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# Epidemiological aspects of ageing

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## SUMMARY

A major societal challenge is to improve quality of life and prevent or reduce disability and dependency in an ageing population. Increasing age is associated with increasing risk of disability and loss of independence, due to functional impairments such as loss of mobility, hearing and vision; a major issue must be how far disability can be prevented. Ageing is associated with loss of bone tissue, reduction in muscle mass, reduced respiratory function, decline in cognitive function, rise in blood pressure and macular degeneration which predispose to disabling conditions such as osteoporosis, heart disease, dementia and blindness.

However, there are considerable variations in different communities in terms of the rate of age-related decline. Large geographic and secular variations in the age-adjusted incidence of major chronic diseases such as stroke, hip fracture, coronary heart disease, cancer, visual loss from cataract, glaucoma and macular degeneration suggest strong environmental determinants in diet, physical activity and smoking habit. The evidence suggests that a substantial proportion of chronic disabling conditions associated with ageing are preventable, or at least postponable and not an inevitable accompaniment of growing old. Postponement or prevention of these conditions may not only increase longevity, but, more importantly, reduce the period of illnesses such that the majority of older persons may live high-quality lives, free of disability, until very shortly before death. We need to understand better the factors influencing the onset of age-related disability in the population, so that we have appropriate strategies to maintain optimal health in an ageing population.

## 1. INTRODUCTION

The ageing of the population is a great success of this century. In most industrialized countries, where data are available, life expectancy has almost doubled this century (table 1) (Kinsella 1996). However, it is easy to forget that the great increases in average life expectancy reflect less extension of maximum life expectancy, than reduction in mortality in earlier years, most notably in infancy and young adulthood. Most of those who would have died in youth from infectious diseases, trauma or malnutrition now are surviving to middle age and beyond. For example, in the US or UK, in the 1900s, 50% of the population could expect to survive to age 55 years or so but in the 1990s, 50% of the population can expect to survive to age 80 years. Although the ageing of the population started earlier in industrialized countries, similar trends are seen around the world. Table 2 shows the numbers and proportion of those aged 65 years and over in selected regions of the world (Kinsella 1996). While there are theoretical debates about the possible extension of maximum life expectancy, the immediate challenge facing ageing populations is how best to maintain health and quality of life in the large numbers of older persons who are surviving to older ages close to the maximum human lifespan, a situation unprecedented in history.

## 2. AGEING, DISABILITY AND HEALTHY LIFE EXPECTANCY

Disability, however variously defined in different studies, increases with increasing age. Table 3 shows the estimated prevalence of disability in Britain by age group and grade of disability (Martin *et al.* 1988). Various estimates can be made of the impact of disability.

These include disability-free life expectancy (DFLE) or disability-adjusted life expectancy (DALE), discussed in more detail elsewhere (Colvez 1996; Kinsella 1996; Murray & Lopez 1997a). Table 4 shows some estimates of life expectancy and disability-adjusted life expectancy in various countries; both vary greatly around the world (Murray & Lopez 1997b).

Several possible scenarios have been postulated as consequences of population ageing (Kramer 1980; Manton 1980; Fries 1980). The increase in age at death could result in three possible changes in the pattern of lifetime experience of disease. First, if the age of onset of morbidity remains unchanged, the result would be more years of ill health before death (Kramer 1980). Second, the age of onset of ill health may increase in parallel with the age of death so that the absolute duration of life with illness is unchanged, but, because people live longer, the proportion of ill health in the

Table 1. *Years of life expectancy at birth in selected industrialized countries, 1900–90*

(Source: Kinsella (1996).)

	1900		1950		1990	
	M	F	M	F	M	F
England and Wales	46.4	50.1	66.2	71.1	73.3	79.2
France	45.5	48.7	63.7	69.4	73.4	81.9
Hungary	36.6	38.2	59.3	63.4	67.2	75.4
Japan	42.8	44.3	59.6	63.4	67.2	75.4
US	48.3	51.1	66.0	71.7	72.1	79.0

average lifetime is reduced. Finally, the age of onset of ill health may increase more quickly than the increase in life expectancy leading to a compression of morbidity (Fries 1980).

