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A REVIEW OF LIFETIME RISK FACTORS FOR MORTALITY

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ABSTRACT

This review was undertaken for the Faculty and Institute of Actuaries as part of their programme to encourage research collaborations between health researchers and actuaries in order to understand better the factors influencing mortality and longevity. The authors presented their findings in a number of linked sessions at the Edinburgh conference (*Joining Forces on Mortality and Longevity*) in October 2009 and contributed to this overview. The purpose is to review evidence for the impact on adult mortality of characteristics of the individual's lifetime socioeconomic or psychosocial environment or phenotype (at the behavioural; multi-system (e.g. cognitive and physical function); or body system level (e.g. vascular and metabolic traits) that may be common risk factors for a number of major causes of death. This review shows there is growing evidence from large studies and systematic reviews that these individual characteristics, measured in pre-adult as well as the adult life, are associated with later mortality risk. The relative contribution of lifetime environment, genetic factors and chance, whether these contributions change with age, and the underlying social and biological pathways are still to be clarified. This review identifies areas where further life course research is warranted.

KEYWORDS

Mortality; Life Course; Socioeconomic Environment; Psychosocial Environment; Individual Temperament and Behaviour; Lifestyles; Dietary Patterns; Body Size; Vascular and Metabolic traits; Physical Function; Cognitive function; Genetic Predisposition

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1. Introduction

Actuaries and physicians share a long history in evaluating factors that affect an individual's risk of mortality. Both derive benefits from being able to assess mortality risk before disease is manifest. Risk factors can be assessed on two dimensions of time (see Figure 1): how distal or proximal is the risk factor along the causal pathway to disease or death (illustrated on the vertical axis); and how early in the life course can individual characteristics associated with premature mortality or longevity be identified and modified (illustrated on the horizontal axis).

In terms of the causal pathway, an adverse socioeconomic or psychosocial environment, measured, for example, by low social class or lack of social support, are strong distal risk factors for cardiovascular disease (CVD) mortality; it is still unclear how these social factors 'get under the skin' and affect proximal risk factors, namely the structure and function of biological systems, such as blood pressure, insulin resistance, or atherosclerosis. The causal pathways that connect individual habits and behaviours, such as diet, activity and smoking to proximal factors for mortality risk are somewhat better understood, and these behaviours may be mediators of social risk. Less well understood are the causal pathways that link individual-level characteristics such as personality, psychological wellbeing, cognitive and physical functioning to mortality risk.

In terms of risk across the life course, evidence is accumulating that individual characteristics during childhood (such as physical growth and development, adolescent temperament and behaviour, and the early socioeconomic and psychosocial environment) are associated with risk of many adult chronic diseases and premature adult mortality (Barker, 1998; Gluckman *et al*., 2009; Kuh & Ben-Shlomo, 2004). Researching the biological, social and psychological pathways that are responsible for these lifelong links is central to the new field of life course epidemiology (Ben-Shlomo & Kuh, 2002; Kuh & Ben-Shlomo, 2004; Kuh *et al*., 2003). This interest in early life factors on mortality risk is not new — indeed actuaries (Davidson & Reid, 1927; Derrick, 1927) and health scientists (Kermack *et al*., 1934) in the first half of the twentieth century both showed changes in cohort mortality patterns that were interpreted by some as evidence of the importance of early life factors. However, these findings were not used to distinguish individuals most at risk of premature death, unless there was a clear chronic condition known to increase the chance of death (such as rheumatic heart disease). The focus on early life factors was eclipsed by the success of longitudinal studies of adults carried out by life insurance companies and clinicians that identified adult lifestyle and proximal risk factors (such as smoking, obesity, high fat diets, high blood pressure, diabetes) that distinguished which individuals are at higher predicted risk of coronary heart disease (CHD) or other chronic diseases.

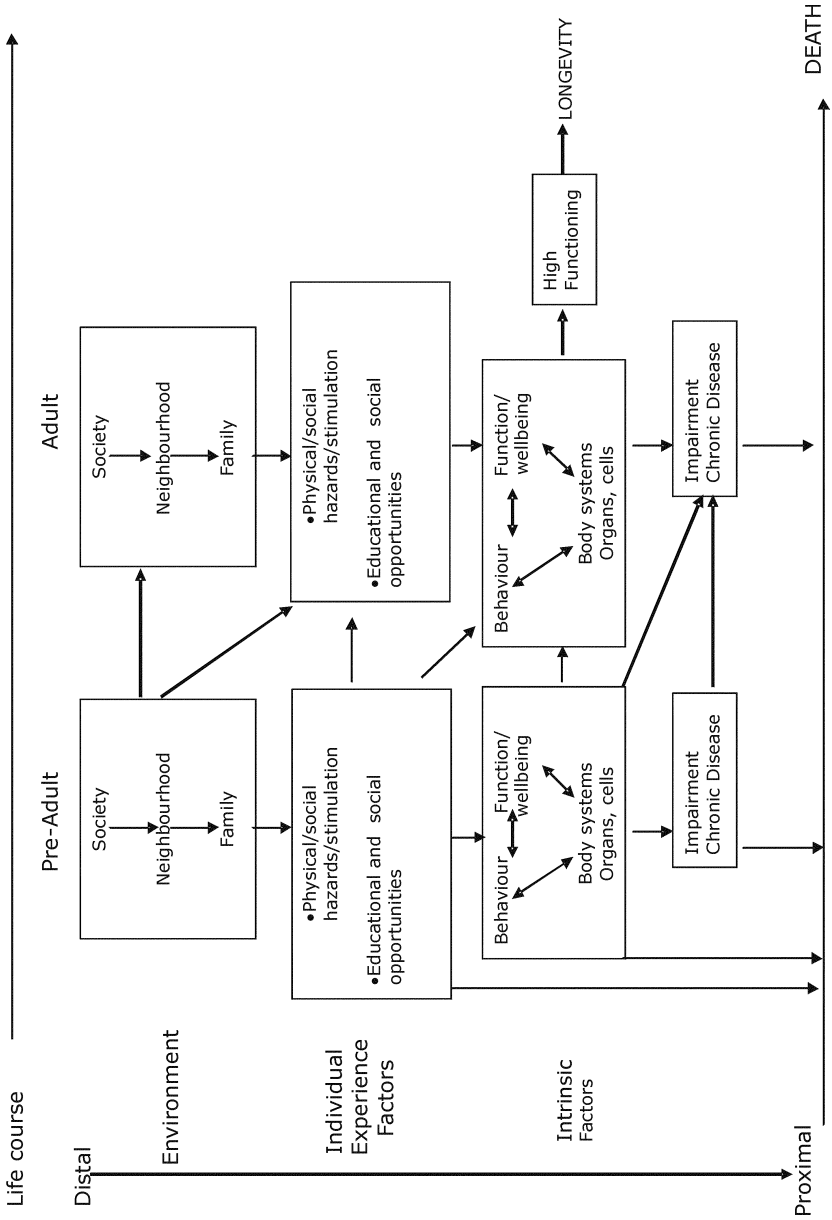

Figure 1. Individual risk factors for mortality and longevity: a life course approach

The purpose of this paper is to review evidence for the impact of these different types of risk on mortality. This is not a systematic review and we have deliberately narrowed the scope to focus on characteristics of the individual's environment or phenotype that may be common risk factors for a number of causes of death or where a previous scoping review had highlighted gaps in the evidence (MacDonald, 2008). The areas we have chosen to review are:

(i) Lifetime socioeconomic environment
(ii) Lifetime psychosocial environment, individual temperament and behaviour
(iii) Lifetime lifestyles
(iv) Lifetime body size
(v) Lifetime physical function
(vi) Lifetime vascular and metabolic traits
(vii) Lifetime cognitive function.

We focus on the following questions:

a. How strong is the evidence for the association of these factors with adult mortality risk and the main causes of adult death in high income countries?
b. Are the associations similar for men and women and across social groups?
c. How early in the life course are associations observed?
d. What are the possible biological (including genetic) or social pathways through which these characteristics affect mortality?
e. Are secular trends in these characteristics likely to pose threats or benefits to future mortality improvements?

We start with brief summaries of the historical background (Section 2) and current age-specific mortality patterns (Section 3), before going on to review these risk factors across the life course that may be particularly relevant for understanding whether individuals will die prematurely or survive to old age (Sections 4-10). To complement these sections, we then briefly review (Section 11) what is known about genetic factors that predispose survivors to a long and healthy life in old age in the context of environmental change. It may be that a life course perspective is of less relevance at this stage of life.

2. Historical Background: Evaluating Mortality Risk

During the nineteenth century, what Ian Hacking calls the 'taming of chance' (Hacking, 1990) led scientists to understand that the world might be regular and yet not subject to universal laws of nature. In effect, society

became statistical. New types of statistical law came into being, expressed in terms of probability. A key event was the discovery and widespread application of the normal distribution. In the 17th century Galileo noticed that the size of errors of measurement of astronomical characteristics had a symmetrical distribution with small errors being more common than large errors, but it was not until the 19th century that this pattern of errors was described as a normal distribution. A symmetrical distribution was also described by Laplace in 1778 when he derived the central limit theorem. Independently the mathematicians Adrian and Gauss in 1808 and 1809, respectively, developed the formula for the normal distribution and showed that most measurement errors fitted this distribution. Laplace in his central limit theorem had shown that even if a distribution is not normal, the means of repeat samples from the distribution are nearly normal and become more normal with larger sample sizes. The discovery of this simple and naturally occurring distribution revolutionised statistics and assessment of probability and associations. Height, for example, was an obvious topic of study. There was almost no information on the height of populations at the beginning of the nineteenth century — by the end such characteristics of populations were well known. Francis Galton, founder of the biometric school of statistical research, wrote in 1889 that the chief law of probability 'reigns with serenity and in complete effacement amidst the wildest confusion' (F Galton. Natural Inheritance, London 1889, p66 quoted by Hacking 1990, p2). By the end of the nineteenth century, Hacking claimed that chance had 'attained the respectability of a Victorian valet, ready to be the loyal servant of the natural, biological and social sciences' (Hacking 1990, p2).

