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"Seminar of Psychiatric Global Clinical Trial in Tokyo"

13:00 – 17:00, Saturday, January 17, 2009

Tokyo Yaesu Hall

In the seminar, we focus on "promotion of global clinical trials for antipsychotics in schizophrenia". We will have discussion on several issues listed below.

- legal/ethical issue conflict with entry of patients with involuntary admission?
- system of screening and entry for potential candidates of trials
- who evaluate psychiatric symptoms, MD or co-medical staff? use standardized psychometric tools of native language?
- support and incentive for doctors
- specific action for promotion of clinical trials by hospital, academia, or government

13:00-13:10, Registration

13:10-13:20, Opening Remarks
Mitsuhiko Yamada, National Center of Neurology and Psychiatry, Japan

13:20- 13:40 , Yoshio Hirayasu, Yokohama City University, Japan
"Introduction: Clinical trials for schizophrenia in Japan"

Session 1: Psychiatirc clinical trial in China
Chiar: Yoshio Hirayasu, Yokohama City University

13:40-14:05, Li Huafang, Shanghai Mental Health Center, China
"Clinical trial of psychotropics in China in past ten years"

14:05-14:30, Sehn Yifeng, Shanghai Mental Health Center, China
"Clinical trials in Shanghai Mental Health Center".

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14:30-14:40, Break

Session 2: Psychiatirc clinical trial in Korea

Chair: Hiroaki Kawasaki, Kyusyu University, Japan

14:40-15:05, Joo-Cheol Shim, Inje University Medical School, Paik Hospital, Korea

" Clinical Trial Infrastructure in Korea: Challenges and Changes"

15:05-15:30, Chi-Un Pae, Catholic University College of Medicine, Korea

"General situation and progress of clinical trials in Korea: regulation and resource"

Session 3: Current issues on global clinical trials for antipsychotics in schizophrenia

Chiar: Nakao Iwata, Fujita Health University, Japan

Yoshio Hirayasu, Yokohama City University, Japan

15:35-16:45, General Discussion

16:45-17:00, Closing

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A decade for psychiatric disorders

There are many ways in which the understanding and treatment of conditions such as schizophrenia are ripe for a revolution.

A media circus surrounded President Bill Clinton's visit to a New York medical centre in 2004 for a quadruple heart bypass. Yet barely a whisper was heard about other high-profile individuals' visits there for the treatment of psychiatric disorders.

In Britain, the public donates £500 million (US$800 million) each year to charities for cancer research. For mental-health research, the figure is a few million, and most of that is for work on neurodegenerative diseases such as Alzheimer's, rather than for earlier-onset conditions that can undermine people's entire lives, such as depressive disorders.

It is time for such disparities to be addressed in a more coherent and aggressive way than in the past. The stigma of psychiatric disorders is misplaced, their burdens on society are significantly greater than more publicized diseases in developed and developing nations alike, and biomedical science is poised to make significant strides. The timescales are daunting and the challenges great — human neurons are less accessible than tumour cells, separating genetic and environmental influences is tough, and the diagnosis of the conditions is highly problematic. There is much to be done, and a decade is the timescale over which enhanced commitment is required.

The problem of stigma persists. In some countries, progress in this regard has been made with depression: a few high-profile and brave sufferers in some Western countries have stood up and identified themselves. By contrast, schizophrenia, when covered by the media at all, is mostly associated with murders carried out by a tiny minority of sufferers who have an acute form of the condition.

Research challenges

Schizophrenia — a combination of delusions, reduced motivation and diminished cognitive functions — exemplifies many of the research challenges posed by psychiatric disorders as a whole. The extreme behaviours covered by the media are far from typical. Population studies indicate that the lifetime prevalence of all psychotic disorders (whose sufferers experience some sort of misperception of reality) is as much as 3%. Schizophrenia is controllable by medication and cognitive therapy, with a significant chance (a few tens of per cent) of beneficial positive outcomes.