The different scenarios have profound implications for society. Much current debate concerns how best to treat, support and care for, the projected great increase in persons with impairments, disabilities and handicaps resulting from the ageing of the population. However, a critical issue for society must also be how far age-associated disability can be prevented, or at least, postponed to achieve the compression in morbidity proposed by Fries (1980). Most studies support the second scenario of proportionate increase in age of onset of morbidity and of age of death. However, Fries (1996) has suggested that more recent data may support compression of morbidity in favoured groups such as persons of high socioeconomic status, with more education, or persons who have particular lifestyles, such as those who are physically active. The existing variations in healthy life expectancy around the world seen in table 4 indicate the potential for improvement in most countries. There is also evidence of secular improvement: Bone *et al.* (1996) have reported that the proportion of men unable to perform four activities of daily living at any specified age has halved between 1976 and 1994 (figure 1).

Table 2. *The elderly population in selected countries, 1965–95*

(Source: Kinsella (1996).)

	elderly (65 + years) population in thousands			elderly as per cent of total population		
	1965	1995	2025	1965	1995	2025
all industrialized countries	90 595	164 633	281 052	9.0	13.2	20.2
all developing countries	87 229	202 903	567 008	3.7	4.5	8.2
Brazil	2667	7359	21 945	3.2	4.6	10.7
China	32 057	73 574	198 343	4.4	6.1	13.7
France	5904	9079	13 982	12.1	15.6	22.6
Germany	9522	12 664	19 979	12.5	15.6	24.4
Japan	6179	17 787	32 164	6.2	14.2	26.1
Nigeria	1133	2918	9115	2.3	2.9	3.7
UK	6526	9220	12 912	12.0	15.8	21.5
US	18 406	33 594	62 423	9.5	12.8	18.4

Table 3. *Estimated prevalence of disability as cumulative rates per thousand by disability grade (1 = minimal and 10 = most severe) for age groups 50–59, 60–69 and 70–79*(Source: Martin *et al.* (1988).)

disability grade	50–59 years	60–69 years	70–79 years
9–10	7	16	32
7–10	22	42	87
5–10	48	84	169
3–10	83	143	267
1–10	133	240	408

### 3. CAUSES OF AGE-RELATED DISABILITY

While it is difficult to quantify precisely the contributions of various conditions to disability, since this depends on how disability is defined, and its severity, most estimates agree that healthy life expectancy is determined by a fairly small number of chronic conditions and diseases which become more common with increasing age. Various studies consistently include cardiovascular disease (mainly coronary heart disease and stroke); musculoskeletal degeneration (for example, arthritis and osteoporosis leading to fractures); neurodegenerative conditions such as dementia and Parkinson's disease, as well as neuropsychiatric disorders such as chronic depression; cancers including breast, prostate, and colorectal cancer; and other conditions such as deafness and cataracts, glaucoma and macular degeneration leading to visual loss. One such recent estimate is shown in table 5 (Murray & Lopez 1997*b*). International variations and secular trends indicate that a large proportion of these conditions are potentially preventable, or at least, postponable to later ages. Mortality rates have been used as surrogates for incident morbidity data which are often not available. Figures 2 to 4 (World Health Organization 1994) give examples of the relationship between age and rates of various important chronic disabling conditions such as heart disease, breast and prostate cancer in different countries; similar examples can be shown for the incidence of many other

Table 4. Life expectancy at age 60 years with and without disability and proportion of life affected by disability

(Disability-free life expectancy (DFLE) is a health-adjusted expectancy based on disability severity weights in the global burden of disease study (Murray & Lopez 1997b).)

region	life expectancy					
	at age 60		disability-adjusted life expectancy at age 60		% of remaining life at age 60 lived with severity-adjusted disability	
	M	F	M	F	M	F
established market economies	19.0	24.1	15.5	19.9	22.4	21.1
former socialist economies of Europe	15.8	20.4	12.5	16.5	26.7	23.6
India	15.1	16.3	11.2	12.2	35.0	33.2
China	15.2	18.0	11.3	13.5	35.3	33.2
Other Asia	16.2	18.6	12.0	14.2	34.8	30.7
sub-Saharan Africa	14.7	15.9	9.6	11.1	52.7	44.2
Latin America	18.5	21.3	13.7	16.2	34.7	31.3
Middle Eastern crescent	16.3	18.6	12.4	14.3	31.8	30.0