Early surveys of population health, and the very idea of measuring health, fitness, morbidity and mortality in populations depended on this taming of chance. Surveys were funded by the state, industry and philanthropy for reasons of efficiency and improved competition, to benefit the nation state, the insurance and other industries, or for broader humanitarian objectives. The state and industry had strong reasons for knowing if there were statistical laws of mortality, morbidity or sickness, even laws of criminality. The emerging modern industrial state needed a fit workforce and industrialisation led to widespread changes in society with profound implications for the health of populations. The outcome of the taming of chance was an avalanche of printed numbers, the enumeration of people and their characteristics, and the generation of new classifications of man and the social and natural world, including the causes of health and disease (Hacking, 1990).

Life insurance companies were among the first to take advantage of the taming of chance, focusing on evaluating individual risk factors for mortality. They were founded in Europe in the eighteenth century and became very popular in the U.S. in the nineteenth century. By 1874 some 200 companies were issuing over a million policies and by 1889 the medical

directors of life insurance companies formed the Association of Life Insurance Medical Directors of America. In the decade 1870 to 1880 a new form of epidemiology emerged, carried out by physicians employed by life insurance companies, of whom there were over 9,000 in the U.S. by 1941. The role of these examining physicians for life insurance companies was to discover the major prognostic signs of asymptomatic disease (Postel-Vinay, 1996). They were quick to start measuring all kinds of individual characteristics routinely such as height, weight and blood pressure and to use their records to relate these measurements to mortality risk. For example Fischer, the medical director of the Northwestern Mutual Life Insurance Company, started to include blood pressure measurements in the examination of life insurance applicants around 1905 (Postel-Vinay, 1996). By 1915, James Mackenzie, who was later to become the founding father of cardiovascular medicine but who then worked for the Prudential Life Insurance Company, had measured over 18,000 applicants (White, 1931). Body build and blood pressure studies based on life insurance data played an important part in understanding the aetiology of CHD (see Sections 7 and 9).

These insurance studies were of growing interest to clinical medicine, and to the emerging speciality of cardiology in particular. Many of the clinicians who became cardiologists and were increasingly concerned about the apparent increase in heart disease in the 1920s-1940s had either worked for life insurance companies or had trained with those who had. For example, Paul Dudley White and Samuel Levine who undertook some of the first longitudinal clinical studies of CHD in the U.S. had both trained with MacKenzie in London. These men were influential in the setting up of cohort studies, such as Framingham, to identify individual risk factors in middle aged men that led to the development of CHD and other forms of heart disease. The clinicians involved in these studies were bound to be more interested in the proximal rather than the distal, and the adult rather than the childhood risks of disease and mortality.

Scientists employed by life insurance companies, such as Louis Dublin of the Metropolitan Life Insurance, were aware of the potential importance of social and physical characteristics in predicting longevity and mortality. Dublin pulled all the evidence together in a book on the length of life and contributing factors published in 1949 with the help of his insurance colleagues (Dublin *et al.*, 1949). He devoted a chapter to the effects of occupation on longevity and mortality. He also noted what an advantage it would be 'if it were possible, even before indications of disease became observable, to appraise the life prospects of an individual on the basis of ordinary physical characteristics or at least to make a tentative judgement regarding the type of illness to which he may be predisposed' (p210). He referred to research being undertaken by scientists in the inter-war period interested in the role of constitution on health. Some of these scientists, such

as Draper (Draper, 1924; Draper *et al*., 1944) and Stockard (1927) had an interest in how the early environment could affect an individual's developing constitution in ways that would be related to mortality risk (Kuh & Davey Smith, 2004, Chapter 2). Measures of the body that were seen as markers of constitution were measured in a number of inter-war studies (Pearl & Ciocco, 1934) and were included in the earlier data collections for the Framingham study (Damon *et al*., 1969).

3. Major Causes of Death at Different Life Stages

Figure 2 shows rates per 100,000 of the top 10 leading broad causes of death for 2008 in England and Wales. Overall the most common cause of death was due to diseases of the circulatory system, which include deaths from ischaemic heart disease (141/100,000), cerebrovascular disease (85/100,000), and acute myocardial infarction (54/100,000). Cancer (neoplasm) was the second most common cause of death and was dominated by cancers of the trachea and bronchus and lung (56/100,000).

Figures 3 and 4 present these statistics, separately for men and women. For men, aged 15-44 years and for women aged 15-24 years, death from external causes of morbidity and mortality, such as accidents and intentional self-harm, comprised the majority of deaths. At older ages and for both sexes, circulatory diseases, cancers and respiratory diseases (including pneumonia, bronchitis, and emphysema) become more common causes of death. For women aged 45-54 years, breast cancer contributes to around 30% of cancer deaths. For men aged 65-74 years, 1 in 10 cancer deaths was due to prostate cancer, this increases to 1 in 7 at ages 75 to 84 years (results not shown). For both men and women aged 45-54 years, diseases of the liver, such as liver cirrhosis, made up over 70% of the deaths due to diseases of the digestive system (the 3rd leading cause of death) (Figures 3 and 4).

To what extent do we expect these patterns to continue? If we looked at longitudinal rather than cross-sectional data, will the cohorts now reaching young, middle and later life show similar patterns in their causes of death? Looking back, for example, secular trends in deaths from coronary heart disease (CHD) in England and Wales show an increase in men and women from 1921 to the early 1940s at which point the increase largely stabilised in women but continued to reach a peak in men in the late 1970s. Thereafter rates have decreased year on year for both genders. Data from other developed countries shows similar patterns over the twentieth century (Lawlor *et al*., 2001). However, there is recent evidence of a flattening out of the downward trend in CHD mortality in the younger ages in both genders. This has been attributed to the adverse trends in risk factors such as obesity and diabetes and the stagnating smoking rates in the younger groups (Allender *et al*., 2008; Capewell & O'Flaherty, 2008; O'Flaherty *et al*., 2009).

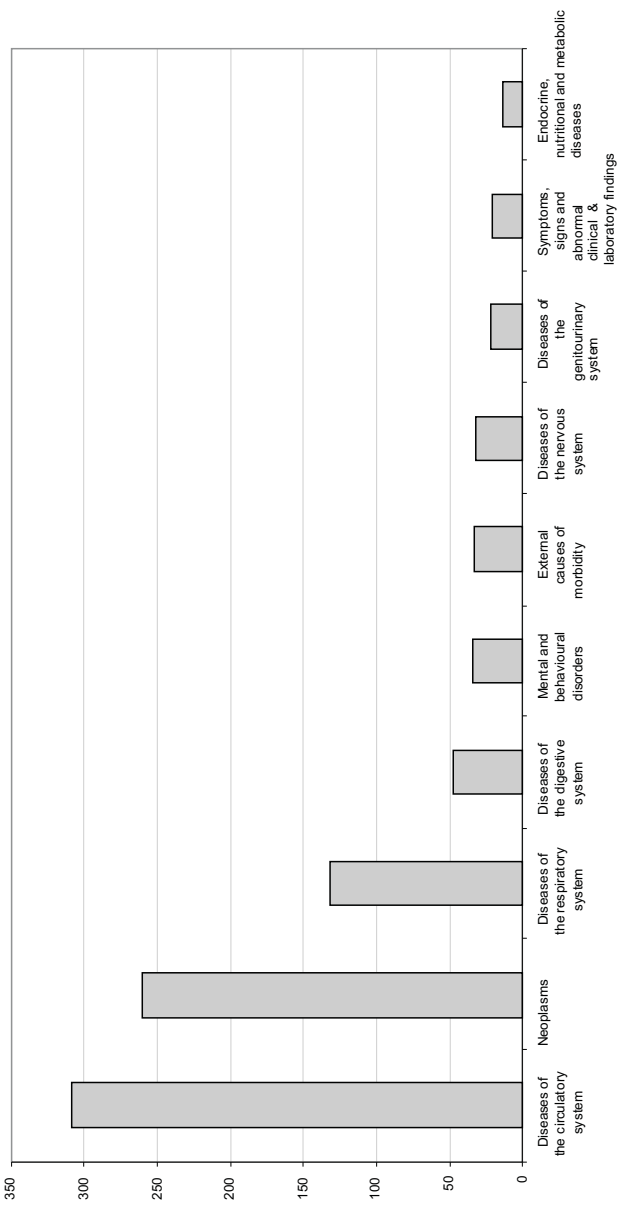

Figure 2. Ten leading causes of death in 2008 in England and Wales (rates per 100,000)

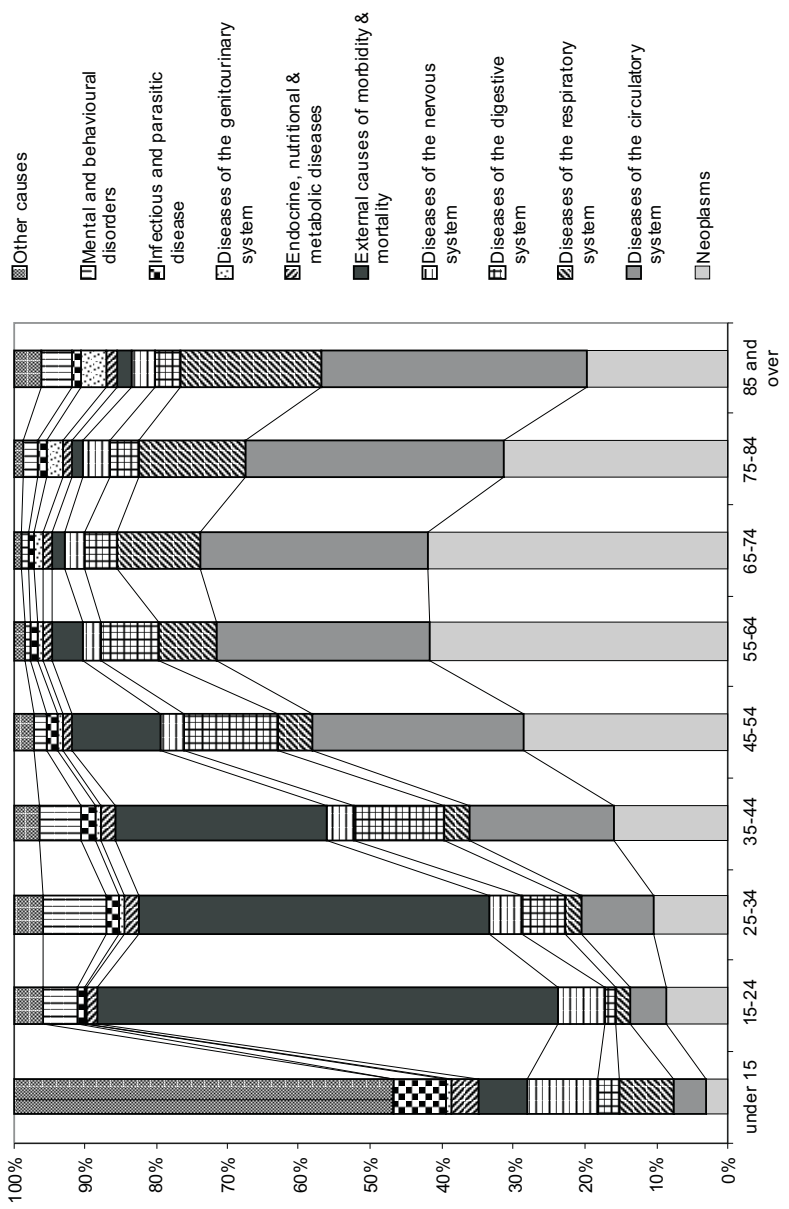

Figure 3. Ten leading causes of death in 2008 in men in England and Wales by age groups