Frustratingly, the effectiveness of medications has stalled. Nobody understands the links between the symptoms of schizophrenia and the crude physiological pathologies that have so far been documented: a decrease in white brain matter, for example, and altered function of the neurotransmitter dopamine. The medications, which are often aimed at the dopamine systems associated with delusions, have advanced over the decades not in their efficacy but in a reduction of their debilitating side effects.

Both diagnosis and drugs primarily address a late stage in the development of schizophrenia — the presentation of delusions. The earlier stages are much less well defined and are ambiguous in that, as currently characterized, they could lead to a number of alternative conditions. Here, above all, is where progress is needed in the form of reliable biomarkers to identify those at risk and to allow biomedical or cognitive interventions to prevent or mitigate the development of the disorders. Early intervention would lead to better outcomes.

A deeper understanding of the underlying biology is essential to improve diagnoses and therapies. New techniques — genome-wide association studies, imaging and the optical manipulation of neural circuits — are ushering in an era in which the neural circuitry underlying cognitive dysfunctions, for example, will be delineated. Tantalizingly, work in genetics is indicating how non-specific some genes are for schizophrenia, having associations in common with bipolar disorder and with autism. This suggests that the earlier stages of psychiatric disorders are multivalent, reinforcing the hope that early detection, coupled with a clearer understanding of the environmental factors, may allow prevention.

"Early detection and a clearer understanding of environmental factors may allow prevention of psychiatric disorders."

Environmental influence

Too little fundamental research is devoted to environmental factors. About 80% of the pattern of schizophrenia in populations seems to be determined by genetics, but part of that genetic influence lies in susceptibility to environmental influences. The remaining 20% of direct environmental influence is also ripe for more extensive investigation — epidemiological studies point to social stress (associated, for example, with migration or urbanization) as a significant influence, albeit in a minority of schizophrenia sufferers. As stated in a recent review of schizophrenia, a "worldwide challenge is to bring together the various disciplines that are needed to examine models of disease causation based on various aspects of gene–environment interplay" (J. van Os and S. Kapur *Lancet* 374, 635–645; 2009).

Of course it won't be just the basic biology of molecules and their circuits that will be essential in understanding the mechanisms of schizophrenia. There is a higher level of explanation required to understand, for example, delusions and their persistence.

Whether for schizophrenia, depression, autism or any other psychiatric disorders, it is clear, as Tom Insel, head of the US National Institute of Mental Health has emphasized (T. R. Insel *J. Clin. Invest.* 119, 700–705; 2009), that understanding of these conditions is entering a scientific phase more penetratingly insightful than has hitherto been possible. But Insel also highlights the disruptive impact of the science on the practices of clinical psychiatrists — as biological insights develop, the crudity of current psychiatric diagnoses will become all too clear. Yet the exposure of many psychiatrists to contemporary biology is shallow at best. That, too, will need to change over the next decade. ■

FEATURE

The mental wealth of nations

Countries must learn how to capitalize on their citizens' cognitive resources if they are to prosper, both economically and socially. Early interventions will be key.

John Beddington, Cary L. Cooper, John Field, Usha Goswami, Felicia A. Huppert, Rachel Jenkins, Hannah S. Jones, Tom B. L. Kirkwood, Barbara J. Sahakian and Sandy M. Thomas

To prosper and flourish in a rapidly changing world, we must make the most of all our resources — both mental and material. Globalization and its associated demands for competitiveness are increasing the pressures in our working lives. Added to this are the demands from evolving family structures and increased care responsibilities, both for children and for older relatives. And increased life expectancy in most industrialized nations means that ever greater numbers of people will be at risk of degenerative disorders in older age.

The UK Government Office for Science is this week announcing the findings of a peer-reviewed study: the Foresight Project on Mental Capital and Wellbeing. This used state-of-the-art scientific and other evidence to investigate the challenges and opportunities that lie ahead in the next 20 years. The report provides an independent assessment that is intended to inform policy-makers both in the United Kingdom and around the world.

