	−1·3%	0·5 (0·3–0·6)	0·3 (0·2–0·4)	−36·7
Alcohol use disorders	74·6 (40·1–119·2)	111·1 (64·0–186·3)	48·9%	1·8 (1·0–2·8)	1·7 (1·0–2·8)	−5·0
Drug use disorders	26·6 (15·5–56·4)	77·6 (48·8–124·4)	191·7%	0·5 (0·3–1·2)	1·1 (0·7–1·8)	112·5
Opioid use disorders	8·9 (5·0–18·7)	43·0 (26·9–68·4)	385·8%	0·2 (0·1–0·4)	0·6 (0·4–1·0)	257·5
Cocaine use disorders	1·2 (0·7–2·7)	0·5 (0·2–0·5)	−55·1%	<0·05 (0·0–0·1)	<0·05 (0·0–0·05)	−67·7
Amphetamine use disorders	0·3 (0·1–0·5)	0·5 (0·1–0·3)	40·1%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	1·5
Other drug use disorders	16·2 (9·6–34·2)	33·6 (21·9–55·9)	107·3%	0·3 (0·2–0·7)	0·5 (0·3–0·8)	50·3
Eating disorders	5·4 (2·4–8·3)	7·3 (4·5–9·9)	35·0%	0·1 (0·1–0·2)	0·1 (0·1–0·1)	−12·8
Other mental and behavioural disorders	11·4 (5·2–17·0)	16·1 (9·8–22·1)	41·7%	0·3 (0·1–0·4)	0·2 (0·1–0·3)	−11·4
Diabetes, urogenital, blood, and endocrine diseases	1544·3 (1420·0–1804·0)	2726·2 (2447·1–2999·1)	76·5%	36·1 (33·4–41·6)	41·0 (36·8–45·1)	13·8
Diabetes mellitus	665·0 (593·3–757·5)	1281·3 (1065·2–1347·9)	92·7%	16·3 (14·5–18·6)	19·5 (16·2–20·5)	19·7
Acute glomerulonephritis	135·2 (57·4–357·3)	84·2 (41·4–191·8)	−37·7%	2·7 (1·2–7·4)	1·2 (0·6–2·8)	−54·5
Chronic kidney diseases	403·5 (354·5–468·9)	735·6 (612·1–810·4)	82·3%	9·6 (8·4–11·2)	11·1 (9·2–12·2)	15·4
Chronic kidney disease due to diabetes mellitus	91·9 (79·7–109·9)	178·3 (147·7–198·4)	94·1%	2·3 (2·0–2·7)	2·7 (2·3–3·0)	19·2
Chronic kidney disease due to hypertension	91·5 (80·1–106·9)	175·3 (147·0–193·3)	91·5%	2·2 (2·0–2·6)	2·6 (2·2–2·9)	18·5
Chronic kidney disease unspecified	220·2 (191·9–252·9)	382·0 (317·9–422·3)	73·5%	5·1 (4·5–5·9)	5·7 (4·8–6·3)	12·3
Urinary diseases and male infertility	140·1 (102·5–172·6)	267·1 (204·5–343·4)	90·7%	3·4 (2·5–4·2)	4·0 (3·0–5·1)	18·0
Tubulointerstitial nephritis, pyelonephritis, and urinary tract infections	83·0 (61·4–107·2)	163·3 (109·1–199·8)	96·7%	2·0 (1·5–2·6)	2·4 (1·6–3·0)	20·0
Urolithiasis	18·4 (12·4–27·8)	19·0 (11·0–26·0)	3·1%	0·5 (0·3–0·7)	0·3 (0·2–0·4)	−36·8
Other urinary diseases	38·6 (26·2–49·3)	84·9 (63·5–114·1)	119·6%	0·9 (0·6–1·1)	1·3 (1·0–1·7)	40·8
Gynaecological diseases	5·1 (3·7–6·4)	7·0 (5·9–8·0)	39·0%	0·1 (0·1–0·1)	0·1 (0·1–0·1)	−9·0
Uterine fibroids	0·4 (0·3–0·5)	0·8 (0·6–0·9)	85·7%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	16·5
Endometriosis	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	91·5%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	28·6
Genital prolapse	0·2 (0·1–0·2)	0·4 (0·3–0·4)	118·5%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	32·5
Other gynaecological diseases	4·5 (3·2–5·7)	5·9 (4·9–6·7)	31·5%	0·1 (0·1–0·1)	0·1 (0·1–0·1)	−13·4
Haemoglobinopathies and haemolytic anaemias	111·4 (72·8–160·4)	114·8 (86·2–151·1)	3·1%	2·1 (1·4–3·0)	1·7 (1·3–2·2)	−22·2
Thalassaemias	25·1 (17·0–34·4)	17·9 (15·1–20·4)	−28·9%	0·4 (0·3–0·6)	0·3 (0·2–0·3)	−41·3
Sickle-cell disorders	23·8 (15·1–32·7)	28·6 (16·8–40·9)	20·5%	0·4 (0·3–0·5)	0·4 (0·2–0·6)	3·6
G6PD deficiency	4·3 (3·4–5·3)	4·0 (3·5–4·6)	−5·6%	0·1 (0·1–0·1)	0·1 (0·1–0·1)	−31·8
Other haemoglobinopathies and haemolytic anaemias	58·3 (36·2–91·2)	64·3 (40·9–89·2)	10·3%	1·2 (0·8–1·8)	0·9 (0·6–1·3)	−23·0
Other endocrine, nutritional, blood, and immune disorders	84·0 (42·3–115·5)	236·1 (148·8–417·9)	181·2%	1·8 (0·9–2·5)	3·5 (2·2–6·2)	91·8
Musculoskeletal disorders	69·5 (46·2–89·6)	153·5 (110·7–214·8)	121·0%	1·7 (1·1–2·2)	2·3 (1·7–3·2)	37·8
Rheumatoid arthritis	33·5 (23·5–43·5)	48·9 (37·9–68·6)	45·8%	0·8 (0·6–1·1)	0·7 (0·6–1·0)	−9·9
Other musculoskeletal disorders	36·0 (25·0–42·8)	104·7 (83·8–143·7)	191·0%	0·8 (0·6–1·0)	1·6 (1·2–2·1)	84·0
Other non-communicable diseases	793·9 (670·6–970·4)	641·7 (524·8–721·4)	−19·2%	12·7 (10·8–15·3)	9·2 (7·5–10·3)	−28·0
Congenital anomalies	663·2 (551·7–843·4)	510·4 (404·7–596·3)	−23·0%	10·1 (8·4–12·7)	7·2 (5·7–8·4)	−28·3
Neural tube defects	118·5 (70·5–173·3)	70·8 (39·8–104·6)	−40·3%	1·7 (1·0–2·5)	1·0 (0·6–1·5)	−42·2
Congenital heart anomalies	278·9 (234·9–355·9)	223·6 (199·5–246·7)	−19·8%	4·3 (3·7–5·3)	3·2 (2·8–3·5)	−26·4
Cleft lip and cleft palate	8·4 (3·3–16·6)	3·7 (2·1–5·5)	−56·2%	0·1 (0·0–0·2)	0·1 (0·0–0·1)	−56·2

(Continues on next page)

	All ages deaths (thousands)			Age-standardised death rates (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
(Continued from previous page)						
Down's syndrome	22·0 (9·8–37·5)	17·4 (11·1–25·4)	−21·0%	0·3 (0·2–0·6)	0·2 (0·2–0·4)	−28·3
Other chromosomal abnormalities	34·6 (11·9–80·3)	18·9 (9·7–33·8)	−45·4%	0·5 (0·2–1·1)	0·3 (0·1–0·5)	−46·8
Other congenital anomalies	200·8 (115·8–298·9)	176·0 (118·9–218·7)	−12·3%	3·1 (1·9–4·5)	2·5 (1·7–3·1)	−19·3
Skin and subcutaneous diseases	100·6 (77·5–118·3)	109·2 (84·9–124·0)	8·5%	2·2 (1·7–2·6)	1·6 (1·3–1·8)	−26·5
Cellulitis	26·1 (19·9–30·8)	26·6 (20·4–30·2)	2·0%	0·6 (0·4–0·7)	0·4 (0·3–0·5)	−28·9
Abscess, impetigo, and other bacterial skin diseases	42·1 (31·2–51·0)	39·7 (31·1–45·1)	−5·7%	0·8 (0·6–1·0)	0·6 (0·5–0·7)	−30·6
Decubitus ulcer	32·1 (26·0–38·5)	42·6 (32·9–48·7)	32·5%	0·8 (0·6–1·0)	0·6 (0·5–0·7)	−20·6
Other skin and subcutaneous diseases	0·3 (0·1–0·1)	0·4 (0·1–0·1)	4·4%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	−28·7
Sudden infant death syndrome	30·0 (15·4–56·7)	22·0 (13·1–36·5)	−26·7%	0·4 (0·2–0·8)	0·3 (0·2–0·5)	−26·7
Injuries	4091·7 (3851·9–4489·7)	5073·3 (4556·7–5548·1)	24·0%	82·0 (77·2–90·3)	74·3 (66·8–81·3)	−9·3
Transport injuries	958·2 (770·4–1175·0)	1396·8 (1101·4–1850·1)	45·8%	19·4 (15·4–23·6)	20·5 (16·1–27·1)	5·9
Road injury	907·9 (764·1–1123·4)	1328·5 (1050·9–1747·0)	46·3%	18·4 (15·4–22·7)	19·5 (15·4–25·6)	6·2
Pedestrian injury by road vehicle	284·1 (210·6–333·9)	461·0 (337·1–617·3)	62·3%	5·8 (4·2–6·7)	6·8 (5·0–9·1)	17·6
Pedal cycle vehicle	54·9 (41·7–66·7)	83·3 (62·3–101·4)	51·7%	1·1 (0·9–1·4)	1·2 (0·9–1·5)	7·8
Motorised vehicle with two wheels	131·7 (99·4–163·4)	206·4 (159·7–233·8)	56·7%	2·6 (2·0–3·3)	3·0 (2·3–3·4)	14·4
Motorised vehicle with three or more wheels	336·9 (268·8–420·5)	474·5 (379·3–581·4)	40·9%	6·8 (5·5–8·4)	7·0 (5·6–8·5)	2·4
Road injury other	100·3 (49·0–182·3)	103·3 (50·7–202·2)	3·0%	2·0 (1·0–3·7)	1·5 (0·7–3·0)	−25·2
Other transport injury	50·2 (41·7–65·1)	68·3 (58·0–82·7)	35·9%	1·0 (0·8–1·3)	1·0 (0·8–1·2)	−0·0
Unintentional injuries other than transport injuries	2030·1 (1896·0–2266·8)	2122·8 (1867·5–2283·8)	4·6%	39·6 (37·1–44·3)	31·0 (27·3–33·4)	−21·6
Falls	348·6 (311·2–415·3)	540·5 (415·2–611·9)	55·0%	7·8 (7·0–9·4)	8·0 (6·1–9·1)	2·0
Drowning	432·9 (353·3–516·1)	349·1 (299·9–437·8)	−19·4%	7·5 (6·3–9·0)	5·1 (4·3–6·3)	−33·1
Fire, heat, and hot substances	280·1 (233·6–330·1)	337·6 (234·7–433·8)	20·5%	5·3 (4·5–6·3)	4·9 (3·4–6·3)	−7·3
Poisonings	202·9 (157·3–326·8)	180·4 (130·1–239·9)	−11·1%	4·0 (3·2–6·5)	2·6 (1·9–3·5)	−34·4
Exposure to mechanical forces	276·0 (199·6–417·1)	215·6 (154·6–255·3)	−21·9%	5·5 (4·0–8·1)	3·2 (2·3–3·7)	−42·2
Mechanical forces (firearm)	127·5 (76·8–206·0)	79·8 (52·0–127·1)	−37·4%	2·5 (1·5–4·1)	1·2 (0·8–1·8)	−53·2
Mechanical forces (other)	148·5 (103·0–197·4)	135·7 (83·5–161·0)	−8·6%	3·0 (2·1–3·9)	2·0 (1·2–2·4)	−33·1
Adverse effects of medical treatment	42·0 (32·7–49·3)	83·7 (64·6–96·2)	99·1%	0·9 (0·7–1·0)	1·2 (1·0–1·4)	41·0
Animal contact	75·0 (50·7–97·5)	64·3 (41·0–88·4)	−14·3%	1·4 (1·0–1·9)	0·9 (0·6–1·3)	−34·4
Animal contact (venomous)	54·9 (30·1–89·3)	47·0 (25·6–84·7)	−14·3%	1·0 (0·6–1·7)	0·7 (0·4–1·2)	−34·4
Animal contact (non-venomous)	20·1 (10·7–30·8)	17·3 (10·0–24·6)	−14·2%	0·4 (0·2–0·6)	0·3 (0·1–0·4)	−34·5
Unintentional injuries not classified elsewhere	372·5 (311·9–403·8)	351·6 (301·4–387·8)	−5·6%	7·1 (6·0–7·7)	5·1 (4·4–5·7)	−27·9
Self-harm and interpersonal violence	1008·5 (838·8–1201·9)	1340·0 (1108·2–1616·9)	32·9%	21·1 (17·5–25·4)	19·7 (16·2–23·8)	−6·9
Self-harm	669·8 (519·5–853·4)	883·7 (655·6–1105·2)	31·9%	14·5 (11·3–18·4)	13·1 (9·7–16·3)	−9·6
Interpersonal violence	338·7 (245·8–416·6)	456·3 (354·9–610·9)	34·7%	6·7 (4·8–8·3)	6·6 (5·1–8·9)	−1·0
Assault by firearm	141·8 (107·4–175·7)	196·2 (153·9–233·6)	38·4%	2·8 (2·1–3·5)	2·8 (2·2–3·4)	1·9
Assault by sharp object	83·1 (55·4–119·8)	126·7 (82·2–188·2)	52·5%	1·7 (1·1–2·4)	1·8 (1·2–2·7)	10·9
Assault by other means	113·8 (85·2–129·3)	133·4 (107·3–159·0)	17·2%	2·2 (1·7–2·5)	1·9 (1·6–2·3)	−13·5
Forces of nature, war, and legal intervention	94·9 (65·0–162·3)	213·7 (119·2–433·5)	125·2%	1·9 (1·3–3·4)	3·1 (1·7–6·3)	62·0
Exposure to forces of nature	31·4 (18·2–60·0)	196·0 (106·9–401·9)	523·5%	0·7 (0·4–1·3)	2·9 (1·6–5·8)	336·4
Collective violence and legal intervention	63·5 (44·3–101·8)	17·7 (12·2–29·6)	−72·2%	1·3 (0·9–2·1)	0·3 (0·2–0·4)	−79·5

Data are deaths (95% uncertainty interval) or % change. %Δ=percentage change. *E coli=Escherichia coli. H influenzae=Haemophilus influenzae.* G6PD=glucose-6-phosphate dehydrogenase. *For these causes the mean value is outside of the 95% uncertainty interval; this occurs because the full distribution of 1000 draws is asymmetric with a long tail. A small number of high values in the uncertainty distribution raises the mean above the 97·5 percentile of the distribution.