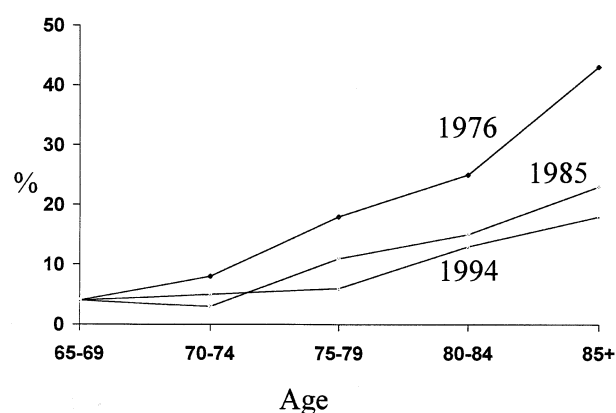


Figure 1. Prevalence by age of men unable to perform four activities of daily living in 1976, 1985 and 1994. Source: Bone *et al.* (1996).

Table 5. Leading causes of disability-adjusted life years (DALYs) in developed regions

(Source: Murray & Lopez (1997b).)

condition	estimated per cent of disability-adjusted life years caused by condition
cardiovascular disorders	22.0
neuropsychiatric disorders	21.8
cancers	17.3
respiratory disorders	6.4
musculoskeletal disorders	4.8

conditions such as cataract, macular degeneration and fractures. While in all populations, rates of these conditions increase with increasing age, the gradients with age and absolute rates differ substantially in different countries: for example, Japanese women aged 65–74 have rates of ischaemic heart disease lower than those for women in the UK aged 55–64 years; rates of breast cancer in Japanese women show little of the increase with

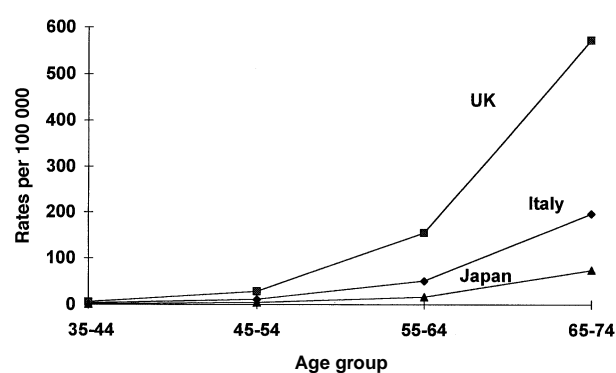


Figure 2. Death rates for ischaemic heart disease for women in the UK, Italy and Japan, 1990.

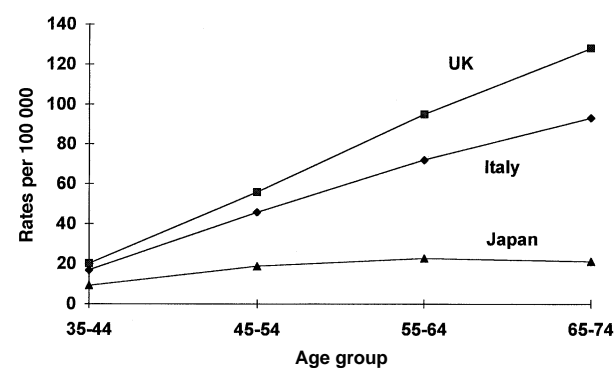


Figure 3. Death rates for breast cancer for women in the UK, Italy and Japan, 1990.

age seen in women in the UK. For both these conditions, women in Italy have substantially lower rates than women of the same age in the UK. Similarly, the increase of prostate cancer with age is hardly seen in men in Hong Kong, but is pronounced in men in the UK. Even within the UK, total mortality, often used as an indicator of overall health status, varies substantially according to social class, and men in social class 1 aged 65–74 years have the same mortality experience as men

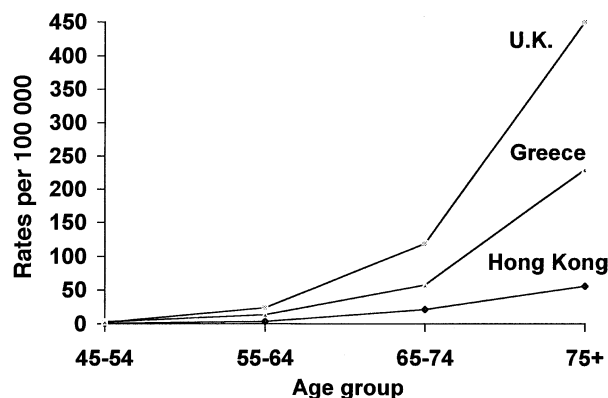


Figure 4. Mortality rates for prostate cancer in men in the UK, Greece and Hong Kong.