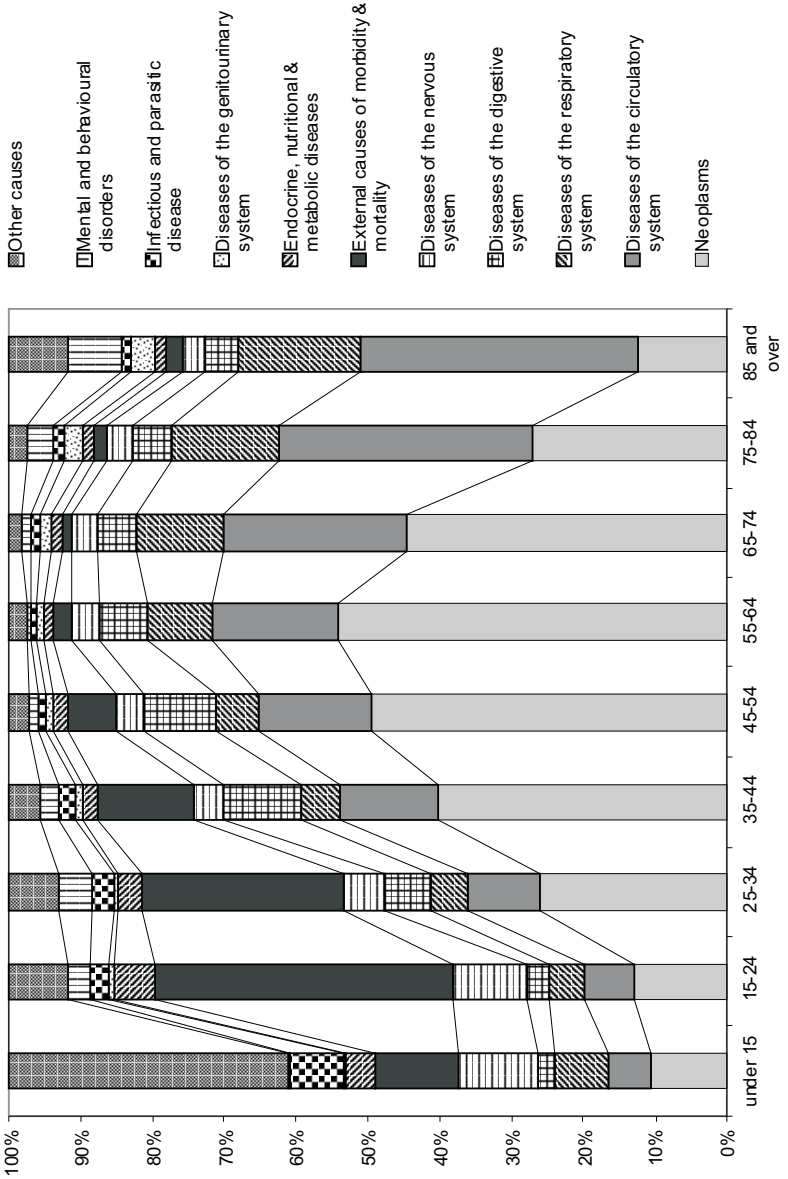

Figure . Ten leading causes of death in 2008 in women in England and Wales by age groups

Another example is the trend in suicide which has recently been investigated (Thomas & Gunnell, in press). From 1861 rates of suicide in men rose reaching a peak in 1905 and another peak in 1934, after which there has been a striking decline, particularly among older men; it is only in the late twentieth century that suicide rates were higher among younger than older men. Suicide rates are lower in women; rates for women rose from 1861 until 1964 and have steadily declined since.

In the review of individual risk factors for mortality that follows, we focus on mortality from all causes and from the most common causes of death.

4. Lifetime Socioeconomic Environment

In the inter-war years some widely cited studies apparently showed higher risks of CHD in the upper social groups, and this was attributed to the supposedly higher stress levels of executive white collar workers compared with other workers. A careful review of the evidence from these older studies (Davey Smith & Lynch, 2004) showed either no association or an inverse association between adult socioeconomic position and CHD incidence or prevalence. Looking over time, between 1921 and 1991, there were rapid declines in mortality for those from the higher social classes and smaller and more inconsistent declines for those from the lower social classes, based on the British Registrar General's occupational classification (Davey Smith & Lynch, 2004). The social gradient in age specific death rates worsened in the last decade of the twentieth century for men and women (Davey Smith *et al*., 2001). Strong gradients can still be seen with age specific death rates in men and women in 2001-2003 across the occupational groupings used for the new social class classification (NS-SEC) (Figure 5).

Many, but not all, causes of adult mortality show strong inverse social class gradients using adult social class (Davey Smith, 2007). There is heterogeneity of associations across cause specific mortality and this may vary by time and place. Strong gradients are normally seen for circulatory and respiratory diseases and for deaths from violence and injuries. Social class gradients in cancers are more mixed; smoking related cancers tend to show a strong gradient, but colorectal and haematopoietic cancers, brain and prostate show no gradient or a positive gradient (Davey Smith, 2007). A review of 20 studies suggested that while the risk of mortality observed was sensitive to the choice of socioeconomic measures, male mortality was more unequal than female mortality across the socioeconomic groups (Mustard & Etches, 2003).

From a life course perspective it is of interest to know whether social class of the family of origin is associated with adult mortality independently of social class of destination as this would provide clues that causal factors

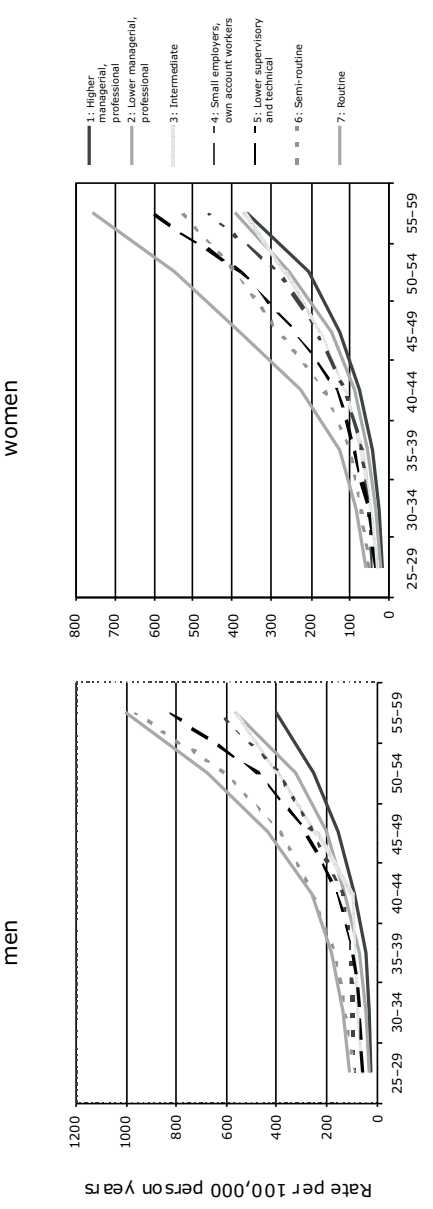

Figure 5. Age-specific mortality rates by the National Statistics Socio-economic Classification (NS-SEC), aged 25-59 years, 2001-2003 using 'own' income for men and 'household' income from women (England and Wales)

for mortality were operating in early life. There is strong evidence of an independent effect of childhood social class on all cause mortality (Kuh *et al*., 2002; Naess *et al*., 2007; Power *et al*., 2005) and CVD mortality (reviewed in Galobardes *et al*., 2004; Galobardes *et al*., 2008; Pollitt *et al*., 2005), especially where measures are based on prospective rather than recall data. There have been few U.K. studies large enough to look across the spectrum of cause specific mortality. One Scottish study in men (Davey Smith *et al*., 1998) showed that adverse socioeconomic circumstances in childhood had a specific influence on the later life risk of stroke and stomach cancer, whereas CHD and respiratory diseases showed effects of both childhood and adult socioeconomic circumstances. The association with stomach cancer probably reflects adverse childhood conditions leading to H pylori infection, a known risk factor for this cancer (Davey Smith, 2007). Some studies have shown that haemorrhagic stroke is particularly associated with adverse early conditions (Davey Smith, 2007) and may also reflect an infectious pathway; however findings are not consistent. A study of more than a million Swedish individuals born between 1944 and 1960 and followed until 1990 (Lawlor *et al*., 2006) showed that those from a manual compared with a non-manual social class of origin had higher risks of dying from CVD, diabetes, respiratory disease, stomach cancer and smoking related cancers, independent of their adult social class. Men from a manual social class of origin also had higher risks of death from unintentional injury, homicide and alcoholic cirrhosis. Overall, these authors found that adjustment for educational attainment attenuated the association of childhood social class with future mortality more so than adjustment for adult social class and suggested that behavioural risk factors may be important mediators of the association of childhood social class with later mortality.