Table 2: **Global deaths for 235 causes in 1990 and 2010 for all ages and both sexes combined (thousands) and age-standardised rates (per 100 000) with 95% UI and percentage change**

Decomposition of changes in numbers of causes of death into demographic and epidemiological factors

To help understand the drivers of change in the numbers of deaths by cause or region, we decomposed change from 1990 to 2010 into growth in total population, change in population age and sex structure, and change in age-specific and sex-specific rates. We computed two counterfactual sets of cause of death numbers: (1) a population growth scenario computed as the number of deaths expected in 2010 if only total population numbers increased to the level of 2010 but the age-sex structure of population stayed the same as in 1990 and age-sex

specific rates remained at 1990 levels; and, (2) a population growth and population ageing scenario computed as the number of deaths expected in 2010, using 1990 age-sex specific rates and 2010 age-specific and sex-specific population numbers. The difference between 1990 numbers and the population growth scenario is the change in death numbers due strictly to the growth in total population. The change from the population growth scenario to the population growth and ageing scenario is the number of deaths due to ageing of the population. The difference between 2010 deaths and the population growth and ageing scenario is the difference in death numbers due to epidemiological change in age-specific and sex-specific death rates. Each of these three differences is also presented as a percentage change with reference to the 1990 death number.

We calculated change in the risk of death, by cause, directly using age standardised death rates, based on the WHO world population standard age structure.[62] Further details on the data and methods used for specific causes of death are available on request.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and the final responsibility to submit for publication.

Results

The GBD 2010 cause list divides causes into three broad groups. At the most aggregate level, communicable, maternal, neonatal, and nutritional causes account for 13·2 million (24·9%) of 52·8 million total deaths at all ages in 2010. Non-communicable causes account for 34·5 million or 65·5%. The third category, injuries, accounts for 5·1 million or 9·6%. The continued decrease in deaths from communicable, maternal, neonatal, and nutritional disorders is striking, if not surprising. The number of deaths from these disorders decreased by 2·7 million from 15·9 million in 1990 to 13·2 million in 2010, representing a 17% decrease from 1990 to 2010. The annual number of deaths from non-communicable diseases, by contrast, rose by just under 8 million, to 34·5 million, or two of every three deaths in 2010. The global fraction of deaths due to injuries increased slightly between 1990 and 2010 (from 8·8% to 9·6%), but this masks some important trends in mortality from these causes.

Table 1 decomposes these global trends into the contribution of total increase in population size, ageing of the population, and changes in age-specific and sex-specific rates. Global population growth alone would have been expected to increase deaths from all causes by 31·8% from 1990 to 2010. Because of the correlation between population growth rates and mortality rates from communicable, maternal, neonatal, and nutritional causes, population growth alone would have increased this category by 46·9%, non-communicable diseases by 22·9%, and injuries by 31·1% (table 1). Ageing of the world's population such that the mean age of the world increased from 26·1 years to 29·5 years contributed to an 11·2% decrease in communicable, maternal, neonatal, and nutritional disorders, a 39·2% increase in non-communicable disease deaths, and a 9·2% increase in injuries (table 1). Declines in age-specific and sex-specific death rates have contributed to a 52·7% decrease in communicable, maternal, neonatal, and nutritional deaths, a 32·1% decrease in non-communicable disease deaths, and a 16·3% decrease in injury deaths. With decreasing age-specific death rates from all three groups of causes, including non-communicable diseases, the global shift towards non-communicable diseases and injuries as leading causes of death is being driven by population growth and ageing, and not by increases in age-sex-cause specific death rates.

At the second level of the GBD 2010 cause hierarchy, there are 21 major cause groups. Figure 1 (A–D) summarises the composition of causes of death for every age-sex group for male and female individuals separately in 1990 and 2010 at this second level of cause disaggregation. The structure of causes of death changed systematically with age. In the neonatal age groups, disorders arising during the neonatal period dominated, but with important contributions from the category of diarrhoeal disease, lower respiratory infections, and other infectious and non-communicable diseases, including congenital causes. By the post-neonatal period, causes of death were dominated by diarrhoea, lower respiratory infections, and other infectious diseases such as measles, among others. At ages 1–4 years, the category neglected tropical diseases and malaria were also an important contributor to global mortality. In the age group 5–14 years, infectious diseases, HIV/tuberculosis (HIV/TB), injuries, and some cancers predominated, although overall mortality at these ages was low. Important sex differences were evident from ages 15–34 years; among male individuals, injuries, HIV/TB, and some non-communicable diseases predominate. Among female individuals of the same age group, injuries were a smaller cause of death with maternal causes making an important contribution. In 2010, maternal causes accounted for 10·7% of deaths of women in this age group. By age 40 years, more than 50% of global deaths in 1990 were from non-communicable diseases—this transition age shifts to 45 years in 2010 because of the HIV epidemic. Beginning at age 50 years, circulatory causes begin a steady rise to become the largest cause of death.

The comparison of the 1990 and 2010 plots shows various shifts in the cause structure by age and sex (figure 1). At younger age groups, neonatal disorders and other non-communicable causes, including congenital anomalies, predominate. The unfolding HIV/AIDS epidemic at the global level is clearly evident from the huge increase in the contribution of HIV/TB to cause of death patterns among young adult men and women. By 2010, for example, HIV/TB and injuries accounted for more than half of all

deaths in the age group 20–39 years in men. Other important shifts, with age, are evident—namely, a rising fraction of deaths in many age groups from diabetes, chronic kidney diseases, blood and endocrine disorders, and cancers, along with a decrease in the fraction due to chronic respiratory deaths in the middle-aged and older groups. For women, the share of deaths at ages 20–39 years due to maternal causes notably decreased.

At a more disaggregated cause level, there is interest in a broad global overview of who dies of what, and how this is

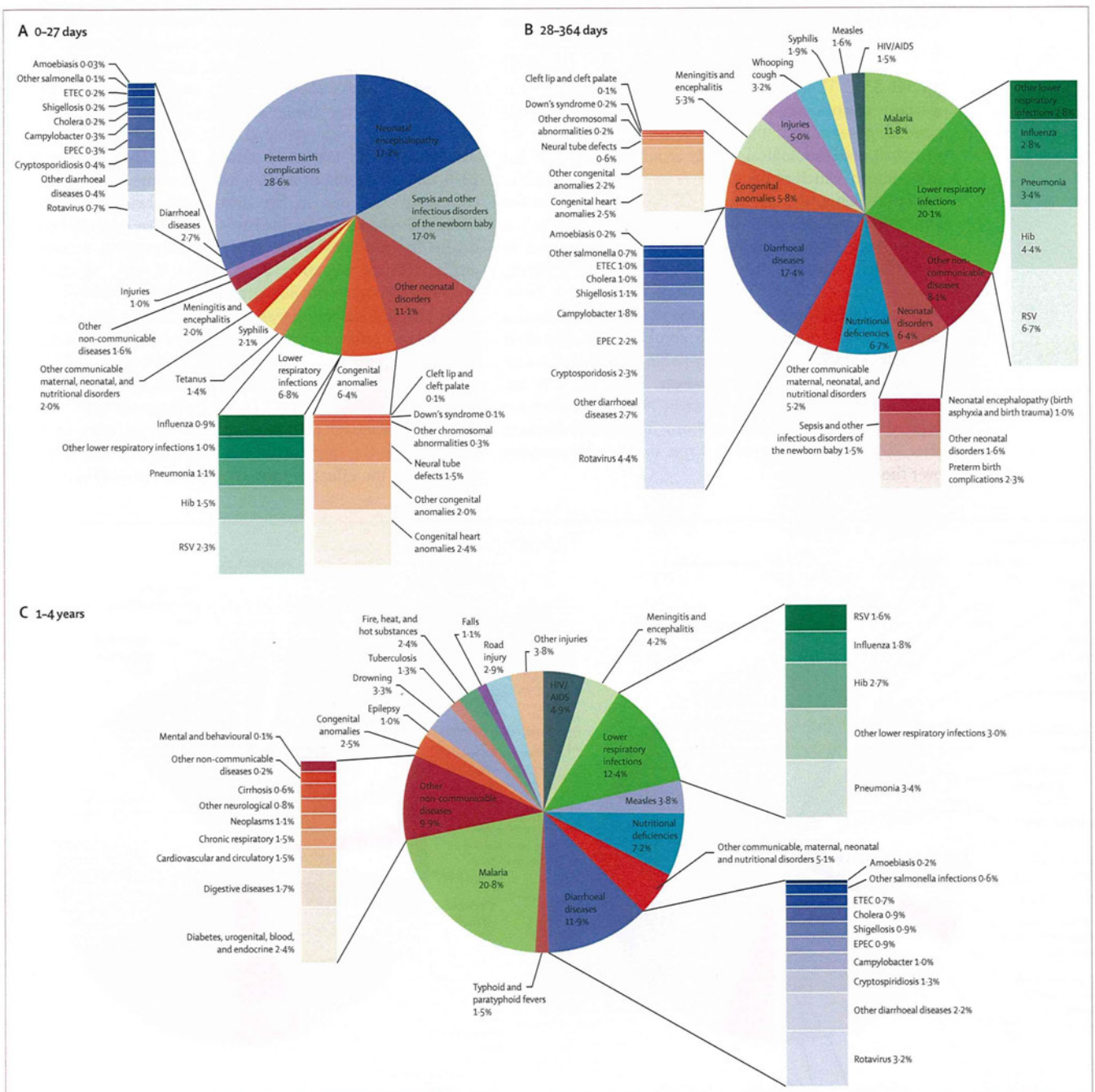

Figure 2: **Pie chart of global neonatal, post-neonatal, and child deaths in 2010 for children of both sexes combined by cause**
(A) Age 0–27 days (neonatal); 2 840 157 total deaths. (B) Age 28–364 days (post-neonatal); 2 031 474 total deaths. (C) Age 1–4 years; 1 969 567 total deaths. ETEC=enterotoxigenic *Escherichia coli*. EPEC=enteropathogenic *E coli*. Hib=*Haemophilus influenzae* type B. RSV=respiratory syncytial virus.

changing. Table 2 provides total numbers of deaths and age-standardised death rates for each cause in 1990 and 2010. Because there is substantial interest in causes of death for different age groups, we provide global deaths for the 20 GBD age groups, by sex, and including 95% UI for 2010 and 1990 (appendix pp 149–340). In addition to the numbers of deaths, we present the death rates by age for 2010 and 1990 in for those readers interested in comparing change in age-sex-specific death rates (appendix pp 341–533). There are many features of the tables that warrant discussion: we limit ourselves here to some general observations that we believe characterise the principal epidemiological trends around the turn of the millennium. Much of the decrease in the communicable, maternal, neonatal, and nutritional causes was due to the substantial reductions in diarrhoeal disease (from 2·5 to 1·4 million), lower respiratory infections (from 3·4 to 2·8 million), neonatal disorders (from 3·1 to 2·2 million), measles (from 0·63 to 0·13 million), and tetanus (from 0·27 to 0·06 million), reflecting the scaling up of effective treatments and technologies to combat these disorders generally associated with poverty (table 2). Not all diseases in this category decreased, however. Table 2 shows the massive increase in deaths between 1990 and 2010 from HIV/AIDS (from 0·3 to 1·5 million), despite the decrease after 2006, as well as a 19·9% rise in malaria mortality over the two decades.