The project tracks the implications of future challenges to our mental development from cradle to grave. Taking two years to complete, it has involved more than 450 experts and stakeholders from many disciplines and from 16 countries. Eighty peer-reviewed papers summarize the latest evidence, and international workshops have brought together experts and policy-makers to discuss what could be done to address the challenges.

Although our project focused on the United Kingdom, the challenges of depression, dementia, learning difficulties and mental ill-health are evident worldwide. The project therefore has far-reaching implications for the course of an individual's life, for societies and for nations. Five reports synthesize the evidence base; and a final report sets out the overall findings and options for policy, which are summarized here. All reports are available at http://tinyurl.com/49jonm. Box 1 shows some of the key findings.

Box 1 | Key findings

- **Boosting brain power in young and old**
  There is huge scope for improving mental capital through different types of intervention. The genetic contribution to mental capital is well below 50% in childhood, rising to more than 60% in adulthood and old age.
- **What science could do in the early years**
  Cognitive neuroscience is already uncovering neural markers, or biomarkers, that can reveal learning difficulties as early as in infancy.
- **Early detection of mental disorders**
  The challenge of tackling mental ill-health is considerable. There is great potential in improving diagnosis and treatment, and in addressing social risk factors such as debt.
- **Learning must continue throughout life**
  This can have a direct effect on mental health and well-being across all age groups, and has particular promise in older people.
- **Changing needs for a changing workplace**
  The workforce is changing both in demographics and in the demands placed on it. Workers' mental well-being is an important factor when attempting to improve the mental capital of economies and societies.

Defining mental capital

The project looked at two main aspects of mental development: mental capital and mental well-being. Mental capital encompasses both cognitive and emotional resources. It includes people's cognitive ability; their flexibility and efficiency at learning; and their 'emotional intelligence', or social skills and resilience in the face of stress. The term therefore captures a key dimension of the elements that establish how well an individual is able to contribute to society and to experience a high quality of life.

Mental well-being, on the other hand, is a dynamic state that refers to individuals' ability to develop their potential, work productively and creatively, build strong and positive relationships with others and contribute to their community.

However, the two concepts are intimately linked both throughout life and across different areas of the project. Positive emotional states or a generally positive approach to life are associated with greater curiosity, more flexible thinking and a greater openness to learning, and these qualities are particularly important during the development of mental capital in childhood and adolescence. Early learning in children can increase their resilience to stress and common mental disorders. Later in life, this resilience helps to engender well-being at work and into old age. And older individuals who report higher levels of well-being also have better cognitive function, even when adjustment has been made for other possible explanatory factors, such as socio-demographic variables, health and lifestyle[1].

Thus, how a nation develops and uses its mental capital not only has a significant effect on its economic competitiveness and prosperity, it is also important for mental health and well-being and social cohesion and inclusion. Because they are so closely linked, mental health and well-being should both therefore be considered when developing policies and designing interventions.

The project comprised two key stages: understanding the evidence and identifying ways forward. Three particular areas of focus were: childhood development; mental health and well-being at work; and making the most of cognitive resources in older age.

Progression through life

Evidence on childhood learning difficulties shows that, left untreated, very small initial differences in the sensory processing systems used by the brain in learning can lead to significant problems later in life[2]. Subtle impairments in auditory processing, for example, can give rise to developmental dyslexia, which can have significant negative effects on a person's passage through life. Moreover, the interactive nature of the developing brain means that a problem in one sensory area can affect development in other areas. By late childhood it can be hard to identify the core problem. The cognitive problems experienced by a child with a learning difficulty can lead to poor self-esteem, or to frustration that results in the child disengaging from learning and lacking the motivation to learn. If a problem is identified later in life, it is often harder for an individual to realize the full potential of their mental capital and well-being.

The brain undergoes significant structural and functional changes during adolescence[3]: the formation of new synapses peaks at around 9–12 years, followed by some 'pruning' of synapses that are surplus or underused. In

addition, adolescents go through significant emotional, hormonal and behavioural adjustment, and are particularly prone to risk-taking behaviour, such as drug and alcohol use. As the brain is still developing, such behaviour is particularly injurious to it at this stage[3], with long-term effects. Neuroimaging and neuropsychological studies indicate that substance use during adolescence is associated with neural disadvantages, particularly in the networks involved in learning, attention and executive function.