5. Lifetime Psychosocial Environment, Individual Temperament and Behaviour

Whereas in the inter-war years there was growing concern that stress in adult life raised CHD risk among executive white collar workers, psychosocial stress is now suggested as an explanation for the greater mortality risk of those in lower socioeconomic positions (Marmot *et al*., 1991; Marmot *et al*., 1997), either assessed objectively or by self report (Nielsen *et al*., 2008). Whether the critical risk factor is extrinsic stress or intrinsic distress or temperament remains unclear. How might these apparently 'soft' psychological variables lead to the ultimate 'hard' outcome of mortality?

The first problem is the nature of the psychological variable under study and the cause of mortality. Psychiatric disorders, personality traits including neuroticism, Type A personality, hostility, and self reported stress have all

been associated with increased mortality, and it is likely that these act in different ways at different times in the life course. For example, research on the 1946 British birth cohort indicated that individuals with low neuroticism in adolescence were more likely to die from accidental causes in their teens and 20s, leading to their having higher all cause mortality up to this point, but then being over-taken by those with high neuroticism who had higher mortality from age 30 onwards (Lee *et al*., 2006). Psychiatric disorders include both 'internalising' disorders such as depression and anxiety as well as 'externalising' disorders characterised by antisocial traits. Whilst both have been found to be associated with higher mortality, it is probable that the mechanisms are different. We illustrate the complexities and challenges inherent in studying the impact of such psychological variables on mortality by focussing on two risk factors — depression and externalising disorders.

Depressed individuals with established chronic disease have increased mortality risk compared with those with the same conditions who are not depressed (Cuijpers & Smit, 2002; Harris & Barraclough, 1998; Joukamaa *et al*., 2001). Many studies have shown an association between common mental disorders in middle years and premature death, mainly from CVD (Barth *et al*., 2004; Carney *et al*., 2002; Wulsin *et al*., 1999) and suicide (Hiroeh *et al*., 2001; Mykletun *et al*., 2007), but also all cause mortality (Cuijpers & Smit, 2002). Many of these studies are limited by not being population based, having short follow ups, or using inadequate measures of mental disorder, leaving open the possibility that reported effects are due merely to confounding by physical health status at baseline. Many also fail to control for life-style risk factors which may be key mediating factors. However, where these are controlled for — e.g. in the Framingham cohort — the effect persists. Similarly, a recent analysis in the 1946 British birth cohort study that showed those with psychiatric disorder at age 36 years had a higher risk of all cause mortality than those with no disorder, even after careful adjustment for physical health status at baseline, and a range of potential confounders and mediators (Henderson *et al*., under review). It seems therefore that there is a genuine effect of depression on mortality which requires explanation.

The most obvious explanations are intermediary lifestyle factors. People with depression smoke more, exercise less, and (in most studies) are more likely to be overweight than people in the general population. A recent finding from a prospective study of British adults has suggested that people with common mental disorders were at increased risk for future obesity (Kivimaki *et al*., 2009). Whilst these factors do not seem to diminish the effect we have observed between depression and mortality these behaviours are usually controlled for in analyses by using a variable measured once in time, and measurement errors may very well lead to residual confounding. Our analyses of the 1946 birth cohort overcame some of this difficulty — for example smoking was recorded at several time points, and its inclusion

made very little difference to the associations we observed between affective symptoms and mortality — however the possibility cannot be entirely ruled out (Henderson *et al.*, under review).

Biological pathways associated with depression may be chiefly responsible for the observed effects. At least when severe, depression is associated with over-activity of the hypothalamic pituitary adrenal axis (the hormones involved in the stress response) leading to an excess of cortisol, the main stress hormone. This in turn has numerous impacts on immune and autonomic function, potentially leading to immune dysregulation, and other metabolic changes. Results from a recent meta-analysis suggest that depression may be a stronger predictor of subsequent type 2 diabetes than vice-versa (Mezuk *et al.*, 2008). Depression is also associated with alterations in serotonergic function, which may impact on platelet aggregation, leading to an increased risk of thromboembolic disease (e.g. myocardial infarction or stroke). These biological mechanisms are certainly intriguing, but no studies have yet demonstrated that the observed association between depression and mortality can be explained by altered biomarkers.

An indirect approach to this problem would be to determine whether treating depression leads to an improvement in cardiac outcomes in people at high risk, for example after a heart attack. This has been tested in several randomised trials comparing antidepressants or psychotherapies to placebos in patients with depression and acute heart disease. Whilst these trials demonstrate that depression in this context can be treated, they do not indicate that the treatment of depression leads to any improvement in serious cardiovascular events. Intriguing though these biological pathways may be, there is not yet compelling evidence that they are at the route of the association.

From a life course perspective, there is considerable evidence that early life risk factors have an impact on cardiovascular disease. Important risk markers such as body weight, serum cholesterol, and blood pressure may be 'programmed' in utero or in early life. Thus the possibility arises that the association between depression and mortality is a result of shared early life risks that might include intrauterine factors, genetic pleiotropy or the early social environment. Indeed, evidence now shows that early psychosocial adversity and childhood emotional/behavioural difficulties may also be important for later life mortality. In relation to adversity, for example, exposure to factors such as abuse or neglect in childhood — estimated to affect quite large proportions of children — is known to be strongly associated with risk for psychiatric disorder in adulthood (Gilbert *et al.*, 2009), and evidence is now emerging that effects of such exposure at sensitive periods in development may become biologically 'embedded', carrying life-long consequences for later health (Shonkoff *et al.*, 2009).

In a similar way, prospective studies have made clear that much adult psychiatric disorder has roots in emotional/behavioural problems already

evident in childhood and adolescence (Kim-Cohen *et al.*, 2003). Taking this longer-term view, evidence has been accumulating for many years that young people who show high rates of antisocial behaviour are at an increased risk of early death as a result of accidents, injuries and exposure to violence (see e.g. Robins, 1966). Follow-ups of these high risk groups suggest that they continue to show increased mortality risk later in the life course, particularly from heart disease (Laub & Vaillant, 2000). New evidence from population studies is also beginning to suggest that these risks are not simply confined to highly disadvantaged young people: across the population, antisocial behaviours in childhood and adolescence appear to be risk factors for all cause mortality (Jokela *et al.*, 2009). Coupled with evidence that problems of this kind may have become more common in recent decades (Collishaw *et al.*, 2004), these findings suggest that vulnerability to early emotional/behavioural difficulties may be increasingly important targets to our understanding of later health risks.

At this stage, these findings raise quite as many questions as they answer. In particular, very little is known about the mechanisms underlying these links, and whether the key risks run through shared genetic liabilities, poor physical health in childhood, continuities in psychiatric disorder, increased risks of stress exposure or adverse lifestyle factors in adulthood, or early programming of stress responses or other biological systems (see Danese *et al.*, 2007).

6. Lifetime Lifestyles

During the inter-war period the possible effects of adult habits and behaviour on mortality risk and chronic disease was already under scrutiny although evidence was inconsistent. For example, occupational studies initially showed that the physical labour of working men shortened life expectancy (Pearl, 1924) and increased the risk of coronary thrombosis (Levine & Brown, 1929) and arteriosclerosis (Hueper, 1945) through elevated blood pressure. However, the classic studies of J. Morris and his colleagues in the early 1950s (Morris *et al.*, 1953a) showed a clear beneficial effect of physical activity on coronary heart disease (CHD). They found that London bus conductors had only 73% the frequency of CHD that was found in the presumably less active bus drivers. His later comparison of London postmen and less active postal clerks produced much the same findings (Morris *et al.*, 1953b). Tobacco and alcohol also came under the spotlight. Life insurance data showed that both reduced life expectancy (Pearl, 1926; Pearl, 1938) and had adverse effects on physiological function (Burnham, 1989; Grollman, 1930). The clinical studies were less clear and the whole debate was shrouded in moral overtones (Burnham, 1989; Weeks, 1938).

In epidemiology, lifestyle refers to one or more health related behaviours

of an individual or group. In the industrial countries, it is estimated that at least one third of all disease burden is attributable to health behaviours, including tobacco use, alcohol abuse, and obesity (WHO, 2002). From a policy perspective, lifestyle is of particular interest since health behaviours are modifiable, that is individuals exert at least some control over them and they are 'open to individual choice'. In this section we review the evidence with respect to mortality risk for key health behaviours: alcohol consumption, smoking, exercise levels, and dietary patterns (specifically fruit and vegetable intake).

6.1 *Alcohol*

Excessive alcohol consumption is one of the leading lifestyle risk factors for premature death due to diseases, such as cirrhosis of the liver and chronic pancreatitis, liver and breast cancers, and ischaemic stroke and heart disease. Alcohol-related deaths also include those due to road traffic injuries, falls, and suicide. By 2007 in the U.K., alcohol-related date rate had nearly doubled to 13.3 per 100,000 population from 6.9 per 100,000 in 1991. A clear sex difference in rates exists, with 18.1 per 100 000 males dying from alcohol-related causes compared with 8.7 for females. There was also a clear difference in trend according to age group with the highest rate of alcohol related deaths occurring in males aged 55-74 (death rate of 44.3 per 100,000 population) (Office for National Statistics, 2009).

The relationship between alcohol consumption is more complicated than these basic statistics imply. In his seminal work from 1926, Pearl reported both the beneficial effect of light-moderate drinking and a detrimental effect of heavy drinking (Pearl, 1926). Over recent decades, meta-analyses have confirmed this 'J' shaped relationship after adjusting for a range of socioeconomic factors: those with low levels of alcohol intake (up to 1-2 drinks per day for women and 2-4 drinks for men) have lower rates of mortality than abstainers, with the highest mortality risk among those consuming higher levels of alcohol (Di Castelnuovo *et al.*, 2006). The lower mortality risk associated with lighter drinking is largely attributable to lower risk of coronary disease and other atherothrombotic vascular conditions (Klatsky & Udaltsova, 2007).