Cancers claimed 8·0 million lives in 2010, 15·1% of all deaths worldwide, with large increases in deaths from trachea, bronchus, and lung cancers, twice the number of deaths from the next two most common sites for mortality (liver and stomach). Roughly half of the total liver cancer mortality was attributed to hepatitis B infection, with smaller fractions due to hepatitis C and alcohol (table 2). The largest cause fraction (13·3%) among all causes of death in 2010 was due to ischaemic heart disease, closely followed by stroke (11·1%), being roughly split equally between ischaemic stroke and haemorrhagic and other non-ischaemic stroke (table 2). Together, ischaemic heart disease and all forms of stroke killed an estimated 12·9 million people in 2010, a quarter of the global total, compared with one in five deaths worldwide 20 years earlier. Cirrhosis of the liver was the cause of a million deaths in 2010, 33% more than in 1990, roughly equally attributable to hepatitis B, hepatitis C, and alcohol. Diabetes deaths worldwide almost doubled, as did deaths from chronic kidney disease. Deaths from Alzheimer's disease and other dementias rose more than three-fold, and deaths from Parkinson's disease doubled. One of the few causes in this group to decrease was COPD, falling from 3·1 to 2·9 million. This is consistent with the decreases observed with development in countries such as the UK in the first part of the 20th century, only to be reversed as the effect of tobacco use becomes evident.[63,64]

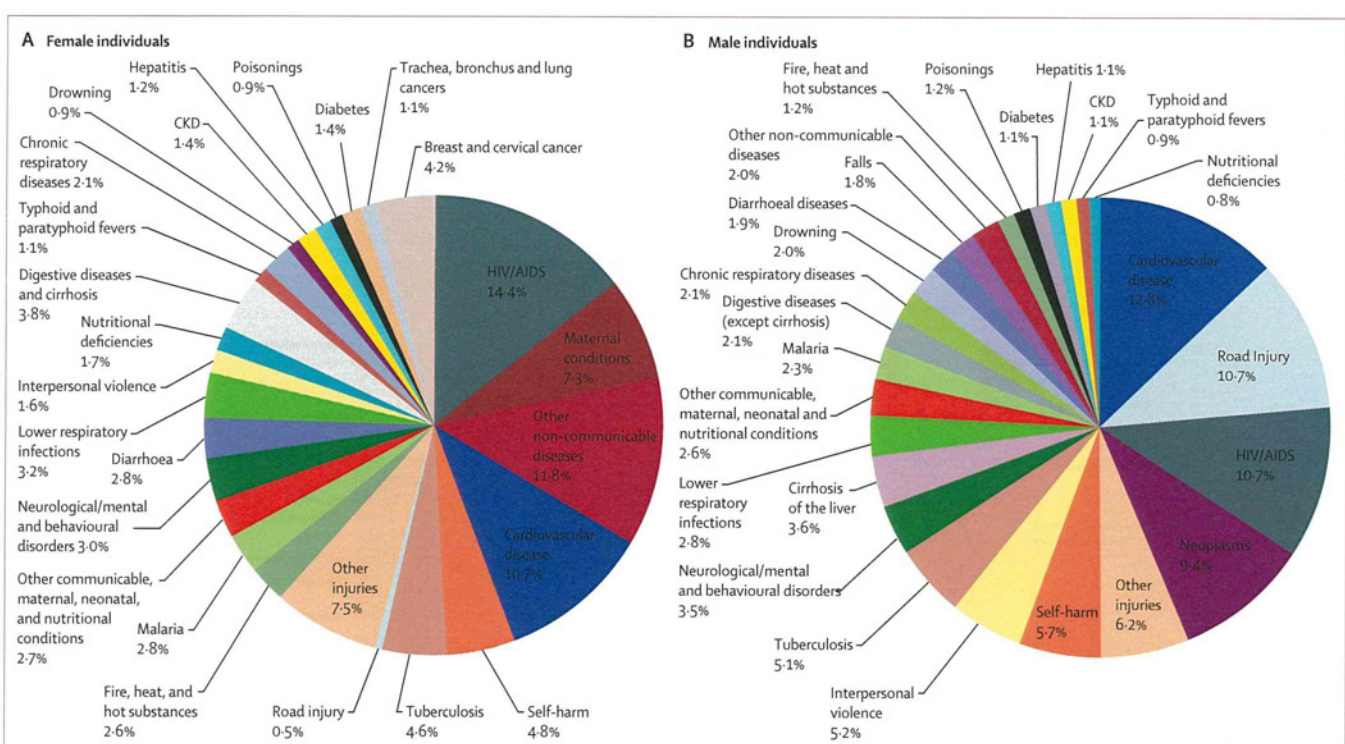

Figure 3: **Global deaths in 2010 for individuals aged 15–49 years**
(A) Female individuals, 3 496 480 total deaths. (B) Male individuals, 5 741 344 total deaths. CKD=chronic kidney disease.

The massive increases in tobacco use since the 1970s, especially in men in less developed countries, might reverse this trend over the next decade or so.[65]

One million more deaths from injuries occurred in 2010 (5·1 million) than two decades earlier, a 24% increase (table 2). This was driven primarily by a 420 600 increase in road traffic deaths, which claimed 1·3 million lives in 2010. Falls also claimed an additional 191 900 lives compared with 1990, with most other accidental causes being relatively constant, or decreasing, especially drowning. Deaths from intentional injuries increased for both self-harm and interpersonal violence. Deaths from forces of nature, war, and legal intervention were more than twice as common than two decades earlier. Given the huge annual fluctuation in deaths from forces of nature and war, trends must be interpreted with caution. The fact that deaths from injuries are rising, and account for one in ten deaths worldwide, argues for far greater policy action to prevent them.

Trends in numbers of deaths are of interest and importance for health services and health policies that are designed to reduce premature mortality from various causes. Yet numbers of deaths alone do not provide a clear indication of whether disease control strategies are working since they are heavily dependent on changes in population size and age structure. By computing age-standardised mortality rates, we effectively controlled for demographic changes across populations over time; however, age-standardised death rates are sensitive to the population standard used. Changes in age-standardised mortality rates between 1990 and 2010 are shown in the right hand panels of table 2. Death rates from all communicable, maternal, neonatal, and nutritional disorders have decreased by 30% since 1990, a much greater reduction than suggested from numbers of deaths alone (table 2). The age-standardised death rate from diarrhoeal diseases fell by 49%, whereas lower respiratory infections decreased by 34%. Interestingly, age-standardised death rates from trachea, bronchus, and lung cancers fell by 8% between 1990 and 2010, despite a 47% increase in numbers of deaths, due to continued decreases in mortality in developed countries and more modest increases in less developed countries where the full impact of smoking, especially in men, has yet to occur. Breast cancer mortality

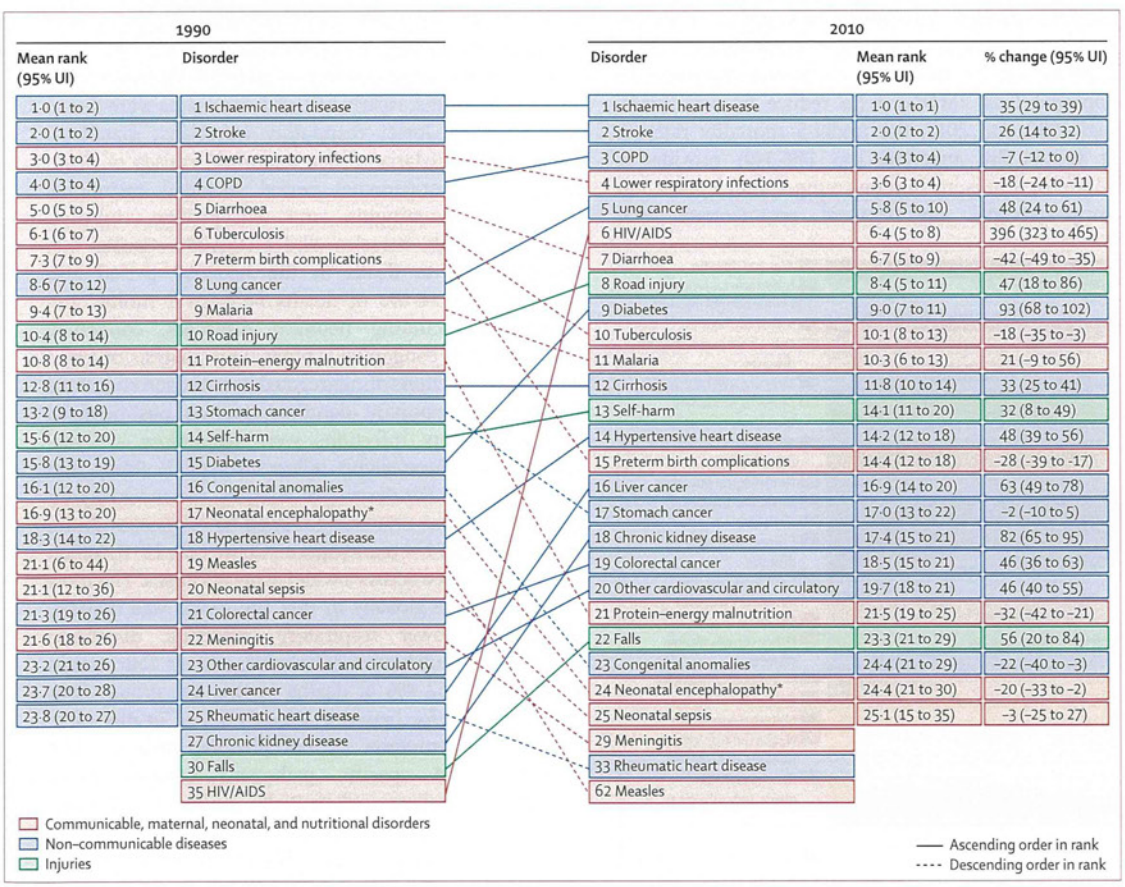

Figure 4: **Global death ranks with 95% UIs for the top 25 causes in 1990 and 2010, and the percentage change with 95% UIs between 1990 and 2010**
UI=uncertainty interval. COPD=chronic obstructive pulmonary disease. *Includes birth asphyxia/trauma. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

rates fell by 15%, even though numbers of deaths from the disease increased by more than a third.

Our findings suggest important decreases (20% or more) in age-standardised death rates from major vascular diseases, especially heart disease and strokes, for the world as whole, even though numbers of vascular disease deaths increased by a third to 15·6 million in 2010 (table 2). Death rates for COPD and liver cirrhosis also decreased, but almost doubled for Alzheimer's disease, and rose for diabetes and chronic kidney disease. These represent important global health challenges that might, or might not, be evident from an assessment of trends in numbers of deaths alone. Globally, although the number of deaths from injury rose by 24% since 1990, death rates decreased modestly, although this masks variable trends for different injuries, with death rates from drownings and poisonings falling by about a third, less dramatically for self-harm and violence, and rising for transport injuries and, interestingly, from adverse effects of medical treatment. Death rates from forces of nature also massively increased (by 336%) comparing 1990 to 2010 because of the earthquake in Haiti in 2010.

Causes of death in children younger than 5 years are of particular interest because of the global focus on improving child survival over the past few decades that has been reinforced by the push to achieve Millennium Development Goal (MDG) 4 (to reduce by two thirds, between 1990 and 2015, the under-5 mortality rate) in recent years. The appendix (pp 149–340) provides a breakdown of deaths in children younger than 5 years into the early neonatal, late neonatal, post-neonatal, and 1–4 years age groups in 2010 and 1990. To facilitate an understanding of the leading causes at different ages under 5 years, we show in figure 2A, B, and C the distribution of deaths in the neonatal periods, the post-neonatal period, and ages 1–4 years, respectively. Of 2·8 million early and late neonatal deaths, we estimate that 2·1 million were from neonatal disorders including preterm birth complications, neonatal sepsis, and neonatal encephalopathy, among others. A further 137000 deaths were also due to disorders that arise in the neonatal period but which lead to death after the first month of life. Among the important neonatal disorders, preterm events accounted for 29% of global neonatal deaths, with nearly equal shares for neonatal sepsis and neonatal encephalopathy—17% each. Of the remaining 741000 neonatal deaths, congenital anomalies accounted for 183000 deaths, although most congenital deaths occured after the first month of life. Injuries accounted for 28000 neonatal deaths; other non-communicable causes including haemoglobinopathies and haemolytic anaemias, some rare cancers, sudden infant death syndrome (SIDS), and other rare causes accounted for 45000 deaths. Among communicable diseases, notably lower respiratory infections (194000), diarrhoea (77000), and meningitis (46000) accounted for the remaining neonatal deaths.

In the post-neonatal period (figure 2B), we estimated 2·0 million deaths. Nearly half of these deaths were due to three diseases: lower respiratory infections, diarrhoeal diseases, and malaria. Other important causes of death during the post-neonatal period included nutritional deficiencies, meningitis and encephalitis, injuries, whooping cough, measles, and HIV/AIDS. Causes that primarily lead to death in the neonatal period also contributed to 14·0% of deaths between 1 month and 11 months including neonatal disorders, congenital anomalies, and congenital syphilis. Our analysis of lower respiratory infections disaggregated by pathogen suggested that the most important identified causes of post-neonatal lower respiratory infections were respiratory syncytial virus (RSV), *Haemophilus influenzae* type B (Hib), and pneumococcus. For diarrhoeal diseases, the most important pathogen was rotavirus followed by cryptosporidium. In the age group 1–4 years (figure 2C), we noted 2·0 million deaths distributed across a wider array of causes. The most important cause globally in this age group was malaria, followed by lower respiratory infections, diarrhoeal diseases, and nutritional deficiencies. These four causes accounted for 52·4% of deaths in this age group. Four causes account for between 3% and 5% of deaths each: HIV/AIDS, meningitis or encephalitis, measles, and drowning. The specific pathogens causing lower respiratory infections substantially shifted in this age group compared with the age groups of under 1 year with a much more substantial part played by pneumococcal deaths. Just under 14% of deaths in this age group were from a long list of non-communicable causes, each of which accounted for a relatively small number of deaths.