To help address these issues, the report came up with three main recommendations. First, training should be available for parents and teachers about issues in child development and how to help children who have learning difficulties to flourish. In addition, a higher priority needs to be placed on supporting children with these difficulties, as well as their carers. Finally, more emphasis needs to be placed on early identification and treatment of intrinsic learning difficulties such as dyslexia and dyscalculia — essentially dyslexia for numbers.

Much more can be done to improve mental well-being as children develop into adults. Occupational professionals should be closely integrated with primary-care givers, and workplaces can promote mental health through well-being audits and widespread availability of flexible working. In addition, demand should be stimulated for continued learning in both individuals and employers by raising awareness and providing incentives. New technologies are also available and constantly being developed to personalize learning. For adults who have problems with depression and alcohol use, for instance, use of best-practice treatments should become more widespread. Treatments for these and other problems should encompass social support (such as working with financial advisers to help reduce debt) and address the underlying social risk factors.

As people move into older age, learning should continue to be promoted and actively encouraged, as this can protect against cognitive decline. In particular, information technology has an important role in helping people to overcome the memory effects of dementias. Governments should also be encouraged to enable and empower people to work longer if they so wish. Older people should also be involved in making these and other policy decisions. In addition, efforts should be made to tackle the negative social stereotypes associated with old age.

Biological basis

As in the case of learning difficulties, mental illnesses should also be a particular target for early identification and prompt action. Neural, genetic and cognitive biomarkers can play an important part in the early identification of many of these diseases.

Alzheimer's disease, for example, accounts for about 60% of all dementia cases. The plaques and neurofibrillary tangles that characterize the disease begin to form many years before any clinical signs start to appear[4]. A range of biomarkers already exists. For instance, altered levels of proteins such as tau protein and Aβ42 (a pathogenic form of amyloid) in cerebrospinal fluid can identify patients in the early stages of Alzheimer's disease[5]. Structural magnetic resonance imaging (MRI) can also be used to measure brain atrophy, particularly in regions that are affected in Alzheimer's, such as the entorhinal cortex and hippocampus[6,7]. Genes have also been shown to play a part in the development of the disease, particularly the E4 variant of the apolipoprotein E (refs 8, 9). Furthermore, new insights into underlying mechanisms, coupled with the use of more selective cohorts in clinical trials (see below), will be essential in the development of effective drugs, including those to enhance cognition or for neuroprotection. This will also allow patients to be diagnosed earlier, allowing them to seek treatment and support, and plan for their futures.

Mechanistic studies coupled with novel biomarkers could also be important in the treatment of depression. One effective way is to measure brain activity in the left amygdala and ventromedial prefrontal cortex using functional MRI. By monitoring brain activity in response to being shown happy or sad faces, researchers can differentiate between unipolar and bipolar depression[10], disorders that require very different treatments.

Similarly, differences in the subgenual anterior cingulate identified by structural and functional neuroimaging can predict the likely responsiveness to treatment[11,12].