Further detail is revealed when mortality risk is examined by age group. In a systematic review published in 2002, White and colleagues found a direct linear relationship of increased all cause mortality with alcohol intake in males aged 16-34 and females aged 16-54 years. But for older age groups (primarily from age 54 and older) a 'U' shaped relationship was evident, leading to upper limits of consumption identified for each age group and by sex (whereby the relative increase in mortality risk was limited to 5%). While some debate remains regarding the role of different types of drink on disease risk, the broad consensus is that the effects on mortality risk relate to the units of alcohol consumed, though there is some variation in how these

are quantified across studies. For males, they recommend an upper limit of 2 units per day aged 35-44, 3 units per day for those aged 45-54, 4 units per day up to age 84 years, while for females, the figures are 1 unit a day up to age 44, 2 units a day up to age 74, and 3 units a day over age 75 (White *et al.*, 2002).

In the absence of randomised controlled trial data, Gmel *et al.* (2003) lists several hypotheses for residual confounding to explain the apparent protection by light-moderate alcohol intake. The sick-quitter hypothesis (Shaper *et al.*, 1988) proposes that the apparent higher risk of mortality in the 'non-drinker' group compared to the 'low' or 'moderate' drinking group may be attributable to some ex-drinkers quitting due to health reasons and therefore have higher mortality risk. However, when studies separate abstainers into lifetime abstainers and ex-drinkers, findings show attenuation or complete disappearance of the beneficial effects of alcohol (Gmel *et al.*, 2003).

6.2 *Tobacco Smoking*

Tobacco smoking is a major cause of global mortality and has been identified as a direct cause of cancer, including those of the lung, oesophagus, mouth and pharynx, stomach, and of urinary cancers. It has also been attributed as causing a range of cardiovascular diseases, such as ischaemic heart disease, stroke, and chronic obstructive pulmonary disease. In the U.K. it is estimated that just over 100,000 people died in 2005 from smoking-attributable causes, or about a fifth of all U.K. deaths (27.5% of male deaths and 10.5% of female deaths) (Allender *et al.*, 2009). This number is thought to have remained more or less stable over the decade prior to 2005.

As the evidence for harmful effects of tobacco use has mounted, epidemiological research has progressed from simply identifying health risks associated with smoking to more detailed studies of the long-term effects of different smoking behaviours on mortality and morbidity. Data from the American Cancer Society's Cancer Prevention Study II (ACS CPS-II) revealed that those who quit smoking before age 50 years halved the risk of dying in the following 15 years compared with continuing smokers (U.S. Department of Health and Human Services, 1990). Doll and colleagues reported that among male doctors prolonged cigarette smoking from early adult life tripled age-specific mortality rates, but cessation at age 50 years halved the hazard and cessation at age 30 years avoided almost all of it (Doll *et al.*, 2004).

The MRC National Survey of Health and Development is a life course study that has provided prospective smoking data spanning more than 30 years. This has produced stark evidence for the differential impact of cigarette smoking behaviours on mortality rate (Clennell *et al.*, 2008). Moreover it illustrated how the strength of this evidence differs according to the way smoking behaviour is characterised. Lifelong smokers, as classified

by their smoking trajectory up to age 53, were at the greatest risk of all cause mortality and by age 60 more than 10% had died. They had a threefold increase in mortality rate compared with never smokers (hazard ratio = 3.2, 95%confidence interval:2.1, 4.8). Whereas just using the most recent smoking status available the effect was reduced: current smokers at age 53 had more than doubled risk of mortality compared to those who had never smoked (HR = 2.4, 95%CI:1.6, 3.5). Lifelong smokers were also more likely to have started smoking in early adulthood (90% had begun smoking by age 18 years). So from a methodological perspective, the life course approach has highlighted the importance of obtaining information about the history of smoking behaviour from former and current smokers and the use of simplified smoking classifications based on lifelong behaviour trajectories to understand the accumulative effects of tobacco use.

6.3 *Physical Activity*

A large body of epidemiological evidence has confirmed an independent inverse relationship between measures of physical activity and mortality that applies at least up to moderate intensity levels (vigorous exercise at least five days a week). This relationship was seen across all age groups, including those with underlying health conditions and who were taking medication. Data from the U.S. suggest that physical inactivity is the fourth largest contributor to deaths (Danaei *et al.*, 2009). Results from meta-analyses and from individual studies reported about a third reduction in all-cause mortality among the active compared with the least active participants. This magnitude of reduction was similar for both men and women (Besson *et al.*, 2008; Oguma *et al.*, 2002). In the U.K., the recommended guidelines for physical activity is a total of at least 30 minutes a day of at least moderate intensity physical activity on 5 or more days of the week. Evidence on trends in physical activity levels comes from the Health Survey for England suggests that between 1997 and 2004 the overall proportion of adults meeting the recommended level of physical activity increased from 32% to 37% in men and from 21% to 25% in women. Even if these trends continue, it will be several decades before even the majority of women comply with the guidelines.

As the overarching relationship regarding the benefits of exercise has become clear, research interest has shifted to focus on the details, particularly on the impact of the types and duration of exercise patterns. Since there is considerable heterogeneity in the way in which physical activity was assessed in published studies, assumptions have been made in order to obtain a minimum level of physical activity that lowers death rates. On the basis of studies from which volume of energy expenditure could be estimated, an energy expenditure of about 4,200 kJ/week (1,000 kcal/week) seemed sufficient to avert premature mortality in both men and women (Oguma *et al.*, 2002). One prospective study has shown the benefit of regular exercise

continues to increase up to the 14,700 kJ/week (3,500 kcal/week) level, but beyond this limit there was a tendency for the trend to reverse (Palatini, 2006). Other studies have demonstrated that in healthy individuals, vigorous activities are safe but do not confer additional benefit beyond that provided by a more moderate intensity (Palatini, 2006). In a recent review on the type of physical activity and all-cause mortality, it was found that physical activity at home (RR 0.81 (0.66-0.99) and exercise (0.66 (0.54-0.80)) lower risk of mortality (Besson *et al.*, 2008); another meta-analysis of 18 studies found an inverse dose response relationship for both walking volume (duration and distance: HR 0.74 (95% CI 0.69-0.80)) and walking pace (intensity: HR = 0.52; 95% CI 0.48-0.57))(Hamer & Chida, 2008).

Observational studies can often suffer from measurement error in self-reported exercise levels. To overcome this, epidemiological studies have used cardiorespiratory fitness (CRF), which is obtained from objective measurement, to determine an inverse association between physical fitness and all-cause mortality in healthy or asymptomatic individuals. In a recent meta-analysis of 33 studies, it was found that participants with 1 metabolic equivalent (MET) higher of maximal aerobic capacity (corresponding to a 1-km/h higher running/jogging speed) had a relative risk for all cause mortality of 0.87 (95% CI 0.84-0.90). Those with a low CFR, estimated by maximum aerobic capacity of less than 7.9 METs, had a significantly higher mortality rates than those with a higher CFR (Kodama *et al.*, 2009).

Researchers are increasingly investigating the role of genetics, and the extent that the genome modulates the effect of physical activity on fitness, and fitness on mortality risk. A substantial body of work from genetic epidemiology studies shows moderate to high heritability estimates for many components of fitness, including cardiorespiratory endurance and muscular strength (Rankinen & Bouchard, 2007).

6.4 *Dietary Patterns and Fruit and Vegetables Intake*

Fruit and vegetables are a key component of a healthy diet. There is a large body of evidence indicating that high intake of fruit and vegetables can reduce the risk of mortality due to major non-communicable diseases, principally cardiovascular disease and cancers of the digestive system. The global burden of disease attributable to suboptimal intake of fruit and vegetables has been estimated at 31% for ischaemic heart disease, 19% for ischaemic stroke, 19% for stomach cancer, and 12% for lung cancer. The World Health Organisation has estimated that across Europe more than 750,000 deaths in 2000 were attributable to too low a fruit and vegetable intake (WHO, 2002).

Like many countries in the developed world, current dietary guidelines in the U.K. suggest a minimum of 5 servings of fruit and vegetables per day as necessary for a healthy diet. Findings from the National Diet and Nutrition Survey (NDNS) in 2002 (Henderson *et. al.*, 2003) indicate that average

consumption of fruit and vegetables had increased since 1987 (when the survey was previously conducted), but was still less than three portions per day, with men having an average daily intake of 2.7 portions and women 2.9 portions (Swan, 2004). The change also varied across age groups; daily consumption by women aged 50 to 64 rose from 3 to 3.8 portions, while people aged 19 to 24 were found to be eating no more fruit and vegetables than in the 1987 survey.

Over recent decades an increasing number of researchers have moved beyond the intakes of specific food groups (and their associated nutrient content) to examine dietary patterns (Crozier *et al.*, 2006; Esmaillzadeh & Azadbakht, 2008; Hu *et al.*, 1999; Kesse-Guyot *et al.*, 2009; Mishra *et al.*, 2002). For instance, the Mediterranean diet that has received considerable attention for its possible health benefits. This is characterised by a diet rich in fruits, vegetables, legumes, cereals, and fish, with olive oil as the main source of fat; there is also moderate consumption of red wine, especially during meals, and a low consumption of red meat. A recent meta-analysis using data from more than a million healthy subjects and 40,000 fatal and non-fatal events, indicated that an increase of two points in the score used to measure the adherence to a Mediterranean diet (and based on the consumption specific food types) was associated with 9% lower risk in both overall mortality and cardiovascular mortality, 6% reduction in cancer incidence and mortality, and 13% decline in the incidence of Parkinson's disease and Alzheimer's disease (Sofi *et al.*, 2008).

The limited research in this area highlights the lack of studies with data from early life and with repeated measures over a long period. Since diet of individuals and populations change over time, repeated measurements of diet to obtain prospective data are essential; these repeated measurements also help to reduce random variation (Willett, 2000).