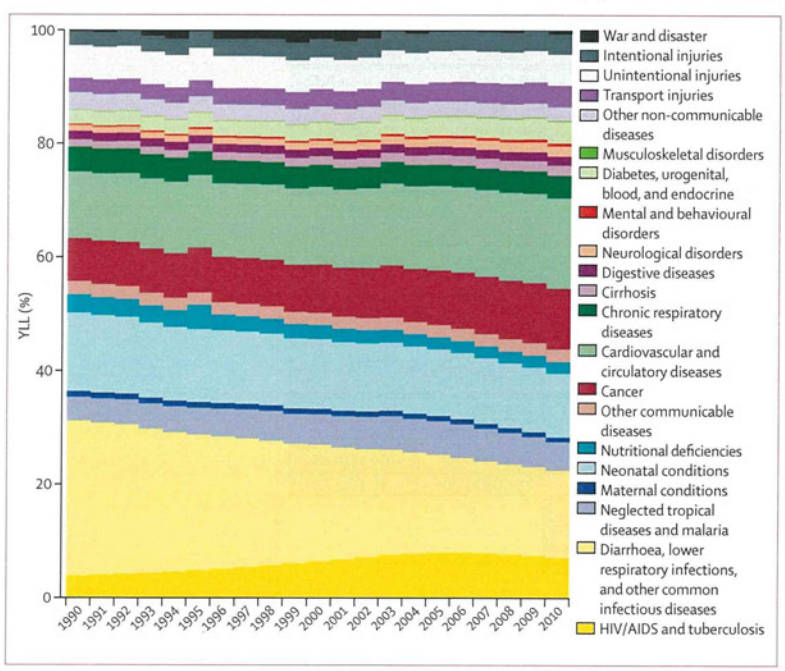

Figure 5: Percentage of global years of life lost (YLLs) from 1990 to 2010 for all ages and both sexes combined by cause and year

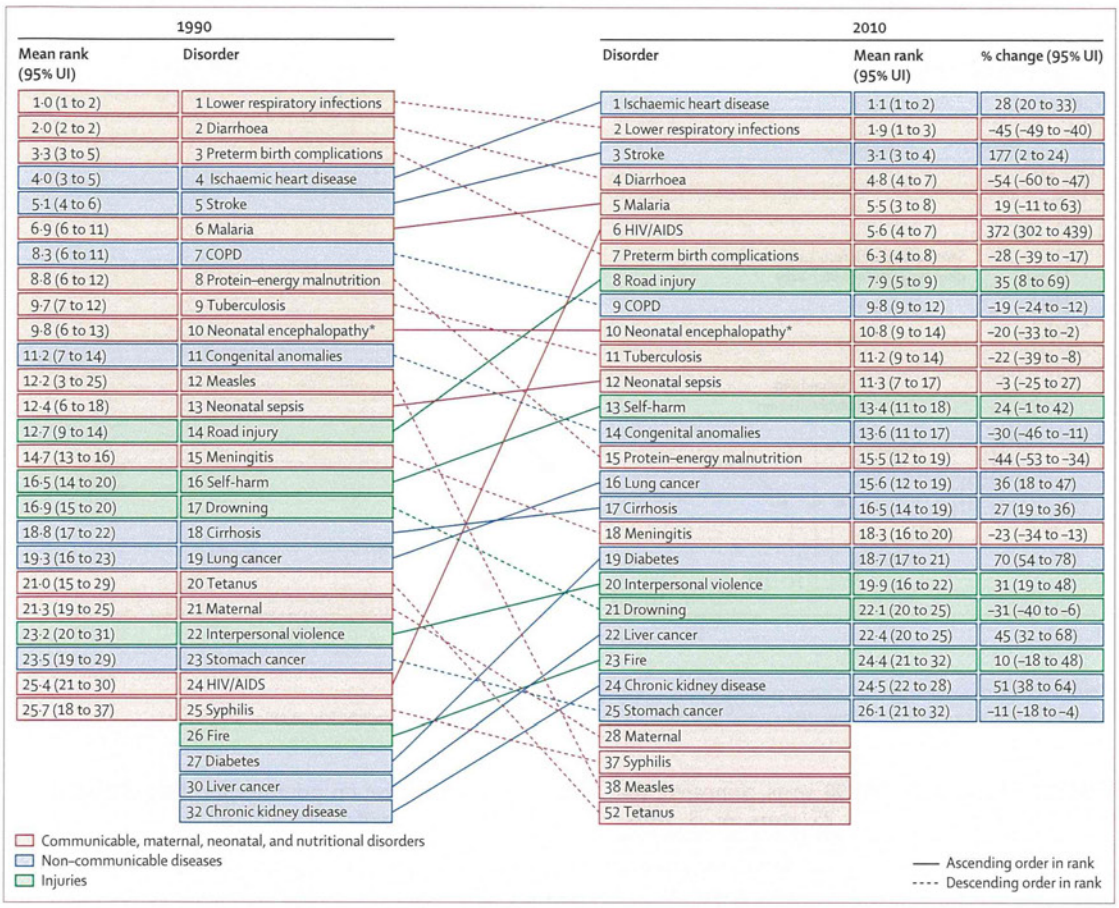

Figure 6: **Global years of life lost (YLLs) ranks with 95% UIs for the top 25 causes in 1990 and 2010, and the percentage change with 95% UIs between 1990 and 2010**

YLLs=years of life lost. UI=uncertainty interval. COPD=chronic obstructive pulmonary disease. *Includes birth asphyxia/trauma. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

Because of the focus of MDG 5 on maternal mortality, the composition of causes of death in women and men of reproductive age is of particular interest. Although deaths related to pregnancy and childbirth have been given special priority in the MDGs, any death in these young adult age groups is a major cause for concern. For women aged 15–49 years, we estimated 3·5 million deaths from all causes in 2010. Figure 3A shows that the leading cause was HIV/AIDS, followed by cardiovascular disease, maternal disorders, suicide, tuberculosis, breast and cervical cancer, and digestive diseases and cirrhosis. The top seven causes accounted for half of the deaths of women in these age groups. Although there is no MDG related specifically to male deaths in the reproductive age groups, disorders targeted by MDG 6 take an important toll on men in the age groups 15–49 years. The leading causes of death for men in this age group, however, were cardiovascular diseases, road traffic injuries, and HIV/AIDS, with other major causes including suicide and interpersonal violence.

Identification of more detailed causes is perhaps more important for priority setting and planning, since interventions are generally cause-specific. Figure 4 shows the top 25 causes of death in the world ranked in 1990 and 2010 with arrows connecting the causes between the two periods. Although the top four causes of death in 1990 remain the top four in 2010, the change in numbers of deaths is noteworthy, with ischaemic heart disease and stroke increasing by 26–35% over the interval, but lower respiratory infections and COPD declining by 7–18%. Lung cancer increased from the 8th cause to the 5th cause in the two decades because of a 48% increase in absolute number of deaths. The largest change was for HIV/AIDS, rising from the 35th cause to the 6th leading cause of death. Diarrhoea, tuberculosis, and malaria all dropped in the global league table. Large increases in absolute number of deaths and their relative importance can be seen for diabetes, liver cancer, falls, and chronic kidney disease. Each of these causes has increased by more than 50% over the two decades.

Whereas the number of deaths from a given cause is a widely understood measure, its utility as a metric for informing public health priorities is limited since it gives

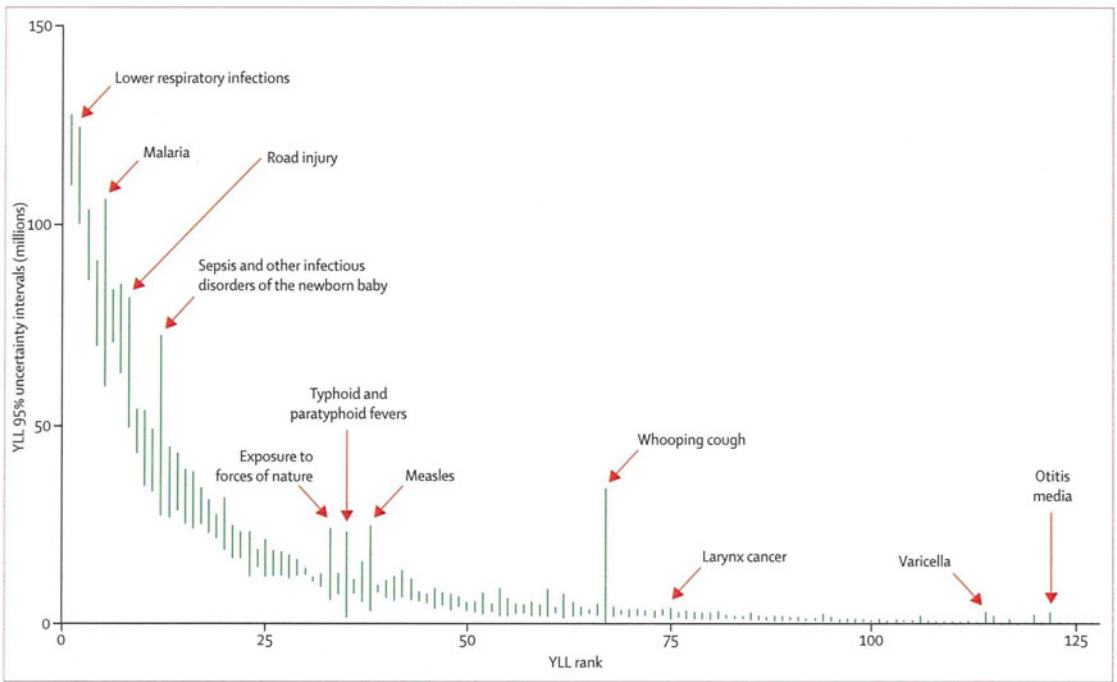

Figure 7: **Global YLLs (millions) with 95 % uncertainty intervals versus rank by cause in 2010**
YLLs=years of life lost. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

equal weight to a death at age 90 years compared, for example, with a death at age 25 years or 5 years. Consequently, the predominance of non-communicable causes might be misleading. In the Global Burden of Disease studies, the computation of years of life lost based on the standard expectation of life at the age of each death quantified the amount of life lost due to premature mortality (YLLs) from each cause. By computing YLLs, we could aggregate information on deaths across all ages to summarise overall patterns of premature mortality. Figure 5 shows the demographic and epidemiological transition, with the change in the composition of YLLs by single year from 1990 to 2010 for both sexes combined. The effect of major mortality shocks such as the Rwanda genocide (1994) and the famine in North Korea (covering most of the 1990s with a peak in 1995), were evident even at the global scale. The fraction of YLLs due to diarrhoea, lower respiratory infections, meningitis, and other common infectious diseases decreased substantially from 27·3% in 1990 to 15·4% in 2010. The percentage due to HIV/TB has increased due to the HIV epidemic. There is a concomitant expansion of YLLs due to non-communicable diseases, particularly cardiovascular diseases. The share of YLLs from non-communicable diseases increased from 33·3% in 1990 to 42·8% in 2010. The appendix (pp 534–725) shows the global YLLs with 95% UIs for 2010 and 1990.

Figure 6 provides a comparison of the top 25 causes of YLLs for both sexes combined, which gives an even more meaningful perspective on priorities for disease control than a simple ranking of causes of death according to the numbers of deaths from each cause. The leading cause of YLLs globally was lower respiratory infections in 1990 and ischaemic heart disease in 2010; in this period, the total number of YLLs from lower respiratory infections decreased by 45% but increased 28% for ischaemic heart disease. More generally, a number of communicable, maternal, neonatal, and nutritional causes declined in both absolute terms and in relative importance as causes of YLLs—most notably measles, tetanus, preterm birth complications, tuberculosis, meningitis, and protein-energy malnutrition. Conversely, several non-communicable diseases increased in importance over the two decades: ischaemic heart disease, stroke, lung cancer, cirrhosis, diabetes, liver cancer, and chronic kidney disease particularly, although COPD and congenital causes have declined in rankings of YLLs. Among injuries, road traffic, self-harm, and interpersonal violence increased substantially in both absolute and relative terms, whereas drowning decreased.

An important innovation in this study was the quantification of uncertainty by cause. UIs varied widely across causes. Figure 7 shows the 95% UIs for YLLs for each cause in 2010, ordered by the mean rank of every cause. The two leading causes—ischaemic heart disease and lower respiratory infections—have nearly overlapping UIs. These two causes are separated by a substantial gap with the next highest ranked cause, stroke. The 12th ranked

cause, neonatal sepsis, has a UI that is nearly three times wider than the 11th ranked cause, COPD. Several causes have much larger UIs than adjacent causes in the rank list. Natural history models for whooping cough, measles, and syphilis have large UIs. This originates from considerable empirical uncertainty on the estimation of incidence and case-fatality rates. By contrast, the HIV/AIDS natural history model developed by UNAIDS has remarkably narrow uncertainty in many countries with large epidemics. Across the causes analysed with CODEm, where the validity of UIs were evaluated using out-of-sample performance, there was also substantial variation across causes reflecting both the coherence of the underlying data, and whether powerful explanatory covariates were identified.