in men aged 45–54 years in social class V (figure 5). Time trends are also marked; whereas for many chronic diseases, such as heart disease and stroke, there has been a secular decrease, hip fracture rates increased much more sharply with age in 1983 than in 1954 (figure 6). These secular trends, as well as migration studies and time trends indicate that these age differences in rates with increasing age are unlikely to be attributable to genetic differences. Japanese living in the US have increased rates of breast and prostate cancer and heart disease resembling more closely those of Caucasians in the US (Worth *et al.* 1975). The impact of such trends is considerable; for example, numbers of hip fractures in Britain are projected to double in the next twenty years but half the hip fractures occurring could be avoided if the rates returned to those of 1953.

#### 4. AGEING, BIOLOGICAL RISK FACTORS AND DISEASE

Many physiological factors change with age and may predispose to chronic disabling conditions. For example, on average, blood pressure and blood cholesterol levels tend to rise with increasing age. A plethora of longitudinal population-based studies demonstrate that raised blood pressure and raised blood cholesterol increase the risk of cardiovascular disease (Neaton & Wentworth 1992; Qizilbash *et al.* 1995). However, there are individuals where changes in these physiological factors with age are not so great and these individuals have substantially lower rates of cardiovascular disease. In the Framingham study, a 60-year-old man who did not have hypertension, hypercholesterolaemia, or diabetes and did not smoke cigarettes had the same chance of developing heart disease as a 45-year-old man with all these risk factors. The increase in cardiovascular disease rates with increasing age was much less in those with lower levels of blood pressure and blood cholesterol (Kannel 1987). To take another example, bone mass appears to reach a peak around age 20, remain at about the same level for some decades, then starts to decline around middle age; reduction in bone mass leads to increased risk of osteoporotic fractures of the spine and hip, which are responsible for much disability in the elderly. However, those who maintain

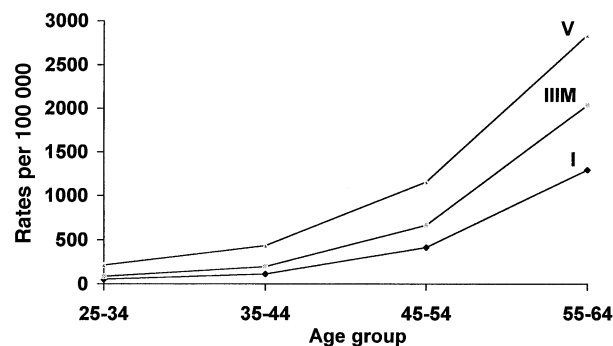


Figure 5. Mortality by social class in men, in England and Wales 1979–80, 1982–83.

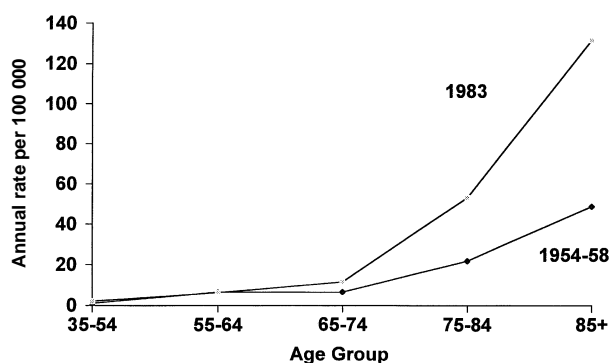


Figure 6. Incidence of fractured proximal femur in men in 1954–58 and 1983 for Oxford.

high bone mass have much lower fracture rates than those who have low bone mass (Cummings & Black 1995). Table 6 documents some of the possible age-related changes and their consequences.

A general model for age-related disability is that deterioration in various physiological factors with age leads to increased risk of disease and disability; identification of the factors, genetic or environmental which influence age-related decline might highlight possible preventive strategies.