6.5 *Lifestyle as a Combination of Health Behaviours*

Given that many individual health behaviours are highly correlated, it is surprising that relatively few epidemiological studies have focussed on lifestyle as a combination of behavioural factors and their effects on mortality. In an investigation of the combined effects of health behaviours, Khaw *et al.* (2008) found from a British prospective study that those who adhere to all of four health behaviours (current non-smoking, not physically inactive, moderate alcohol intake (1-14 units per week), and plasma vitamin $C > 50$ mmol/l indicating fruit and vegetable intake of at least five servings a day) had a four-fold decrease in mortality risk compared to those who complied with none. There was a significant negative trend with total mortality rates decreasing as the number of health behaviours adhered to increased. Using data from the U.S. Nurses' Health Study, Van Dam *et al.* (2008) combined four lifestyle factors (cigarette smoking, taking little moderate to vigorous physical activity, not light to moderate alcohol intake,

and having a low diet quality score) with being overweight and showed that cardiovascular, cancer, and all-cause mortality increased with an increasing number of risk factors. These studies suggest that addressing lifestyle change in ways that encompass a range of health behaviours could have a marked effect on reducing mortality risk.

7. Lifetime Body Size

The examining physicians of life insurance companies were among the first to show that body build, in terms of shorter height and heavier weight were related to premature mortality (Du Bray, 1925; Dublin, 1930; Dublin & Marks, 1937; Dublin & Marks, 1938).

In most recent studies, height has generally been found to be inversely related with all-cause mortality. However, the association is probably relatively weak and there is a suggestion that the association may be weaker in women than men. There is stronger evidence of inverse associations between height and CVD and respiratory disease (Batty *et al*., 2009). In contrast, positive associations have been found between height and deaths from cancers unrelated to smoking, particularly for cancer of the colorectum, breast, central nervous system, skin, endometrium, thyroid and blood (Gunnell *et al*., 2001). Stomach cancer has shown to be an exception in some studies, showing an inverse relationship and probably reflects H pylori infection (see Section 4). Most of these findings were in high income countries. However, recent studies from Asia found similar findings for Asian cohorts (Batty *et al*., 2009; Lee *et al*., 2009). These findings were not confounded or mediated by socioeconomic position, nor explained by loss of height in the early stages of disease (Batty *et al*., 2009). Final height has been used as a marker of childhood circumstances that influence growth such as childhood nutrition, socioeconomic and psychosocial childhood environment. More recently leg length has been utilised as a marker of early childhood growth (Gunnell, 2001). Long leg length is associated with lower CVD risk, but the evidence for cancers is less clear. Few studies have measures of childhood growth and components of height. Although an original analysis of the Boyd Orr cohort suggested that taller height and taller childhood leg length were associated with increased cancer risk and decreased CHD risk (Gunnell *et al*., 1998a), a more recent updated analysis shows the associations are no longer significant (Whitely *et al*., 2009). It remains possible that the positive associations with certain cancer sites may reflect energy intake and childhood growth rates.

However, most of the above findings are in relatively homogeneous populations. In contrast, studies have found short populations in both traditional and western societies have low CVD compared to taller Western populations (Samaras *et al*., 2004). It is therefore suggested that across

populations, individuals with smaller bodies have lower death rates, especially past mid-life and longer average life spans (Samaras, 2009; Samaras *et al.*, 2003). The view is backed up by animal experiments which show that smaller animals within the same species live longer than larger ones. Samaras *et al.* (2003) also conclude that the shorter height of women explains their longer life expectancy. It is possible that cohort effects exist, as secular increases in height in many populations, and it may be that association will change as populations reach their genetic potential, and environmental factors become less important.

In regard to adult weight and mortality there is plenty of evidence to show that adult Body Mass Index (BMI) has a positive association with mortality, and obesity is a strong risk factor for all-cause mortality. More contentious is whether low BMI carries a mortality risk. Recent large studies have confirmed a 'J' shaped relationship (Prospective Studies Collaboration, 2009). The increased risk in those of low BMI was largely a result of smoking-related diseases, while the increase in those of high BMI was due to CHD mortality.

From a life course perspective, there is an interest at what stage in life BMI is associated with later mortality. Given the increases in BMI and obesity in both childhood and adulthood in recent years, the impact of childhood BMI is of increasing public health relevance. A few studies have found an association between high BMI in adolescence and increased adult all-cause mortality risk (Bjorge *et al.*, 2008; Engeland *et al.*, 2003; Engeland *et al.*, 2004; Hoffmans *et al.*, 1988; Must *et al.*, 1992; Yarnell *et al.*, 2000). A limited number of studies have considered childhood BMI, although all also included adolescents as well as children, and relationships with mortality were either positive (Mossberg, 1989; Nieto *et al.*, 1992) or J-shaped (Gunnell *et al.*, 1998b). The increased mortality among the underweight in this latter study was only significant when BMI was measured before 8 years. In the other studies, childhood BMI was not distinguished from adolescent BMI and hence there is very limited evidence of an association between pre-adolescent BMI and mortality. In addition, the majority of studies had only one measure of adolescent and/or childhood BMI and most had no measure of body size in adult life. Hence, not all are able to assess the question of whether associations with BMI in early life are simply due to tracking of BMI into adulthood. Two studies that were able to adjust for adult BMI produced conflicting findings, one finding the association between adolescent BMI was independent of adult BMI in men (Must *et al.*, 1992) and the other that the association in men was largely explained by adult BMI (Engeland *et al.*, 2004). A systematic review (Owen *et al.*, 2009) of studies relating childhood, adolescent and early adult BMI to CHD finds a positive association in studies with young adult (18-30 years) BMI, a weak positive association between adolescent (ages 7 up to 18 years) BMI (Pooled RR = 1.09, 95% CI: 1.00 to 1.20), but no relationship in the 3 studies with

BMI measured at ages under 7 years. This strengthening of the association with age during childhood and adolescence is consistent with a large Danish study with annual measurements of BMI between age 7 and 13 years (Baker *et al*., 2007). This study showed a steady strengthening of the positive association with CHD events with increasing age. Such studies with multiple measures of body size are required to assess whether length of time being overweight is important to mortality risk or the time at which adiposity is laid down. It has been suggested that the distribution of fat deposition in adolescence may be particularly detrimental to health. It is known that overweight children have poorer CVD risk factors than children of lower weight (see Section 8).

Birth weight is a crude marker of the foetal environment and has been used to test hypotheses related to the foetal origins of adult disease. Birth weight has been shown to have a U-shaped relationship with all-cause mortality (Baker *et al*., 2008). Differences in association were observed with different causes with a positive relationship with cancers and a U-shaped relationship with CHD mortality. Recent systematic reviews have shown robust associations with specific disease. Birth weight was shown to be strongly associated with CHD disease in a meta-analysis of 18 studies (Huxley *et al*., 2007) and with diabetes in 23 out of 31 studies (Whincup *et al*., 2008). Birth weight has also been shown to be positively related to breast cancer (dos Santos Silva *et al*., 2008).

At the other end of the life course, the association between BMI in older age and mortality remains unclear. Higher BMI at these ages may be associated with a lower risk of mortality. It is possible that this is due to reverse causality whereby weight is being lost during illness, although some studies suggest low weight to be an independent risk factor (Gulsvik *et al*., 2009). However, it is possible that the type of body mass is important as both fat and muscle loss occur in later adulthood, so having greater muscle mass is an advantage in older age. The above review has focussed on BMI, as this is by far the most commonly used measure of adiposity. In a U.S. study, the attributable fractions of deaths were similar for other measures of adiposity, such as waist-hip ratio, as they were for BMI (Flegal & Graubard, 2009). A review, however, suggested that waist circumference and waist-hip ratio were better indicators of all-cause mortality than BMI, particularly in older populations (Seidell, in press). Huxley *et al*. (2010) reviewed evidence from studies comparing different measures of adiposity with CVD events. They concluded that current findings were conflicting, since although most studies found the magnitude of the relationships between BMI and measures of central obesity were broadly consistent, much of the evidence was based on cross-sectional studies. Further, a notable and important exception was the INTERHEART study, a large case-control study in 52 countries, which suggested that waist to hip ratio was more strongly related to risk of myocardial infarction than either BMI or waist circumference (Yusuf *et al*.,

2005). To understand better the underlying mechanisms linking adiposity and mortality, the contribution of fat and lean mass needs to be better understood. Future studies with life course measures of body composition will be important in this respect.

8. Lifetime Vascular and Metabolic Traits

This section focuses on vascular and metabolic risk factors, many of which are themselves consequences of greater adiposity, which is discussed in Section 7.0. A number of publications linking blood pressure and mortality were from life insurance companies, culminating in the 'Build and Blood Pressure Study 1959, Volume 1 Society of Actuaries' which included 15 companies and 1.3 million policy holders aged 15-69 years and an analysis of mortality from 1935-54. This study provided robust evidence for the association of higher blood pressure with increased mortality risk. Other risk factors for all-cause and cardiovascular disease mortality, including dyslipidaemia, higher circulating glucose and insulin levels and diabetes, have emerged since the 1970s, and have been less extensively covered by insurance epidemiology. These observations were confirmed by clinicians who set up geographical studies and cohort studies of coronary heart disease, such as Framingham (Castelli, 1987). Subsequent randomised controlled trials of treatments for high blood pressure and high total and low density lipoprotein cholesterol confirm their causal role in cardiovascular disease and mortality (Sacks *et al.*, 1996; Scandinavian Simvastatin Survival Study Group, 1994; Shepherd *et al.*, 1995; Turnbull, 2003).

There is evidence that cardiovascular risk begins in early life, possibly around the time of adolescence. Lipid rich deposits are found in the aorta of almost all children over 3 years of age, but adolescence/early adulthood (from age 15 years) is the key age when these fatty streaks convert to pathologically important raised atherosclerotic lesions (McGill, Jr. *et al.*, 2000). This also corresponds to the age at which adiposity increases in those who go on to develop a range of adverse cardiovascular risk factors (Ferreira *et al.*, 2005). At this age there is also a physiological increase in insulin resistance and its associated risk factors (Smith *et al.*, 1988). In recent years epidemiologists have been investigating cardiovascular risk factors in childhood and how they track into adult life. However, given the long time-lag, few studies have been able to examine whether variation in cardiovascular risk factors (such as blood pressure and fasting glucose, insulin and lipids in childhood) are related to future cardiovascular and all-cause mortality.