Figure 8 shows the composition of causes of death at the second level of aggregation (21 cause groups) for the 21 GBD regions in 1990 and 2010 for both sexes combined. The regions were ordered by the mean age at death, a crude but informative measure of the demographic and epidemiological transition.[40] At both time periods, there was substantial variation across regions in the relative importance of different causes, with communicable diseases and related causes being much more important in parts of sub-Saharan Africa and parts of Asia than in north Africa, and vascular diseases and cancer predominating in most other regions. By 2010, substantial progress was achieved, even in Africa, in reducing YLLs from communicable, maternal, neonatal, and nutritional causes particularly, although these still accounted for three out of four premature deaths in Africa. The predominance of vascular diseases as a cause of premature mortality in eastern Europe is clear from figure 8, especially compared with other developed regions, where cancer causes as much, if not more, premature death. The impact of the civil violence in Papua New Guinea in 1990 and the 2010 earthquake in Haiti led to notable shifts due to war and disaster. The combination of road injuries, other unintentional injuries, and intentional injuries ranges from a high of 23% of YLLs in 2010 in central Latin America to a low of 6% in the Caribbean, nearly a four-fold variation.

Figure 9 shows the rank for every cause that was either in the global top 25 causes of YLLs in 2010 or appeared in the top 25 causes of YLLs for any region. The appendix (p 726) presents the same information for 1990. Different colours represent different bands of ranks (figure 9). Such heat maps help to visualise important variations in ranking of YLLs across regions. In both 1990 and 2010, a similar number of causes (60 or so) appeared in the rankings, but with very substantial regional variations. At the top of figure 9, causes highest in global rankings of YLLs, such as lower respiratory diseases, ischaemic heart

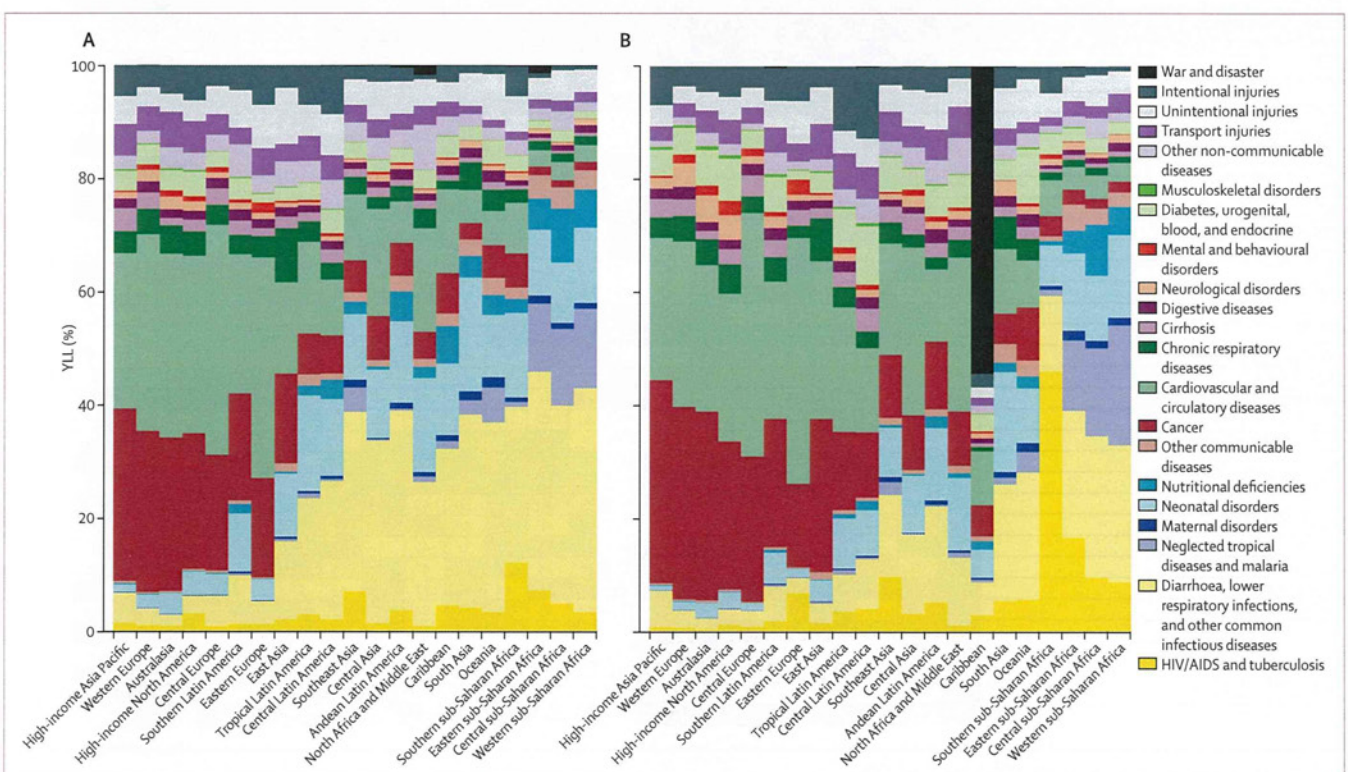

Figure 8: **Percentage of YLLs for all ages and both sexes combined by cause and region in 1990 and 2010**
YLLs=years of life lost. (A) 1990. (B) 2010. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

Ranking Legend: 1–10, 11–20, 21–30, 31–50, 51–90, 91–176

Cause	Global	High-income Asia Pacific	Western Europe	Australasia	High-income North America	Central Europe	Southern Latin America	Eastern Europe	East Asia	Tropical Latin America	Central Latin America	Southeast Asia	Central Asia	Andean Latin America	North Africa and Middle East	Caribbean	South Asia	Oceania	Southern sub-Saharan Africa	Eastern sub-Saharan Africa	Central sub-Saharan Africa	Western sub-Saharan Africa
Ischaemic heart disease	1	2	1	1	1	1	1	1	2	2	2	4	1	3	1	2	4	5	11	17	16	17
Lower respiratory infections	2	5	9	14	11	8	3	9	9	5	4	3	2	1	3	4	1	1	2	3	4	2
Cerebrovascular disease	3	1	2	3	3	2	2	2	1	3	10	1	3	5	2	3	9	8	7	14	13	12
Diarrhoeal diseases	4	57	61	76	54	80	55	44	61	23	12	6	14	8	7	7	3	3	3	4	2	3
Malaria	5	119	120	117	120	119	122	119	119	109	108	19	116	98	41	39	36	4	14	2	1	1
HIV/AIDS	6	65	40	56	26	44	20	3	23	8	11	9	20	9	38	5	13	10	1	1	5	4
Preterm birth complications	7	38	30	17	14	24	6	26	18	6	7	7	5	4	4	6	2	7	6	5	6	7
Road injury	8	10	11	6	5	7	4	5	4	4	3	5	7	2	6	11	11	19	12	11	11	9
Chronic obstructive pulmonary disease	9	12	5	7	4	10	11	13	3	11	14	17	11	23	17	27	5	27	27	29	25	32
Neonatal encephalopathy*	10	63	51	32	41	54	28	29	20	12	13	10	4	7	12	13	7	17	9	9	10	10
Tuberculosis	11	32	73	82	82	40	47	15	29	33	31	2	10	14	34	14	8	6	5	8	8	11
Sepsis	12	71	74	68	62	68	29	55	79	13	16	24	35	11	10	10	6	20	18	7	12	5
Self-harm	13	3	6	5	6	5	5	4	8	15	15	20	9	18	22	21	10	22	16	24	30	50
Congenital anomalies	14	24	23	13	19	20	8	17	11	9	9	12	8	6	5	12	12	14	13	15	7	15
Protein-energy malnutrition	15	67	76	79	73	82	52	84	59	38	19	38	50	19	25	19	16	16	29	6	3	6
Trachea, bronchus, and lung cancers	16	4	3	2	2	3	7	6	5	17	21	15	15	27	14	16	34	45	33	66	54	64
Cirrhosis of the liver	17	9	7	18	9	4	9	7	14	10	8	11	6	12	9	20	15	12	28	23	21	20
Meningitis	18	69	69	67	67	61	39	61	51	36	30	26	23	24	19	18	17	9	19	10	9	8
Diabetes mellitus	19	14	13	10	7	14	10	33	15	7	5	8	17	16	11	9	19	2	8	26	26	24
Interpersonal violence	20	49	50	38	12	31	12	8	31	1	1	16	13	10	20	8	27	24	4	18	17	23
Drowning	21	25	54	34	40	29	26	18	12	19	17	22	12	17	24	31	18	28	26	22	18	29
Liver cancer	22	7	20	28	30	21	33	37	6	34	26	18	29	31	29	30	57	21	41	45	47	30
Fire, heat, and hot substances	23	47	66	63	46	53	36	25	52	51	44	40	30	39	28	33	14	26	23	16	19	13
Chronic kidney diseases	24	13	22	21	16	22	16	31	22	16	6	14	16	13	16	22	25	11	17	32	36	31
Stomach cancer	25	6	15	25	34	13	18	12	7	24	18	33	19	15	27	34	43	31	50	52	56	60
Falls	26	21	21	29	29	17	40	21	16	28	27	29	33	33	32	36	23	42	55	27	31	19
Hypertensive heart disease	27	20	18	40	21	9	17	24	17	14	22	21	21	25	13	17	30	52	15	38	39	46
Maternal disorders	28	85	89	88	78	85	61	75	55	48	41	27	51	26	39	29	24	18	20	13	15	14
Colon and rectum cancers	29	8	4	4	10	6	13	14	13	21	28	31	31	34	33	25	55	50	40	56	63	63
Other cardiovascular and circulatory diseases	30	17	10	19	17	11	15	52	21	20	24	23	26	21	8	23	45	39	30	37	35	39
Breast cancer	31	16	8	8	13	12	14	19	24	22	25	30	28	32	26	28	47	35	38	46	55	59
Cardiomyopathy and myocarditis	32	28	24	26	20	15	19	16	34	18	38	37	22	28	15	32	38	40	22	35	32	38
Exposure to forces of nature	33	122	120	117	120	119	58	119	124	125	90	123	124	123	124	1	125	120	126	127	126	124
Exposure to mechanical forces	34	50	64	53	48	50	38	11	35	50	35	36	18	29	21	41	28	32	10	28	22	40
Typhoid and paratyphoid fevers	35	95	110	102	102	113	49	111	39	62	50	13	119	53	36	69	21	76	21	25	37	27
Leukaemia	36	19	19	15	22	23	22	28	19	29	20	32	27	20	23	38	48	23	49	68	62	66
Syphilis	37	102	101	83	101	87	82	98	74	61	57	48	66	30	47	24	41	41	31	12	14	18
Measles	38	106	105	101	108	105	103	110	103	106	93	34	83	58	94	106	20	54	35	19	38	22
Oesophageal cancer	39	18	28	30	33	39	30	41	10	35	61	52	32	66	58	55	46	61	36	44	57	78
Rheumatic heart disease	40	36	41	49	60	36	34	36	28	41	51	28	24	48	18	48	32	36	37	43	44	49
Epilepsy	41	56	48	43	63	48	57	49	43	44	33	39	25	36	42	46	53	30	25	20	24	16
Asthma	42	42	60	50	57	59	65	50	49	54	46	25	41	62	30	45	26	13	32	40	34	33
Poisonings	43	64	65	42	25	47	68	20	25	95	58	57	34	60	40	85	31	15	43	30	28	43
Encephalitis	44	82	96	103	90	84	109	66	99	75	97	69	48	105	45	96	22	91	46	41	42	42
Cervical cancer	46	34	44	48	45	25	24	34	38	27	23	35	40	22	67	35	52	29	34	31	43	41
Pancreatic cancer	47	11	14	12	18	16	21	22	27	37	39	50	43	47	50	40	73	78	53	83	80	87
Brain and nervous system cancers	48	30	17	20	28	19	37	32	26	26	32	42	38	43	31	44	64	88	54	87	70	104
Non-Hodgkin lymphoma	49	23	26	16	24	33	31	51	37	40	40	43	45	35	46	42	51	47	45	48	58	54
Alzheimer's disease and other dementias	50	26	12	9	8	43	27	53	41	45	66	82	79	76	68	37	81	66	58	80	86	75
Tetanus	52	112	113	113	114	110	118	114	86	108	109	64	121	103	79	59	40	51	104	33	45	25
Acute hepatitis A	54	100	103	104	104	99	108	92	78	101	94	91	91	92	54	104	33	25	98	53	64	44
Alcohol use disorders	55	55	31	47	32	18	41	10	73	25	29	59	39	49	108	54	76	72	61	103	99	117
Kidney and other urinary organ cancers	57	29	25	24	23	27	32	27	36	57	47	75	49	63	57	58	85	80	76	84	85	79
Drug use disorders	58	72	34	22	15	57	69	23	64	71	52	70	37	40	35	52	93	56	24	59	72	69
Prostate cancer	63	31	16	11	27	26	23	42	72	30	34	77	59	42	56	26	100	68	47	75	79	74
Whooping cough	67	99	95	84	87	94	87	95	93	105	65	44	63	37	59	43	37	33	56	21	29	21
Gallbladder and biliary tract cancer	68	15	39	51	58	37	25	59	40	49	45	60	60	44	71	67	63	67	89	113	98	84
Iron-deficiency anaemia	72	77	83	90	81	90	74	89	90	63	43	85	73	38	114	15	75	55	44	54	27	26
Interstitial lung disease and pulmonary sarcoidosis	78	22	47	46	38	70	54	76	71	72	59	100	75	46	65	101	62	81	70	77	77	85
Sickle-cell disorders	80	109	94	107	86	104	105	107	120	80	88	122	117	102	64	51	108	115	100	67	20	28
Malignant melanoma of skin	91	73	38	23	44	45	71	56	77	70	77	106	72	84	103	94	117	48	88	116	113	111
African trypanosomiasis	106	122	120	117	120	119	125	119	124	125	127	123	124	123	124	123	125	120	124	76	23	68