Theories of biological ageing abound, discussed in detail elsewhere; amongst others, they include the 'genetic programme' theory, that is, that the ageing process is under active genetic control, or the 'wear and tear' theory, that is, that ageing is the result of cumulative damage. Kirkwood & Wolff (1995) have suggested, in their 'disposable soma' theory, that organisms allocate metabolic resources between maintenance and reproduction; thus, the different lifespans of different species reflect the differing distribution of investment in these two processes which have evolved in response to extrinsic circumstances. This theory predicts that there is unlikely to be any single mechanism of ageing; rather, that the mechanisms responsible for ageing are those types of damage for which maintenance and repair processes are metabolically costly. Molecular mechanisms include DNA damage and mutations, free radical oxidative damage, accumulation of aberrant proteins, and defective mitochondria. To take one example, free radicals are reactive molecules produced as by-products of cell



Table 6. Age-related changes and consequences

age-related change	clinical consequence
bone loss	osteoporosis, fractures
raised blood pressure	heart attacks and strokes
raised blood cholesterol	
decreased glucose tolerance	diabetes
brain cell loss/damage	memory loss, senile dementia Alzheimer's, Parkinson's
lung damage	emphysema, bronchitis
cartilage damage	arthritis
loss of cell differentiation	cancer
clouding of lens	cataracts
raised eye pressure	glaucoma

metabolism which cause oxidative damage to cell components including proteins, nucleic acids and membranes. Free radical damage in different tissues has been postulated to be responsible for deterioration in lung function, atherosclerotic disease in blood vessels, and neurological damage leading to such conditions as bronchitis, heart disease and stroke, and dementia. Antioxidants such as vitamin C, may mitigate damage produced by free radicals.

How do such theories translate to human experience? There is substantial evidence from epidemiological studies that many age-related biological changes progress at different rates in different populations living in different environments. For example, in most Western communities, average blood pressure, blood cholesterol and blood glucose levels tend to rise with increasing age, contributing to the rise in rates of cardiovascular disease. However, there are communities in which average blood pressure, blood cholesterol and blood glucose levels are low throughout life; thus, increases in the levels of these factors are not necessary concomitants of the ageing process. These communities also have low rates of cardiovascular disease, even in the elderly. As with overt disease, migration studies indicate that the primary determinants are environmental not genetic; members of the Luo tribe living in Kenya with low blood pressures in the rural environment have blood pressures that increase with age when they move to urban Nairobi (Poulter *et al.* 1990). Caucasians living on diets of Buddhist monks have similar low cholesterol levels to Japanese in Japan, whereas Japanese in the US army have higher cholesterol levels resembling those of Caucasians in the US army (Kesteloot 1989; Kita *et al.* 1986). Dutch women living in the Antilles have high bone mass and lower rates of fractures than Dutch women of the same age in The Netherlands (Dubbelman *et al.* 1993).

### 5. EXTRINSIC REASONS INFLUENCING AGE-RELATED CONDITIONS

A major challenge is therefore to identify the extrinsic reasons for the variability in age-related conditions as they provide the potential for preventive interventions. A wealth of data from clinical, laboratory and epidemiological studies indicate many possibilities

for action throughout life. Barker (1994) has hypothesized that early life influences such as the intra-uterine environment may programme metabolic processes and development and have a lasting effect throughout life on a whole range of conditions including susceptibility to cardiovascular disease. Nutrition and physical activity patterns during early childhood and adolescence influence growth and achievement of peak bone and muscle mass, and hence, available reserves in later life when bone and muscle mass start to decline. In later life, it may be possible to reduce potential damage (for example, from toxins, infection or trauma), increase protection (for example, by increasing antioxidant intake), or to prevent loss from disuse. Extrinsic factors which influence ageing thus include environmental factors such as infection, toxins and pollution, psychosocial factors such as stress and social support, and lifestyle factors such as diet, physical activity and cigarette smoking habit. Table 7 indicates some possible extrinsic factors which may influence physiological processes and their consequences.