8.1 *Blood Pressure*

The most widely studied early life risk factor has been blood pressure

(BP). Sufficient studies of blood pressure tracking have been conducted to make inferences year on year (e.g. comparing the correlation between age 1 and 2 years, to that between 2 and 3 years, and so on). Results suggest relatively weak correlation in infancy and early childhood (e.g. 0.1 in the first 2 years of life) with this increasing monotonically until puberty, when there is a temporary decrease, and then rising to 0.7 from age 18-19 years onwards and staying relatively steady at this level throughout adulthood (Chen & Wang, 2008; Lawlor & Smith, 2005). From comparison across different study populations, this pattern of tracking across the lifecourse appears similar in males and females and across populations from different socioeconomic backgrounds (Lawlor & Smith, 2005). Importantly, there is a positive and linear association between BP assessed in early adulthood and risk of cardiovascular disease mortality. In the Harvard and Pennsylvania alumni studies, and more recently in the Chicago Heart Project, elevated blood pressure at ages 15-29 was associated with increased stroke and CHD mortality (Miura *et al.*, 2001; Paffenbarger & Wing, 1967; Paffenbarger & Wing, 1969). These findings have been replicated in a U.K. population, showing BP assessed in Glasgow Alumini aged 17-21 years was positively associated with future stroke and CHD mortality risk (McCarron *et al.*, 2000; McCarron *et al.*, 2002). The magnitude of the associations of BP in early adulthood (ages 15-25 years) with CVD is similar to those found for BP in middle age and older (Perkovic *et al.*, 2007). These alumni study have generally included no, or too few women, to robustly assess associations in women and examine whether gender differences in the associations exist. Furthermore, since they are completed on cohorts who entered further education at a time when access to this amongst those from lower socioeconomic groups was limited, the cohorts are of higher socioeconomic groups than the general population and are therefore unable to examine whether associations are similar across all social groups. Nonetheless the association of higher blood pressure in middle and older age with future cardiovascular and all-cause mortality is similar in women and men and across socioeconomic groups, as is the beneficial effect of treatment with antihypertensives. Thus, it is likely that associations of higher blood pressure in adolescence and early adulthood with future cardiovascular mortality is similar across all subgroups of the population.

Secular changes in blood pressure and comparisons between geographical locations provide valuable information about the nature of variation in blood pressure. For decades assessment of blood pressure in Western populations shows steady increases in systolic blood pressure with age from adolescence to old age; levels rise from 120-125 mmHg at age 16-18 years to 140-145 mmHg by ages over 75 years in men and from 110-115 mmHg to 145-150 mmHg in women over the same age range (Burt *et al.*, 1995). Diastolic blood pressure increases with age until 50-55 years and then declines. This has led some to believe that systolic blood pressure inevitably increases with

age in humans as blood vessels naturally age and stiffen. But evidence from isolated populations, such as the Yanomamo Indians, Xingu Indians in Brazil, groups in Papua New Guinea and isolated groups in Africa show low mean levels of systolic and diastolic blood pressure (100-110 mmHg for systolic and 60-70 mmHg for diastolic) with no changes with age (Carvalho *et al.*, 1989), suggesting that age related increases are not inevitable.

There have been reductions in mean systolic and diastolic BP in Western populations over the last 50 years and this decline is seen in children and young adults (i.e. those aged 5-34 years) (McCarron *et al.*, 2000; McCarron *et al.*, 2002) as well as middle-aged and older adults. There is also evidence that these population declines in BP have resulted in important secular declines in risk of coronary heart disease mortality (Unal *et al.*, 2005). As with the evidence from isolated populations, these secular trends in BP decline suggest that population level changes in BP in early and later adulthood are feasible.

Despite these important decreases in blood pressure over recent decades, mean blood pressure still remains relatively high in Western populations, as does CVD risk, and there are concerns that the obesity epidemic which affects all ages may result in a reversal in the favourable secular trends in CVD risk factors and events seen in recent decades (see Section 7 on obesity).

8.2 *Lipid and Glucose Levels*

Tracking correlations for fasting lipid levels have been assessed in the Bogalusa (US based) and the Cardiovascular Risk in Young Finns cohort studies (Porkka & Viikari, 1995; Webber *et al.*, 1991). In both studies there was no clear pattern of differences by age but this was assessed by comparing correlations in broad age strata (e.g. those aged 2-8 years at baseline compared to those aged 9-14 years). The tracking correlations for total cholesterol (ranging from 0.42 to 0.66 for different age, gender and ethnic groups in the two studies) and low density lipoprotein cholesterol (0.44-0.69) appeared to be stronger than for high density lipoprotein cholesterol and triglycerides (0.18-0.42). No studies yet have examined the association of lipids measured in childhood with later adult mortality, but variation in lipids in childhood do predict dyslipidaemia in middle-age (Magnussen *et al.*, 2008). Variations in lipids in childhood have been related to carotid intima media thickness in early adulthood as discussed in Section 8.3.

In one relatively small study that found similar magnitudes of tracking correlations between baseline (age 8-18 years) and follow-up 12 years later for blood pressure and lipids to those seen in other studies discussed above, there was only a weak correlation for fasting glucose (0.14) (Katzmarzyk *et al.*, 2001). As with lipids, studies have not yet been able to examine the association of variation in fasting (or postload) glucose or insulin in childhood with adult all-cause and cardiovascular mortality.

To our knowledge studies have not specifically examined whether tracking correlations vary by gender or across socioeconomic groups.

8.3 *Vascular Structure and Function*

There is a new generation of vascular measures of structure and function — coronary artery calcification, carotid intima media thickness (CIMT), pulse wave velocity and pulse wave analysis, and arterial distensibility that are increasingly used in epidemiological research in children and adults. Of these CIMT has been most extensively studied. CIMT is an accepted valid measure of atherosclerosis in both sexes. It has been shown to predict CHD and stroke events equally in women and men, and has been used as a valid endpoint (now FDA approved) in trials assessing the effectiveness of preventive cardiovascular treatments in both sexes (Lorenz *et al*., 2007). As yet no studies are available that can relate CIMT assessed in childhood with adulthood all-cause and cardiovascular mortality, but in one study, in which CIMT was measured at baseline in a population ranging in age from 19 to 90 years and associations with CVD events and mortality over 4.5 years of follow-up were examined, there was some evidence that the associations were stronger in those under 45 years at baseline than older individuals. Whilst these findings require further replication and examination at younger ages, they do suggest that CIMT in early life might be a valuable marker of CVD risk (Lorenz *et al*., 2007).

The cardiovascular risk in young Finns' study has examined the association of a range of cardiovascular risk factors measured in childhood (age 3-18 years) with variation in CIMT assessed when these participants were aged 24-39 years (Raitakari *et al*., 2003). It found that low density lipoprotein levels, systolic blood pressure, body mass index and smoking at baseline (age 3-18 years) were positively associated with CIMT measured in early adulthood; high density lipoprotein cholesterol and diastolic blood pressure were not related to later CIMT (Raitakari *et al*., 2003). There was no evidence in this study that associations varied by gender.

An increasing number of studies are undertaking more detailed measurements of vascular structure and function in children and young adults and will allow their long-term impact on mortality risk to be assessed eventually. A key focus of this research should be on the extent to which these measurements (and other more invasive/resource intensive measurements such as those based on fasting blood samples) add to risk prediction that can be obtained from more simple measures such as body mass index and blood pressure.

9. Lifetime Physical Function

Interest in physical function dates back over many years with early surveys of anthropometry also including measures of physical fitness and function (such as vital capacity, heart rate and muscular strength). For example, about 10,000 people came to Francis Galton's Anthropometric Laboratory at the International Health Exhibition in London 1884-85 and paid 3d to be measured. Galton took various measurements of the body including elbow length and sitting height, as well as assessing eyesight, hearing, reaction time, strength and breathing capacity (Gillham, 2001).

Physical function can be assessed in a number of ways. In this review we focus on physical function assessed objectively through the measurement of grip strength and other physical performance tests, while acknowledging that other measures including self-reports are often also used. At the beginning of the twentieth century grip strength and similar measures were assessed in studies of children and young adults such as army recruits as there was considerable interest in their levels of physical fitness, because of concerns that the physical condition of the population was deteriorating and having an impact on national efficiency. Since then such measures have come to be included in population based studies, allowing an investigation of their relationships with mortality risk. The first study that we are aware of that linked adult grip strength to mortality risk in a community-dwelling population was published in 1984 (Milne & Maule, 1984). A recent systematic review (Cooper *et al.*, in press) has identified a total of 19 publications reporting on this association up to May 2009. In meta-analyses of these results and those from another 4 studies which provided unpublished data, consistent evidence of associations between weaker grip strength and higher all-cause mortality rates was found in studies with follow-up ranging from a few years up to 40 years, after taking age, sex and body size into account. There was no clear evidence to suggest that these associations differed by sex or age and while the majority of studies of this association have been undertaken in older populations (i.e. aged 65 years and older) it has also been demonstrated in younger populations with one study including males as young as 18 years (Metter *et al.*, 2002) and other studies including people who were in early adulthood at the start of follow-up. However, no study identified has investigated the association between grip strength in childhood and mortality risk.

Other objective measures of physical function that are assessed in population-based studies include tests of chair rising, gait speed, and standing balance (Guralnik *et al.*, 1989). As these tests were introduced to detect deficits in function, rather than variability in function across the full range, they have usually been used in older populations. The systematic review referred to above (Cooper *et al.*, 2009) identified 11 studies which had examined the association between gait speed and mortality in community-

dwelling population, seven which had examined chair rise time and five which had examined standing balance performance. There was consistent evidence in these studies of associations between poor physical function (indicated by slower gait speed, longer chair rise time and poor balance) and increased all-cause mortality rates. However, these associations have only been examined in populations aged 60 years and older and with follow-up of less than 10 years, and there are too few studies to investigate formally differences in association by sex.