Figure 9: **Regional ranking of leading causes of years of life lost (YLLs), 2010**

Causes in the figure are ordered according to global ranks for causes. The figure shows all causes that are in the 25 leading causes in at least one region. Ranks are also colour-shaded to indicate rank intervals. *Includes birth asphyxia/trauma. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

disease, and stroke were the top ten causes of premature death in almost all regions in 2010, as were complications of preterm birth in all regions except Europe, high-income Asia Pacific, and east Asia. The massive effect of HIV/AIDS on mortality in most developing regions by 2010 was also clear, with north Africa and Middle East, east Asia, central Asia, and southern Latin America being notable exceptions. Malaria was a leading global cause but a minor cause in most regions outside sub-Saharan Africa and Oceania. Road injury was a remarkably consistent cause of YLLs; its lowest regional ranking is 19th in Oceania and it was in the top five causes in eight regions. All the neonatal causes and tuberculosis were important causes in some developing regions but minor causes in the more epidemiologically and demographically advanced regions. Figure 9 also highlights causes that were not in the top 25 global rankings but were important in selected regions. In some cases, these regional patterns gave a glimpse of future patterns and trends. Suicide was a top ten cause in the eight regions with the most advanced health transition. Other causes that seemed to be strongly related to the epidemiological and demographic transition included colon and rectum cancer, breast cancer, pancreatic cancer, brain cancer, non-Hodgkin lymphoma, Alzheimer's disease, kidney cancer, and prostate cancer. Other diseases had a more focal regional pattern that was not directly related to the broad health transition. More notable examples highlighted by multicoloured rows include: cirrhosis, diabetes, interpersonal violence, sickle-cell disease, whooping cough, poisonings, oesophageal cancer, drug use, gallbladder cancer, malignant melanoma, and African trypanosomiasis. Generally, the distribution of ranks by cause for YLLs was much more heterogeneous than for YLDs.[52] This was true for both time periods and suggests marked regional variation in disease and injury control priorities to improve survival.

Marked variation was noted in cancer rates by site and overall across regions in 2010 (figure 10). Figure 10 shows crude death rates to highlight the mixture of cancers recorded in health systems of every region but to remove the effect of variation in population size across regions. Crude rates are affected both by variation in age-specific and site-specific death rates and by population age-structure. In general, crude cancer death rates were higher in the regions with a more advanced demographic transition. But regions such as high-income Asia Pacific had a substantially different cancer profile from that in western Europe due to breast cancer, liver cancer, and stomach cancer along with a number of smaller cancers. At the other end of the epidemiological spectrum, crude cancer rates in three of the sub-Saharan African regions were the lowest. Central Latin America, tropical Latin America, and Andean Latin America have low cancer rates overall, whereas the Caribbean had higher rates than expected for its demographic transition.

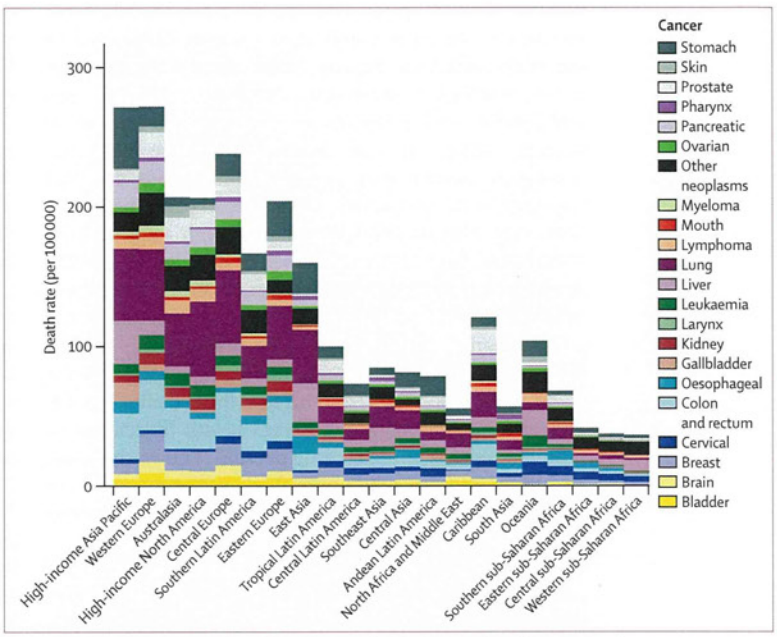

Figure 10: **Cancer death rates in 2010 for all ages and both sexes combined by cause and region**

Discussion

The GBD 2010 is the most comprehensive and systematic analysis of causes of death undertaken to date. The addition of time trends over 1980–2010 and quantification of uncertainty increases both the utility and the methodological rigour of the results. The global health community can now draw on annual estimates of mortality, by age and sex, for 21 regions of the world, for each year from 1980 to 2010, for 235 separate causes, each with 95% UIs to aid interpretation. These estimates of cause of death at the regional level are constructed from separate estimates of cause of death at the country level for 187 countries. No such resource for policy makers, donors, or scholars currently exists. At the most aggregate level, we have documented great changes in cause of death structure in regions such as central Latin America and tropical Latin America. We have also identified regions, such as eastern Europe and central Asia, where mortality has increased profoundly over the past two decades but the cause of death structure has not changed dramatically, at least for leading causes.

The shifting pattern of the number of deaths by cause across time, regions, and age groups is consistent with the three key drivers of change: rising total population, rising average age of the world's population, and the broad epidemiological transition. For communicable, maternal, neonatal, and nutritional causes, the increase expected because of population growth alone is reversed by population ageing and decreases in age-sex-specific death rates. By contrast, both population growth and ageing are driving up the number of deaths from non-communicable diseases and injuries more than the decreases expected

because of lower age and sex-specific rates. Overall, these factors are leading to a shift from a pattern dominated by the main infectious disease killers of children (such as lower respiratory infections, diarrhoea, malaria, and meningitis), and tuberculosis and maternal causes in younger adults, to one dominated by the non-communicable causes over age 40 years. Quite different regional stories are overlaid on this broad pattern. Injuries have very distinct regional patterns, with violent death being much more common in selected regions. The HIV epidemic has had massive effects in eastern and southern sub-Saharan Africa. Diabetes has a major effect in central Latin America, the Caribbean, north Africa the Middle-East, and Oceania. Theories of the epidemiological transition need to be nuanced to capture these distinct trends and patterns that suggest different health trajectories in different regions in the coming decades. Our findings are also different from many published studies on causes of death in some age groups or for specific causes; these differences warrant careful discussion.

The HIV epidemic has greatly changed the pattern of causes of death between 1990 and 2010 in eastern and southern sub-Saharan Africa. We estimated that, in 2010, 1·47 million deaths were due to HIV/AIDS compared with UNAIDS estimates of 1·77 million, which is a 21% difference at the global level. For specific countries and regions, the differences are much larger. We used UNAIDS estimates as the input to CoDCorrect for most countries, so the difference is almost entirely due to the juxtaposition of evidence on levels of all-cause mortality and natural history model estimates of HIV/AIDS deaths. We believe that this is an important strength of the burden of disease approach. Some differences are also due to the data from Thailand, where in the 2012 UNAIDS assessment mortality doubled compared with their 2010 assessment. Even the 2010 UNAIDS assessment was twice the magnitude recorded in two studies of national verbal autopsy and vital registration data.[66,67] We chose to use the 2010 UNAIDS revision estimates for Thailand because of the implausible nature of the 2012 revision estimates. Nigeria is another example of a country whose estimates contribute to a substantial part of the differences between global data from UNAIDS and GBD 2010. Since Nigeria is a country with a large population, a major HIV/AIDS epidemic, and poor data quality, when we fit our HIV/AIDS estimates for Nigeria into the country's all-cause mortality levels our estimates are much lower (27·9% in 2010) than those of UNAIDS and this large difference in death is reflected at the global level. The uncertainty distributions for UNAIDS estimates of mortality in some countries in sub-Saharan Africa are implausibly narrow; for example, at the peak of the epidemic in Malawi, the UI for deaths at all ages provided by UNAIDS varied by plus 8·5% or minus 8·1%. Our UIs based on the UNAIDS figures were also implausibly narrow. Improved estimation of mortality from HIV/AIDS including uncertainty in the future will come both from continued progress in the estimation of the timecourse of the HIV epidemic by UNAIDS and from further data on the levels of adult mortality in some key countries such as Nigeria.

On the basis of a single-cause analysis, Murray and colleagues[25] reported 1·24 million malaria deaths in 2010 of which 42% were in individuals older than 5 years. These estimates had very large UIs; for example, the number of deaths in those older than 5 years in sub-Saharan Africa was estimated to range from 307 000 to 658 000. Large uncertainty in the results reflected both the sparse data available on causes of death in adults and the large variation in results across different models included in the final ensemble model. In these GBD 2010 results, where the sum of cause-specific estimates must equal the number of deaths from the demographic analysis for each country-age-sex-year, the number of malaria deaths in 2010 was estimated to be about 5% less or about 1·17 million. For deaths in children younger than 5 years, the change was from 714 000 to 676 000. For deaths in individuals older than 5 years, the change was from 524 000 to 494 000. Our finding of substantial deaths due to malaria in populations older than 5 years is driven by the evidence from verbal autopsy studies in endemic areas.[25] Validation studies suggest that verbal autopsy studies overestimate adult deaths at low malaria cause fractions and underestimate adult malaria deaths when malaria deaths are common.[68] The findings of adult deaths from malaria are consistent with data of hospital discharge and death in endemic areas but remain controversial.[69-72] Our UI for global deaths in individuals older than 5 years from malaria was 365 356 to 643 977, partly depicting the uncertainty in the underlying data sources.

An innovative dimension of the GBD 2010 has been the addition of estimates of deaths due to different diarrhoea and lower respiratory infection pathogens. These are important both for the prioritisation of existing treatments, such as rotavirus or pneumococcal vaccines, and for the development of future technologies. Making sense of the data by aetiology is extremely challenging. For diarrhoea, many pathogens can be cultured from the stool of individuals without diarrhoea. Studies such as the Global Enterics Multi-Center Study (GEMS)[73] are trying to estimate relative risks of diarrhoea in the presence of different pathogens. In the available observational data that do not use this relative risk approach, the relation between the prevalence of a given pathogen and the number of pathogens tested is strong. Studies testing only one pathogen effectively report higher fractions due to a pathogen than do studies that test for multiple pathogens. This finding is probably caused by the frequency of various pathogens in the same stool sample and rules for allocating shares of diarrhoea to pathogens such that the sum of the pathogen cause fractions total to 100%. In our analysis, we adjusted study results to be equivalent to studies reporting two to eight pathogens. Because of both the huge heterogeneity of results and the variation in the number of

pathogens tested across studies, great caution should be used in interpreting our findings on the diarrhoea aetiologies. When large multicentre studies such as GEMS publish their results, their findings will be an important addition to this analysis; future revisions of the GBD should make use of these results as they become available. Nevertheless, our results are notably different from widely cited findings. For example, we reported 173 000 deaths due to rotavirus in children younger than 5 years and 78 000 deaths in individuals older than 5 years in 2010; these findings contrast with claims from WHO of 453 000 rotavirus deaths in children younger than 5 years alone in 2008.[74] Higher numbers were probably reported by WHO for three reasons: higher all-cause global deaths in children younger than 5 years than currently estimated by UNICEF or the GBD 2010; a much higher fraction of deaths in children younger than 5 years attributed at the time to diarrhoea; and a higher fraction of diarrhoea attributed to rotavirus. Because rotavirus remains an important cause of death in many countries, the GBD estimates by country, when released, will be an important method to assist in understanding where its burden is greatest.