### 6. EVIDENCE OF EFFECT OF POTENTIAL INTERVENTIONS

We need to identify the qualitative factors which may contribute to specific age-related disabling conditions and to quantify their potential impact in individuals and in populations. To take the example of cardiovascular disease: intervention trials have demonstrated that reduction of blood pressure by 6 mm Hg reduces stroke risk by 40% and heart attack risk by 15%; reduction of blood cholesterol levels by 10% will reduce coronary heart disease by 30% (Collins *et al.* 1990; Scandinavian Simvastatin Survival Study Group 1994). Thus, reducing the levels of blood pressure and cholesterol in the older population could have a profound impact on reducing the burden of cardiovascular disease. International studies and trials have implicated high dietary sodium intake in the aetiology of the age-related rise in blood pressure, and high dietary saturated fat as a cause of high cholesterol levels and coronary heart disease rates. Relatively modest reductions in salt and saturated fat intake may have a big effect at the population level (Law *et al.* 1991a,b; Clarke *et al.* 1997). Additionally, other risk factors such as cigarette smoking, and physical activity may act through these or other mechanisms such as clotting tendency or hormonal status (Doll *et al.* 1994; Curfman 1993). Other dietary factors appear to be protective such as omega 3 fatty acids (found in oily fish), antioxidants such as vitamin C and vitamin E, minerals such as calcium and potassium as well as dietary fibre and flavonoids, all of which are found in diets high in fruit and vegetables (Department of Health 1992, 1994). The magnitude of impact is not trivial: one intervention trial in persons who already had heart disease reported that those allocated to a Mediterranean diet had a 70% reduction in subsequent heart attacks and deaths compared with those on a standard low fat diet (de Lorgeril *et al.* 1994). To take another example, it has been suggested that the loss of bone mass, increasing the risk of

Table 7. *Examples of extrinsic factors which have been implicated in age-related conditions*

process	extrinsic factor	effect
early life		
metabolic programming	maternal nutrition	susceptibility to cardiovascular disease
build reserves	nutrition, physical activity	muscle and bone health
later life		
reduce damage	smoking, pollution infection	lung function heart disease
increase protection	antioxidants	heart disease, lung function, visual loss, cancer susceptibility
prevent disuse	physical activity mental activity	osteoporosis dementia

osteoporotic fractures, may be related to suboptimal vitamin D and calcium status in older persons. A trial of vitamin D and calcium supplementation in women aged over 75 years reduced fracture rates by a third (Chapuy *et al.* 1992). These examples are only illustrative; the issue of prevention of chronic disease in older persons is more fully discussed elsewhere (Ebrahim & Kalache 1996).

## 7. CONCLUSIONS

The ageing of the population is a success story but presents society with new challenges. Much discussion revolves around strategies for the support and care of large numbers of older person with disabilities, but a primary concern must also be how to maintain health and quality of life in an ageing population. A major research priority should be the identification of the major determinants of onset of age-related decline and disability in the population and quantitative assessment of their impact. The epidemiological evidence indicates substantial potential for the prevention of age-related disability and maintenance of optimal health. For those conditions for which interventions have been identified, the magnitude of effect is surprisingly large for modest and feasible changes in extrinsic factors for both the individual and the population as a whole. The social framework and policies necessary for appropriate strategies to promote successful ageing must also be a prime consideration.