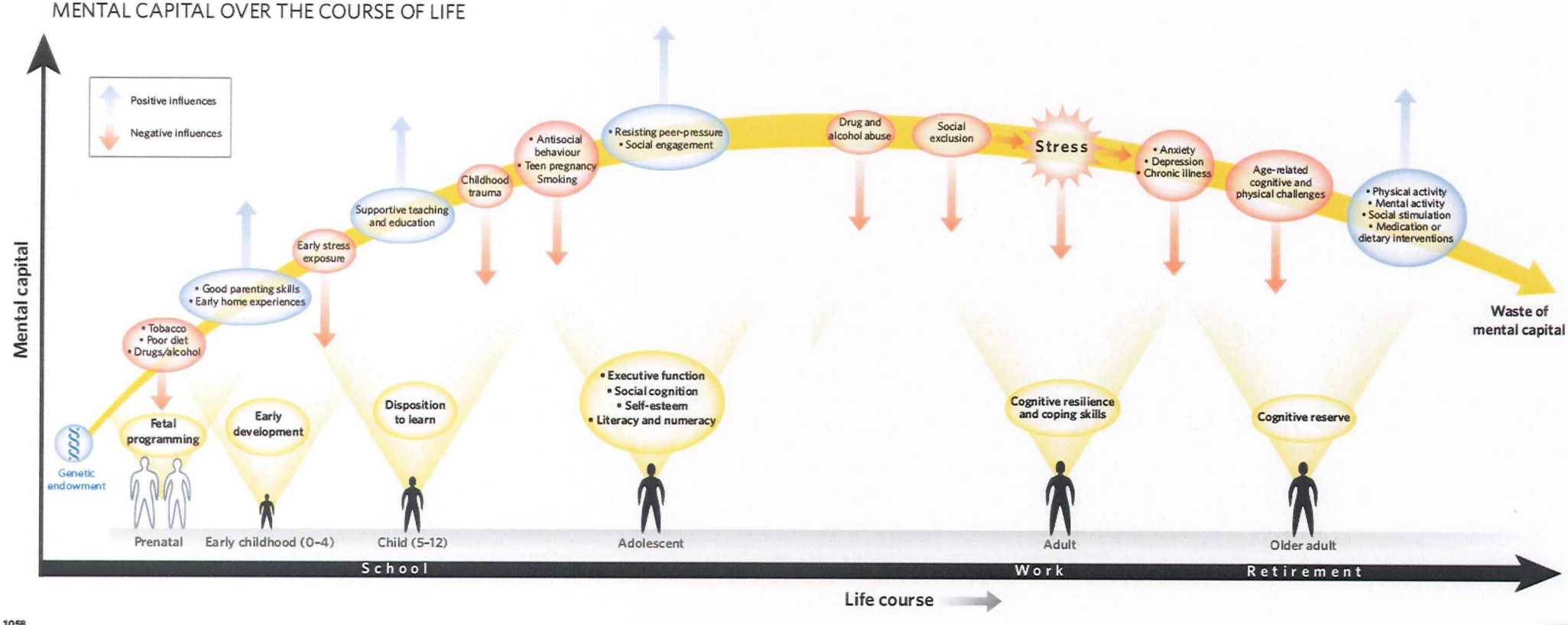
Implications for future research

Future research will be key to improving both mental capital and mental well-being, as well as diagnosis and treatment of disease.

One strategy for identifying complex combinations of risk factors and for validating potential biomarkers of learning difficulties, dementia and depression is the development of large, publicly available cohorts. Cohorts containing tens of thousands of people have helped to identify susceptibility genes in diseases such as type 2 diabetes. In much the same way, an international collaboration to generate similar cohorts for various mental illnesses could prove very valuable. Large public–privately funded consortia could play an important part here.

The challenge also extends to the research community. Research is needed to identify factors that directly affect our mental capital and well-being, as well as those that are merely associated with them. To deepen our understanding of causes and effects, multidisciplinary longitudinal studies involving genetics, neuroscience, social risk factors and behaviour will be required. For instance, we need to explore the underlying neuroscientific basis of the strong associations between mental disorders and lone parenting[13], bullying[14] and debt[15].

Significant gaps also exist in medications for the treatment of mental disorders, particularly antipsychotics, antidepressants,



mood stabilizers, and neuroprotective agents for Alzheimer's. Improved techniques and longer-acting medications are needed to tackle addiction, and developing these will require innovative approaches. Furthermore, although many treatments are available for depression, most work by increasing levels of monoamine neurotransmitters. More effective therapies with different mechanisms of action and fewer side effects are urgently needed.

Behavioural and other non-pharmaceutical interventions for improving well-being also need to be developed. This would encompass the treatment of people affected and prevention of the disorders in high-risk groups, as well as the enhancement of mental capital and well-being for all members of the population.