For respiratory pathogens, even greater challenges exist. In many observational studies, no pathogen is identified in a substantial fraction of cases. Even in severe cases that lead to hospital admission, the case-fatality rate is likely to vary substantially by pathogen, which confounds the analysis. The substantial differences in our results from published assessments by O'Brien and colleagues[35] for pneumococcal lower respiratory infections, Nair and colleagues[75] for RSV, and Watt and colleagues[76] for Hib deserve exploration. Our findings of 168 000 deaths due to pneumococcal lower respiratory infection in children younger than 5 years in 2010 and 381 000 in 1990 contrast sharply with the 826 000 for the year 2000 published by O'Brien and colleagues.[35] in 2009, these investigators used an estimate of 10·6 million deaths in children younger than 5 years from all causes for the year 2000, which contrasts with our estimate of 9·4 million and UNICEF's estimate of 9·6 million. They used a higher estimated fraction of deaths in children younger than 5 years due to lower respiratory infections than in our study, 27% and 18%, respectively. The fraction of lower respiratory deaths in children younger than 5 years due to pneumococcal pneumonia was 35·8% (UI 16·0–50·9) in 2000 compared with 19·8% (16·1–24·8) in the GBD 2010 for 2010. The 95% UIs for these cause fractions substantially overlap. Differences in the mean estimate result largely from the exclusive use by O'Brien and colleagues of the results of four vaccine trials in the Gambia, the Philippines, the USA, and South Africa to estimate an average fraction of pneumonia in children younger than 5 years. Although they reviewed the literature, they chose not to use the published observational studies. These observational data suggest substantial variation across regions; for example, pneumococcus might be less common in south Asia. We used both the trials and observational data to generate different breakdowns by pathogen by region giving extra weight to the trials; our findings, however, still showed variation by region and age. For RSV lower respiratory infections, our findings of 234 000 deaths in children younger than 5 years in 2010 and 520 000 in 1990 are notably higher than the 66 000 to 199 000 deaths for the year 2005 reported by Nair and colleagues[75] in 2010. They reviewed the published studies on RSV but chose, on the basis of expert opinion, to assume no RSV deaths in individuals older than 2 years;[75] the scientific literature, however, records deaths in those older than 2 years.[77,78] Data on hospital admission in the USA, for example, suggests substantial burden of severe RSV at least in the ages 3–5 years. Other investigators[79,80] argue that RSV is an important and often missed pathogen causing severe lower respiratory infections in elderly people. Studies, however, vary markedly in their sampling, culturing, and identification protocols, which might also account for some heterogeneity. Most studies show high fractions of neonatal lower respiratory deaths due to RSV, so the extent to which RSV is a major cause of post-neonatal lower respiratory deaths needs the most attention. For deaths due to Hib lower respiratory infection, Watt and colleagues[76] published in 2009 for the year 2000, an estimate of 292 000 deaths that compares well with our finding of 184 000 (95% UI 154 053–219 456) in 2010 and 447 000 (385 717–506 594) in 1990. The similarity of the result, however, is somewhat misleading. They used a much higher estimate of all-cause under-5 mortality and a higher cause fraction due to lower respiratory infection than we used. In other words, we estimated a larger fraction of lower respiratory infection deaths in children younger than 5 years due to Hib than did Watt and colleagues. The main reason for this difference is that Watt and colleagues assumed that Hib in individuals older than 2 years does not cause death; the available observational data,[81–84] however, show Hib mortality at all ages. For example, results from the study in Japan[84] showed severe cases of hospital-acquired and community-acquired pneumonia related to Hib, the differences in these assessments for all the respiratory pathogens is even more striking. New multicentre studies such as PERCH[85] will hopefully provide much needed data to strengthen the analysis of pathogens by region.

We estimate that in 2010 1·20 million deaths were due to tuberculosis, about 14% more than the WHO estimate of 1·05 million (2011 WHO TB Report). Our analysis and that of WHO use fundamentally different methods but do not yield, at the aggregate level, substantially different conclusions. The key difference lies in how the case-detection rate in every country was estimated; WHO used locally informed expert consultation to assess both under-diagnosis and under-reporting whereas we used a statistical model to try and estimate the case detection rate. Our models also captured more of the temporal and spatial correlation structure in the cause of death data yielding quite different estimates than did the WHO

where data were strong (eg, Japan and Thailand). These differences result in important variations between our estimates and those from WHO at the country and regional levels that deserve further investigation. Despite these variations, for some countries, such as Ecuador, our estimates, WHO estimates, and the cause of death data were in close alignment. Assessments at the global and regional level point to substantial continued and sustained progress in reducing tuberculosis mortality. Our higher levels of mortality for tuberculosis in 2010 suggest that tuberculosis should remain a major priority.

Deaths due to maternal causes have been reported in various studies[86,87] in the peer-reviewed scientific literature and UN reports.[88] These studies, however, focused on the maternal mortality ratio. ICD 10 rules recommend that pregnancy-related deaths due to HIV should be included in the computation of the maternal mortality ratio but reported in cause of death tabulations for HIV. The GBD 2010 follows this convention so that our 255 000 maternal deaths in 2010 do not include 18 970 HIV-related deaths in pregnancy included in the HIV totals. We also revised the method used to estimate the fraction of maternal deaths related to HIV/AIDS in this study compared with Lozano and colleagues.[23] In GBD 2010, our estimates of the fraction of maternal deaths related to HIV/AIDS come from a review and statistical analysis of available data that provide a detailed breakdown of maternal deaths. Further, the deaths due to maternal causes reported here are after the application of the CoDCorrect algorithm, which is a strength of the comprehensive burden of disease approach. The global number of deaths due to maternal causes was reduced by 9·8% through the application of CoDCorrect. The revised approach for maternal mortality presented here also highlights the major causes of maternal death. The largest specific cause of maternal death is maternal haemorrhage accounting for 23% of deaths in 2010, followed by hypertensive disorders causing 18%, abortion causing 15%, sepsis causing 9%, and obstructed labour causing 4%. These results contrast with various estimates reported by WHO—one estimate for 2005, which is based on 35 197 deaths reported in various published studies[89] and one largely based on vital registration data for 2008.[16] The 2005 WHO report estimated that abortion caused only 8% of maternal deaths but 14% in the 2008 study.[16] There are also substantial differences for other maternal causes as well. Our findings are based on a larger set of published studies, including reports from 18 countries such as India, South Africa, Bangladesh, Ghana, and Pakistan, which contribute 22 943 additional maternal deaths on the detailed causes of maternal death.

For deaths in children younger than 5 years, our results differ from those published by CHERG[20] for the same year in several key ways: CHERG estimated 1·40 million deaths due to lower respiratory infection compared with 847 000 in our study; CHERG estimated 801 000 for diarrhoeal diseases versus 666 000 in the GBD 2010; for malaria CHERG estimated 564 000 versus 676 000 here. Within the neonatal causes, there are also striking differences in the composition of specific neonatal causes, with CHERG estimating much higher fractions due to preterm birth complications and lower fractions due to sepsis and other disorders. In exploring these differences, it is crucial to distinguish between the neonatal age group (under 28 days) and causes arising during the neonatal period that can cause mortality both under 28 days and in the post-neonatal period and less commonly over age 1 year. Understanding the source of the differences for neonatal causes, however, is challenging. Differences must arise from any or all of the following: the datasets used, the adjustments to the data, and the modelling strategies. In their analysis of post-neonatal child mortality (1–59 months), CHERG reported using vital registration data for 578 country-years between 1998 and 2009, whereas we used 1125 country-years for that period. They used 113 study years between 1980 and 2008; by contrast, we used 294 years. CHERG used a reduced number of studies because of their decision to use only studies that report on six major causes. The largest differences and the ones likely to explain the differing results lie in the modelling strategy. For a single cause such as diarrhoeal diseases or lower respiratory infections, we developed one ensemble model using all the data. The one ensemble model included component models with a wide variety of functional forms but all included age group fixed effects. CHERG tested and developed four different models with no relation between them: for under-5 mortality rates (UFMR) lower than 35 for babies younger than 1 month, for UFMR higher than 35 for babies younger than 1 month, for UFMR lower than 35 for children aged 1–59 months, and for UFMR higher than 35 for children aged 1–59 months. The relations between covariates in these different models were estimated as completely independent. Covariate selection was done for every cause of death independently for each of the four models. They used multinomial logistic models to make estimates for six causes of death simultaneously, a method found to perform worse than modelling causes individually and then scaling to all-cause mortality (appendix pp 146–148). Their model structure does not allow for spatial or temporal patterns in the residuals, probably substantially reducing model performance.[22] Model performance is difficult to assess and compare with ours: they reported undertaking a cross-validation study but no metrics of model performance were reported such as the coverage of their UIs or a measure of prediction error. Further, in their cross-validation study they left out 10% of the data at random; as shown in previous studies,[23] this is the easiest task for prediction. A much harder task, which was used in the GBD 2010, is to leave out long sequences or all data for some countries and see how well the models perform. Additionally, leaving out data for one cause without also dropping it for the other causes in that country-year makes for an even simpler task in a multinomial logistic model

such as the one CHERG used. The high levels of mortality for lower respiratory infections might be related to the bias in physician diagnosis of verbal autopsies, which was demonstrated in a rigorous validation study.[68] Although this study[68] used physician-certified verbal autopsy data on lower respiratory infections, by separating the data into four components and not including country random effects in their models, the bias towards higher such infections in verbal autopsy studies might have had a larger effect on their estimation procedure. Finally, the CHERG estimation strategy uses multinomial models for a subset of models and then adds on estimates for selected causes in selected countries such as HIV/AIDS, measles, tetanus, and malaria. The differential treatment of some causes and not others in the modelling strategy might also have caused distortions in the results. Interestingly, given the substantial difference in modelling approaches, the results for 2010 between the two approaches were actually surprisingly close.

The health-related MDGs place special priority on reducing under-5 mortality, maternal mortality, and deaths from HIV, tuberculosis, and malaria. These causes collectively accounted for 42·4% of YLLs in 2010. Even though the computation of YLLs heavily weights deaths in children younger than 5 years, more than half (57·6%) of global YLLs in 2010 were due to non-MDG diseases and injuries. Important global causes that are not included in the MDGs include ischaemic heart disease, stroke, COPD, road traffic injuries, and self-harm. The predominance of these causes in YLL rankings is not merely a volume issue: many of those who die from these causes do so at young adult ages. A more holistic view of preventable mortality within the MDG platform would argue that these causes ought to be included in any evidence-based framework for reducing avoidable deaths. Examination of the trends from 1990 to 2010 indicated that the MDG-related YLLs were declining at 2·0% per year, whereas the non-MDG related YLLs were increasing at 0·8% per year. Population ageing and the substantial if incomplete progress in reducing age-specific death rates from the MDG related causes all suggest that these trends will continue. Indeed, if they do, then non-MDG related causes are likely to account for more than two-thirds (67·6%) of YLLs by 2025. These findings highlight the importance of looking more critically and comprehensively at what are the leading causes of death and YLLs worldwide, and how these are changing. Our analyses, for the first time, allow such comparative assessments and are important inputs into discussions about goals and targets for the post-MDG era.[90] The rapid and global rise in premature death from leading non-communicable diseases argues strongly for inclusion of these disorders, and their principal causes, in this agenda, particularly in view of their close relation to poverty reduction goals.[91–96] It also stresses the need to understand the effective and affordable options for prevention of non-communicable diseases and injuries and treatment including both medical and surgical interventions.[97]

Our study suggests that the number of deaths where chronic kidney disease is the ICD underlying cause of death increased by 82% from 1990 to 2010. In addition to these deaths, a reduced glomerular filtration rate (GFR) has been associated with an increased risk of death.[98] Even chronic kidney disease stages II–IV are associated with increased risk of death. The directly coded deaths due to chronic kidney disease that we estimated probably capture only those deaths due to end-stage renal disease. Other diseases such as diabetes are also associated with an increased risk of death from other causes. For diabetes, the risk factor analysis[99] provides an assessment of all mortality associated with hyperglycaemia. This number is substantially larger than the number of deaths directly coded to diabetes estimated here.

Those who study the health effects of war will be surprised by the 17 670 deaths related to direct conflict estimated for 2010. This number should be interpreted with great caution. First, in the ICD cause list, only direct deaths are assigned to this cause; 17 670 is not the total number of deaths related to conflict, which would include indirect deaths mediated through various mechanisms such as the destruction of health-care infrastructure.[100] Second, the number of direct deaths varies substantially from year to year. During 1990–2010, direct deaths peaked at 496 400 in 1994 with a low in 2001 of 14 700 and 17 700 in 2010. In 2011, because of the conflict in Libya, for example, direct deaths were likely to have been much higher, closer to 61 000. For episodic events such as wars or natural disasters, it is important to consider the burden of disease over longer periods of time to fully appreciate their effect on human populations.

For the first time in the GBD enterprise, we included deaths that were mainly related to hepatitis B, hepatitis C, alcohol, and other causes as disaggregated causes for cirrhosis and liver cancer. These categorical breakdowns are not counterfactual assessments but rather an attempt to assign deaths to the primary or dominant cause. Interactions exist between hepatitis and alcohol consumption, such that assessment of these conditions as a risk factor would give different results. Nevertheless, this categorical attribution provides a useful assessment of the magnitude of direct burden, particularly for guiding intervention priorities. The total number of deaths due to hepatitis B in 2010 was estimated to be 786 000 and those due to hepatitis C 499 000. If all deaths related to these diseases were directly counted in the main GBD 2010 cause list, hepatitis B would be the 15th ranked cause of death and hepatitis C would be the 25th ranked cause of death. Cirrhosis rates vary greatly across countries, with Egypt having the highest level related to an iatrogenic epidemic of hepatitis C that began as early as the 1920s.[101] Some regions have high rates such as central Asia, Oceania, eastern and western sub-Saharan Africa, eastern Europe, and central Latin America. Not all this regional and country variation can be explained by hepatitis B, hepatitis C, or total alcohol consumption. For

example, high rates in eastern Europe might be related to the content rather than volume of alcohol consumed. Theories on this distinction include hepatotoxic alcohol constituents in homemade poor quality alcohol, which is common in these regions.[102] Given that much of the burden of cirrhosis can be preventable, its substantial global mortality deserves more policy attention.

The much more detailed categories of causes of death for injuries in the GBD 2010 provide some important insights into the global epidemic of road injuries. The number of deaths increased from 908 000 in 1990 to 1·329 million in 2010. These results are similar to the 1·237 million reported for 2007 by WHO.[103] The composition of this increase in road injuries, however, has differed by sub-cause. Road deaths to pedestrians were the major cause, rising from 284 000 in 1990 to 461 000 in 2010. Road deaths of occupants in motorised vehicles with three or more wheels and road deaths of riders of motorised vehicles with two wheels each have also increased by about 200 000 in the past two decades. Regional detail shows road deaths in east Asia, south Asia, and eastern and western sub-Saharan Africa rapidly escalating over the past two decades, whereas in high-income areas with a history of road safety programmes such as western Europe and high-income North America, road deaths have decreased.