## REFERENCES

- Barker, D. J. P. 1994 Maternal and fetal origins of coronary heart disease. *J. R. Coll. Phys. Lond.* **28**, 544–551.
- Bone, M., Bebbington, A., Jagger, C. *et al.* 1996 Calculations of trends in health expectancies 1976–1992. In *Health expectancy and its uses*. London: Her Majesty's Stationery Office.
- Chapuy, M. C., Arlot, M. E., Duboeuf, F. *et al.* 1992 Vitamin D3 and calcium to prevent hip fractures in elderly women. *New Engl. J. Med.* **32**, 1637–1642.
- Clarke, R., Frost, C., Collins, R., Appleby, P. & Peto, R. 1997 Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *Br. Med. J.* **314**, 112–117.
- Collins, R., Peto, R., MacMahon, S. *et al.* 1990 Blood pressure, stroke, and coronary heart disease. 2. short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* **335**, 827–838.
- Colvez, A. 1996 Disability free life expectancy. In *Epidemiology in old age*, ch. 5 (ed. S. Ebrahim & A. Kalache), pp. 41–48. London: British Medical Journal.
- Cummings, S. R. & Black, D. 1995 Bone mass measurements and risk of fracture in Caucasian women: a review of findings from prospective studies. *Am. J. Med.* **98** (2A), 24S–28S.
- Curfman, G. D. 1993 The health benefits of exercise. *New Engl. J. Med.* **328**, 574–576.
- de Lorgeril, M., Renaud, S., Mamelle, S. *et al.* 1994 Mediterranean alphalinolenic acid rich diet in secondary prevention of coronary heart disease. *Lancet* **343**, 1454–1459.
- Department of Health 1992 *The nutrition of elderly people*. Report on health and social subjects, no 43. London: Her Majesty's Stationery Office.
- Department of Health 1994 *Nutritional aspects of cardiovascular disease*. Report of the cardiovascular review group committee on medical aspects of food policy. London: Her Majesty's Stationery Office.
- Doll, R., Peto, R., Wheatley, K., Gray, R. & Sutherland, I. 1994 Mortality in relation to smoking: 40 years' observations on male British doctors. *Br. Med. J.* **309**, 901–911.
- Dubbelman, R., Jonxis, J. H. P., Muskiet, F. A. J. & Saleh, A. E. C. 1993 Age-dependent vitamin D status and vertebral condition of white women living in Curaçao (The Netherlands Antilles) as compared with their counterparts in The Netherlands. *Am. J. Clin. Nutr.* **58**, 106–109.
- Ebrahim, S. & Kalache, A. (eds) 1996 *Epidemiology in old age*. London: British Medical Journal.
- Fries, J. F. 1980 Ageing, natural death, and the compression of morbidity. *New Engl. J. Med.* **313**, 407–428.
- Fries, J. F. 1996 Physical activity, the compression of morbidity and the health of the elderly. *J. R. Soc. Med.* **89**, 64–68.
- Kannel, W. B., Doyle, J. T., Shephard, R. J., Stamler, J. & Vokonas, P. S. 1987 Prevention of cardiovascular disease in the elderly. *J. Am. Coll. Cardiol.* **10**, 25A–28A.
- Kesteloot, H. 1989 Changing trends in mortality. In *New horizons in preventing cardiovascular diseases* (ed. Y. Yamori & T. Strasser). Amsterdam: Elsevier.
- Kinsella, K. 1996 Demographic aspects. In *Epidemiology in old age*, ch. 4 (ed. S. Ebrahim & A. Kalache), pp. 32–40. London: British Medical Journal.
- Kirkwood, T. B. L. & Wolff, S. P. 1995 The biological basis of ageing. *Age and Ageing* **24**, 167–171.
- Kita, T., Ishii, K., Kuma, N. *et al.* 1986 The level of serum cholesterol in Caucasian and Japanese Zen monks. *Circulation* **74** (suppl. II), 131.
- Kramer, M. 1980 The rising pandemic of mental disorders and associated chronic diseases and disabilities. *Acta Psychiatr. Scand.* **62** (285), 382–397.
- Law, M. R., Frost, C. D. & Wald, N. J. 1991a By how much does dietary salt reduction lower blood pressure? I. Analysis of observational data among populations. *Br. Med. J.* **302**, 811–815.

- Law, M. R., Frost, C. D. & Wald, N. J. 1991*b* By how much does dietary salt reduction lower blood pressure? III. Analysis of data from trials of salt reduction. *Br. Med. J.* **302**, 819–824.
- Martin, J., Meltzer, H. & Elliot, D. 1988 *OPCS surveys of disability in Great Britain. 1. The prevalence of disability among adults*. London: Her Majesty's Stationery Office.
- Manton, K. G. 1980 Changing concepts of morbidity and mortality in the elderly population. *Milbank Quarterly* **60**, 183–244.
- Murray, C. J. L. & Lopez, A. D. 1997*a* Regional patterns of disability-free life expectancy and disability-adjusted life expectancy: global burden of disease study. *Lancet* **349**, 1347–1352.
- Murray, C. J. L. & Lopez, A. D. 1997*b* Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* **349**, 1498–1504.
- Neaton, J. D. & Wentworth, D. 1992 Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. *Arch. Int. Med.* **152**, 56–64.
- Poulter, N. R., Khaw, K.-T., Hopwood, B. E. C. *et al.* 1990 The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *Br. Med. J.* **300**, 967–972.
- Qizilbash, N., Lewington, S., Duffy, S., Peto, R., Smith, T. & Spiegelhalter, D. 1995 Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet* **346**, 1647–1653.
- Scandinavian Simvastatin Survival Study Group 1994 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* **344**, 1383–1389.
- World Health Organization 1994 *World Health Statistics Annual*. Geneva: World Health Organization.
- Worth, R. M., Kato, H., Rhoads, G. G., Kagan, A. & Syme, S. L. 1975 Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: mortality. *Am. J. Epidemiol.* **102**, 481–490.



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