A range of skills and behaviours is crucial in empowering people to develop and maintain their mental capital and well-being. These include executive function (self-regulation) skills; an eagerness to learn, train and retrain throughout life; the resilience to cope with stress and life events; and behaviours that can promote a healthy lifestyle and protect against decline in old age. Multidisciplinary research, in the natural and social sciences, will be needed to investigate the systematic relations between these skills, to determine how they can best be developed.

The costs of inaction

Our project shows that governments and others have tremendous opportunities to create environments in which mental capital and well-being flourish. However, failure to act could have severe consequences.

Already, we have found that learning difficulties such as dyslexia, which affects up to 10% of children, reduce the probability of achieving good grades at school[16]. In turn, disengagement with the educational system can lead to behavioural problems, social exclusion and crime and reduced employment prospects (which in turn make mental ill-health more likely). This in turn can have adverse consequences for cognitive function throughout life. In addition, developmental dyscalculia is currently the poor relation of dyslexia, with a much lower public profile[2]. But the consequences of dyscalculia are at least as severe as those for dyslexia.

Mental ill-health is more widespread than many realize, with 16% of adults in Britain having a common mental disorder such as depression at any one time[17]. Worldwide, the prevalence of having any mental disorder in the year prior to assessment varies from 4% in Shanghai in China to 26% in the United States[18].

Furthermore, depression is the leading global cause of years lived with disability[19]. The annual costs from mental ill-health in England alone are about £36 billion (US$62 billion) for economic costs, rising to £77 billion when wider impacts are included, such as a reduction in quality of life[20]. Measures to improve mental health would therefore yield benefits well in excess of costs.

Future demographic changes mean that this figure could rise substantially. The age profile of the population will change as life expectancy increases and fecundity levels fall. The UK Office of National Statistics[21] estimates that, by 2071, the number of people older than 65 could double to nearly 21.3 million, and those aged 80 and over could more than treble to 9.5 million. This would probably lead to much more cognitive decline and dementia, and an expenditure time bomb: over the next 30 years, the number of people with dementia in the United Kingdom could double to 1.4 million, and costs to the UK economy could treble to more than £50 billion[22]. In addition, as the number of older people increases, there is a pressing case to take steps to prevent the wastage of their mental capital that occurs in part through marginalization.

The effects of mental capital and well-being on an individual's life course are profound, and governments have considerable scope to more fully realize a long-term and strategic perspective that spans the life course. As discussed earlier, this Foresight project has delivered some specific policy recommendations. It will now be for the UK government to consider how best to take these forward.

However, a cross-governmental approach is needed to realize the full benefits. Early intervention in education could provide benefits for reducing crime, improving productivity in work, and reducing pressure on health and care systems by preserving mental capital in older age. Departments will need to work together more closely. And interventions may have long timescales before they see any returns. Implementing these recommendations will require significant changes in the nature of governance, placing mental capital and well-being at the heart of policy-making. ■

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Reprints and permissions information is available at www.nature.com/reprints. The authors declare competing financial interests: details accompany the full-text HTML version of the paper at www.nature.com/nature. Correspondence should be addressed to S.M.T. (sandy.thomas@dius.gsi.gov.uk).

Ten leading causes of burden of disease, world, 2004 and 2030

2004 Disease or injury	As % of total DALYs	Rank		Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1		1	6.2	Unipolar depressive disorders
Diarrhoeal diseases	4.8	2		2	5.5	Ischaemic heart disease
Unipolar depressive disorders	4.3	3		3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4		4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5		5	3.8	COPD
Cerebrovascular disease	3.1	6		6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7		7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8		8	2.7	Refractive errors
Road traffic accidents	2.7	9		9	2.5	HIV/AIDS
Neonatal infections and other[a]	2.7	10		10	2.3	Diabetes mellitus
COPD	2.0	13		11	1.9	Neonatal infections and other[a]
Refractive errors	1.8	14		12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15		15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19		18	1.6	Diarrhoeal diseases