Violence as a cause of death is one of the most heterogeneous across different regions. Crude death rates for violence are lowest in high-income Asia Pacific at one per 100 000. The rate in 2010 in high-income North America dominated by the USA of seven per 100 000 was nearly seven times higher than high-income Asia Pacific, western Europe, or Australasia. But in tropical Latin America, the rates are substantially greater still, at 30 per 100 000, and even higher in central Latin America and southern sub-Saharan Africa, at 33 per 100 000. The huge variation in violence raises important questions about the origins and sociopolitical context of violence, the drivers of change in violence-related mortality, and the effectiveness of public health strategies in reducing deaths from violence. In men from tropical Latin America, violence is the number one cause of YLLs. In 2010, men in the 20–24 years age group alone had 653 600 YLLs, three quarters the size of the 824 000 YLLs in men in high-income North America of all ages combined.

An important dimension to the GBD is the requirement that estimates of causes of death sum to estimates of all-cause mortality. The discipline of requiring this internal consistency has been a hallmark of burden of disease analysis since the GBD 1990. As quantified in the appendix (p 144) the effect is to reduce the number of deaths estimated for many causes compared with single-cause analyses. The correction factor is an indication of inconsistency at the country-age-sex-year level between demographic analysis and the cause-specific analyses. We believe that for causes for which the magnitude of these corrections is comparatively large, future research should be targeted to try to build a better understanding of the strengths and weaknesses of the various data sources, whether epidemiological or demographic. In some sense, the CoDCorrect ratios can help direct attention to settings in which the data are the most inconsistent and our knowledge the most uncertain. The substantial difference between single-cause-model estimates and those presented here raises questions about the value of publishing single-cause assessments. Some organisations such as WHO have in recent years been producing both types of assessments: WHO with CHERG produces estimates for 16 major causes of child death but also publishes single-cause estimates for tuberculosis, HIV/AIDS, malaria, maternal mortality, and other causes. Should leading scientific journals continue to review and publish studies on single-causes of death? Due consideration of the value of single-cause models to bring attention to neglected issues or stimulate innovation in methods or new data collection will need to be balanced against the greater robustness of more comprehensive assessments such as those presented here.

A study of this size and scope has many limitations. The ambition to estimate mortality from 235 causes with uncertainty for 187 countries over time from 1980 to 2010 means that many choices about data sources, quality adjustments to data, and modelling strategies had to be made. We highlight some key limitations. First, data on cause of death, even in settings with medical certification, might not always accurately capture the underlying cause of death. Results from autopsy studies[104–106] have shown that medically certified causes of death might be incorrect. Second, our approach to garbage code redistribution, although an improvement over past efforts, could benefit strongly from more empirical information on misclassification obtained in places where gold standard cause of death assignment is possible. We were not able to develop uncertainty distributions around garbage code redistribution algorithms; to the extent that this is poorly known, our UIs for some causes might be underestimated. Third, we made extensive use of verbal autopsy data, especially in low-income settings. Verbal autopsy validation studies[68] suggest that verbal autopsy is accurate for some causes such as breast cancer, drowning, or road injury, but less accurate for other causes. Verbal autopsy performance for some key causes of child death such as lower respiratory infections is particularly poor. Much could be learned about causes of death in countries where death certification is poor through the more widespread testing and application of recent advances in verbal autopsy methods, which greatly reduce heterogeneity in diagnostic practices across populations in which verbal autopsy is currently used.[107] Fourth, for some causes of death such as kidney cancer, poisonings, or paralytic ileus, only weak covariates have been identified that explain the spatial or temporal variation in the cause. Inevitably, model estimates for these causes will have wide UIs. The use of negative binomial models and fixed proportion models where data are extremely weak is another area for

which better data and improved methods could strengthen the overall findings. Fifth, where natural history models have been used, their validation is extremely difficult at present. Natural history models are in principle used when concerns exist that data on direct cause of death are potentially biased. Improvements in data on cause of death for some causes such as HIV/AIDS might allow in the future opportunities to validate natural history models in selected countries. Where natural history models have been used, these approaches potentially will tend to yield higher estimates than those using more empirical strategies such as CODEm. Sixth, our use of CODEm for most major causes of death means that our UIs have in most cases been shown to be valid, but for causes where we have had to use other methods such as negative binomial, fixed proportion, or natural history models, the UIs have not been independently validated. Seventh, CODEm can be improved in the future by including an even broader set of model families. Ultimately, the greatest limitation is the availability of data on cause of death itself. Finally, in cases where expert opinion and the available data diverge, we tended to follow the available data. Examples of this practice include estimating deaths from malaria in individuals older than 5 years or deaths from Hib in those older than 2 years. Subsequent more detailed studies might affirm that expert opinion was correct and the available data substantially biased. Nevertheless, we believe that to follow the balance of the available data that meet our quality criteria is important.

Improving data collection on cause of death in the future is the most direct and obvious pathway to improved estimation of global, regional, and national causes of death with narrower UIs. Improved verbal autopsy methods[108–111] mean that it might soon be feasible to apply them routinely to generate comparable data on cause of death cost effectively in populations in which we are still substantially ignorant about the leading causes of death. Opportunities for strengthening death registration, cause of death certification, and the more widespread use of verbal autopsy exist. Some countries have civil registration systems that capture less than 70% of deaths; the priority in such cases is to improve certification and coding of cause of death. Other countries such as Saudi Arabia have functioning civil registration run by Ministries of the Interior that are not fully used by Ministries of Health. Collectively, the global health community would benefit enormously by placing much greater priority on strengthening vital registration systems to improve measurement of cause of death. This is now the key focus of the Health Metrics Network and it is reasonable to expect that substantial progress can be made with appropriate leadership, attention, and collaboration among global development partners.[112]

In the GBD 2010, a substantially new set of analytical approaches and methods have been developed and applied. These methods range from improved diagnostic redistribution methods to CODEm and CoDCorrect, drawing on information for almost a billion deaths and time series for hundreds of covariates that affect mortality. This is a massive endeavour, but, with appropriate investment and leadership, updating results as new data on causes of death or alternative covariates become available will be much more feasible than hitherto. Rather than huge periodic revisions of the GBD every decade, it is now feasible to conduct annual updates so that the consumers of health intelligence have the most recent and comprehensive information on comparative causes of disease burden available where and when it is required to help guide public health decision making. Public health priorities everywhere are changing, or soon will be, as large and avoidable causes of disease burden become more common with development. To not have strategically important and comparable health information available and used to inform the new health dialogue and disease control priorities, as we have shown here it can be, would be a massive missed opportunity for global health.

Contributors

CJLM, ADL, and RL prepared the first draft. RL, MN, KF, SL, KS, ADL, and CJLM finalised the draft on the basis of comments from other authors and reviewer feedback. ADL and CJLM conceived the study and provided overall guidance. All other authors developed cause-specific models, reviewed results, provided guidance on the selection of key covariates, and reviewed the report.

Conflicts of interest

E R Dorsey has received consulting fees from Medtronic and Lundbeck and research support from Lundbeck and Prana Biotechnology. M Ezzati chaired a session and gave a talk at the World Cardiology Congress (WCC), with travel cost reimbursed by the World Heart Federation. At the WCC, he also gave a talk at a session organised by PepsiCo with no financial or other renumeration. P J Hotez reports holding several positions: Dean, National School of Tropical Medicine, Baylor College of Medicine; Director, Sabin Vaccine Institute Texas Children's Hospital Center for Vaccine Development; and President, Sabin Vaccine Institute. He also is an inventor on several patents: 5,527,937 "Hookworm Anticoagulant"; 5,753,787 "Nucleic Acids for Ancylostoma Secreted Proteins"; 7,303,752 B2 "Hookworm vaccine"; 12/492,734 "Human Hookworm Vaccine"; 61/077,256 "Multivalent Anthelminthic Vaccine"; and PCT-20100701/0.20.5.18 "Malaria Transmission blocking vaccine". G A Mensah is a former employee of PepsiCo. F Perez-Ruiz was an adviser for Ardea, Menarini, Novartis, and Metabolex; was a member of the Speaker's Bureau for Menarini, Novartis; an adviser for educational issues for Savient; led an investigation grants for the Spanish Health Ministry, Hospital de Cruces Rheumatology Association; and was principal investigator in clinical trials for Ardea.

Acknowledgments

We would like to thank the countless individuals who have contributed to the Global Burden of Disease 2010 Study in various capacities. We would also like to specifically acknowledge the important contribution to this work from multiple staff members of the WHO. We also wish to thank the following organisations that hosted consultations during the final stages of the analytic process, providing valuable feedback about the results and the data to improve the study's findings overall: Pan American Health Organisation; Eastern Mediterranean Regional Office of WHO; UNAIDS; Ministry of Health, Brazil; China Centers for Disease Control; and the University of Zambia. We would like to thank Cynthia Boschi Pinto for her input into the analyses and estimates. Finally, we would like to acknowledge the extensive support from all staff members at the Institute for Health Metrics and Evaluation and specifically thank: James Bullard, Andrew Ernst, and Serkan Yalcin for their tireless support of the computational infrastructure required to produce the results; Linda A Ettinger for her expert administrative support and facilitating communication and coordination among the authors; Peter Speyer, Abigail McLain, Katherine Leach-Kemon, and Eden Stork for their

persistent and invaluable work to gain access to and catalogue as much data as possible to inform the estimates; and Erin C Mullany for her systematic efforts in organising drafts of papers, formatting correspondence with expert groups, and preparing the final manuscript. The following individuals would like to acknowledge various forms of institutional support. J P Abraham acknowledges the World Bank Global Road Safety Facility and Department of Global Health & Population, Harvard School of Public Health, and the WHO Violence and Injury Prevention. K Bhalla was supported by the World Bank Global Road Safety Facility for researcher salaries, to pay for many small projects in Africa to digitise secondary data sources, and supporting several gatherings of the injury expert group over the past 6 years. B Bikbov acknowledges the Moscow State University of Medicine and Dentistry, Moscow, Russia; Academician V I Shumakov Federal Research Centre of Transplantology and Artificial Organs, Moscow, Russia; and International Society of Nephrology. G L Birbeck has received research funding from the US NIH, the Dana Foundation, and the Doris Duke Charitable Foundation; she has also received travel grants from the WHO for related work. H Chen acknowledges his participation in this study was in part supported by the intramural research program of the NIH, the National Institute of Environmental Health Sciences. L E Coffeng received financial support from the African Programme for Onchocerciasis Control (WHO/APOC) for work on onchocerciasis. M Cortinovis, F Gaspari, and N Perico acknowledge the International Society of Nephrology (ISN) on the behalf of the entire Genitourinary Expert Group. M Cross and L March acknowledge the University of Sydney (USYD); Institute of Bone and Joint Research, University of Sydney, Department of Rheumatology, Royal North Shore Hospital, St Leonards NSW 2065 Australia. N Dahodwala was supported by NIH grant K23 AG034236 and the Parkinson Council while working on this project. L Degenhardt is supported by an Australian NHMRC Senior Research Fellowship and funding to support work on illicit drug dependence was provided by the Australian National Drug and Alcohol Research Centre of the University of New South Wales, NSW, Australia. R Havmoeller is supported by a grant from the Swedish Research Council (#2011-1071). D Hoy was supported by the Bill & Melinda Gates Foundation and the Australian National Health and Medical Research Council. P J Hotez acknowledges grant support from several sources: the Bill & Melinda Gates Foundation regarding human hookworm vaccine through the Sabin Institute (Human Hookworm Vaccine Initiative 1 Human Hookworm Vaccine Initiative; Human Hookworm Vaccine Initiative 3 Clinical Development and Evaluation of the Na-GST-1 and Na-APR-1 Hookworm Vaccine Antigen); the National Institutes of Health (Product development of a membrane tetraspanin vaccine against schistosomiasis; RBD Recombinant Protein-based SARS Vaccine for Biodefense); and the Dutch Government (Product Development Support of the Human Hookworm Vaccine). K H Jacobsen was supported by the WHO for her work on Hepatitis A. B M Mayosi was funded by the Lily and Ernst Hausmann Research Trust. T R Merriman acknowledges the Health Research Council of New Zealand. D Ozgediz is grateful for the collaboration colleagues at Mulago Hospital and Makerere University in Kampala, Uganda. B Pahari would like to thank the Mario Negri Institute. U Sampson was funded in part by The Harold Amos Medical Faculty Development Award of the Robert Wood Johnson Foundation and The Vanderbilt Clinical and Translational Scholars Award. M Segui-Gomez's participation was partly supported by funds of the European Center for Injury Prevention, Universidad de Navarra. E Smith acknowledges Department of Health and Ageing, Commonwealth Government of Australia, Institute of Bone and Joint Research (IBJR), University of Sydney (USYD), Department of Rheumatology, Royal North Shore Hospital, St Leonards NSW 2065 Australia. L Rushton was supported by honorarium for board membership of the European Centre for Ecotoxicology and Toxicology of Chemicals; research grants to Imperial College London (as PI) from the European Chemical Industry Council (CEFIC) and CONCAWE (Conservation of Clean Air and Water Europe). P Yip was supported by a General Research Grant at the University of Hong Kong.

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