These objective measures of physical function are now seen as summary markers of ageing and low levels have also been shown to be associated with other adverse outcomes such as specific diseases, disability, and hospitalisation (Guralnik *et al*., 1994; Rantanen, 2003; Silventoinen *et al*., 2009; Cooper *et al*., in press). A number of explanations for finding associations between such measures of physical function and mortality have been proposed. First is the possibility that these measures of physical function are good markers of disease and general health status; those people who have poor general health may perform less well in tests of physical function and also have higher risk of mortality. A related possibility is that underlying ageing processes lead to poorer performance and a higher probability of chronic disease and death. Walking speed, chair rising and standing balance require strength, balance and motor control; walking speed and chair rising also require muscle power and speed, and adequate cardiorespiratory function; standing balance requires mental concentration. These functions decline with age, may co-vary, and contribute to the risk of frailty. The progressive dysregulation of homeostatic equilibrium across multiple systems may be the biological basis of frailty; common pathways proposed include endocrine dysfunction, inflammation, oxidative stress and disequilibrium between the sympathetic and para-sympathetic systems (Walston *et al*., 2006). One way of exploring this further would be to examine associations with cause-specific mortality, however only a few studies which have examined the associations between physical function and mortality have reported on these (Dumurgier *et al*., 2009; Fujita *et al*., 1995; Gale *et al*., 2007; Sasaki *et al*., 2007; Silventoinen *et al*., 2009; Takata *et al*., 2007). As functional status in later life reflects the peak achieved during growth and development as well as the rate of decline, the relationship between these measures of physical function and mortality risk could also reflect initial differences in development that impact on both.

10. Lifetime Cognitive Function

Dementia and Alzheimer's disease become leading causes of death after the age of 75 years. A review of the literature in 2001 concluded that there was evidence that adult cognitive impairment (based on 23 studies) and

dementia (based on 32 studies) increase the risk of mortality (Dewey & Saz, 2001). A recent systematic review also found evidence that mild cognitive impairment leads to dementia, even after five years of follow-up (Mitchell & Shiri-Feshki, 2008). Adult cognition has also been shown to be a risk factor for physical chronic diseases, including CVD (Hemmingsson *et al.*, 2007; Kuh *et al.*, 2009a).

Two population studies have shown that childhood cognitive function predicts the rate of adult cognitive decline (Deary *et al.*, 2004; Richards *et al.*, 2004). More widely, over the last decade, evidence has been accumulating that childhood cognitive function is associated with subsequent all-cause mortality (Batty *et al.*, 2007; Kuh *et al.*, 2009b), CVD disease and psychiatric disorders (Gale *et al.*, 2008; Hart *et al.*, 2005; Hemmingsson *et al.*, 2007). A forthcoming updated review (Batty, personal communication) has found 23 studies that have investigated this association. A growing number of studies are also linking childhood cognitive function to various aspects of adult health (Gale *et al.*, 2009).

Childhood cognitive function is based on performance in a range of verbal and non verbal cognitive tests, some taken as early as age 7 years and some as late as 15 years. These scores are markers of neurodevelopment and mental capital (Kirkwood *et al.*, 2008). Possible reasons for associations between these cognitive measures and later health and chronic disease risk are that childhood cognitive ability may be (1) a mediator of early disadvantage, (2) predict entry to safe adult environments, (3) predict emotional resources and health behaviours, (4) reflect 'physiological integrity', or, (5) be linked through common cause mechanisms (i.e. confounding). 'Physiological integrity' means a 'well functioning body' and it could be that higher intelligence might be one aspect of a body that is generally 'well-wired' and that responds more efficiently to environmental challenges or 'allostatic load' (Chandola *et al.*, 2006; Gale *et al.*, 2009; Kuh *et al.*, 2005; Kuh *et al.*, 2009a).

Only a few studies have tested whether cognitive function in childhood (Hemmingsson *et al.*, 2009; Kuh *et al.*, 2009b; Osler *et al.*, 2003) or adulthood (Batty *et al.*, 2006) is an explanation for socioeconomic differences in mortality. The evidence so far is inconsistent; the two studies that suggest that cognition attenuates the effect of socioeconomic position, did not also test whether the alternative is true — that socioeconomic position attenuates the effects of cognition. The latter was the explanation in findings from the 1946 British birth cohort study, suggesting that cognitive function is a rather well-characterised marker of socioeconomic position (Kuh *et al.*, 2009b). Further research in this area is warranted.

11. Genetic Predisposition for a Long and Healthy Old Age in the Context of Environmental Change

Lifespan (the length of life) is an integral part of life-history. It ultimately results from the expression of our population genome under specific environmental conditions, a process in which chance plays an important element. Mean life expectancy of humans in developed countries has increased dramatically over the last century (Oeppen & Vaupel, 2002). In Japan, for instance, the mean life expectancy has increased from 50 years to 80 years in no more than six decades. It is unlikely that changes in population genome over this time-period can explain the observed increase in lifespan, which is more likely because of improvement of environmental conditions and medical care. The increase in mean life expectancy of the total population, however, has left the marked inter-individual variance in lifespan unaltered. Studies of twins and long-lived families have estimated that 20-30% of the variation in human lifespan is determined by genetic factors, which become more important for survival at older ages (Herskind *et al*., 1996; Hjelmborg *et al*., 2006; Mitchell *et al*., 2001). Siblings of centenarians have a significantly higher chance of becoming a centenarian themselves when compared to other members of their birth cohort (Perls *et al*., 2002). In addition, it has been shown that offspring of long-lived sibling pairs have a lower mortality risk already at middle age, whereas their spouses, with whom they have shared a common environment, do not show this survival benefit (Schoenmaker *et al*., 2006; Westendorp *et al*., 2009).

Over the years several evolutionary theories of ageing have been proposed, which help to understand why there are genetic factors that influence ageing and lifespan (Austad, 2008). Ageing or senescence is the progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age. It has been proposed that ageing has evolved as a by-product of natural selection for the optimisation of reproductive schedules. Genes with beneficial effects early in life, but detrimental effects on fitness late in life would be selected because of the diminished power of natural selection with age. This antagonistic pleiotropy theory of ageing (Williams, 1957), was further developed in the disposable soma theory, which emphasises the trade-off between reproduction and somatic repair and maintenance (Kirkwood, 1977). The existence of such trade-offs has been demonstrated in various studies and the most common trade-off that has been observed is between lifespan and fertility (Austad, 2008). The latter trade-off has also been observed in humans (Westendorp & Kirkwood, 1998).

Studies with model organisms have considerably contributed to the identification of genes and physiological processes that influence lifespan. The first evidence that genes can influence lifespan came from studies with C. elegans. It was discovered that mutations in dauer formation (Daf)

genes, such as age-1 and daf-2, lead to lifespan extension. Molecular characterisation of these genes revealed that they belong to the evolutionarily conserved insulin and insulin-like growth factor (IGF) signalling (IIS) pathway (Bartke, 2008). Most of the genes indentified to influence lifespan in model organisms are evolutionarily conserved and present in a variety of organisms, including humans. It has been observed that centenarians are enriched for genetic variants that lead to reduced IGF-1 signaling (Bonafe & Olivieri, 2009; Suh *et al*., 2008). Similar findings have been observed in a prospective follow-up study of elderly Dutch subjects where polymorphisms in the insulin-like growth factor (IGF) signalling (IIS) pathway, which controls IGF-1 activity, was associated with longevity in females (van Heemst *et al*., 2005).

Studies of candidate genes that are important for lipid metabolism, antioxidant enzymes and macromolecule repair mechanisms, including DNA, have also identified variants that associate with longevity. The effects of the separate variants however, are small and not consistently replicated in additional cohorts (Kuningas *et al*., in press). The studies on candidate genes have been followed by whole-genome screening. The advent of genome-wide association studies (GWAS) has successfully led to the discovery of novel genetic variants that have strong evidence for replication and that are outside of traditional candidate gene regions for several common diseases such as breast cancer and cardiovascular disease (Easton *et al*., 2007; Helgadottir *et al*., 2007). The detection of novel genetic variants associated with longevity holds the promise to provide important insights to biologic pathways in the ageing process and thus the potential to develop innovative strategies to promote a long and healthy life. Recently a meta-analysis of GWAS findings for longevity was published (Newman *et al*., 2010). In this analysis longevity was defined as survival to age 90 years or older and a comparison group was drawn from the cohort. Several genetic variants were identified that could be replicated in additional cohorts but none of them reached genome wide statistical significance. The findings suggest that pathways in basic mechanisms of cellular function are important in longevity.

It is well known that environment has a vast influence on the expression of genetic information. This is also the case for lifespan. Studies with model organisms have demonstrated that lifespan is very plastic i.e. different environmental factors (temperature, nutrition, population density) can have a considerable effect on lifespan. The phenotypic plasticity, which is defined as the ability of a genotype to change phenotypically when exposed to environmental change, allows organisms to adjust their life-history in response to environmental cues. For instance, in optimal environments organisms might invest into reproductive success at the expense of future survival, whereas in stressful environments organisms might switch to increased investment into survival until conditions for reproduction have improved (Flatt & Schmidt, 2009).

Even for humans, the environment in which the genome effectively evolved has changed. Many aspects of our modern environment and lifestyle, including diet, exercise, exposure to chemicals and hygienic practices are mismatched to our bodies' evolutionary state. Genes that were originally selected for survival in adverse environments are now expressed under completely new, affluent environmental conditions. Such mismatch is believed to underlie many currently prevalent diseases such as diabetes, obesity, and cardiovascular disease (Stearns *et al*., 2008). For instance, genes that increased the efficiency to store energy in times of abundance and use these storages in times of famine contributed to a survival advantage. In modern Western societies, where food is constantly abundant, these genes are thought to underlie the increased prevalence of storage diseases, such as obesity and diabetes. This reinforces the idea that our genomes have been optimised to increase fitness under adverse environmental conditions and not under modern affluent conditions, resulting in new interactions with outcomes that are both unknown and unpredictable. For lifespan, we have observed an increase in Western societies, but such increase is likely to come at a cost. Despite the accumulating evidence from model organisms and humans it still remains unclear how exactly lifespan evolves when populations adapt to novel diets or other environments and whether there are long-term benefits and costs associated with responding to such environmental change.

12. Concluding Remarks

Individual characteristics are the phenotypic expression of the match or mismatch of our genes with our lifetime environment, coupled with a good dose of chance. This review has shown that these individual characteristics, measured in the pre-adult as well as the adult life, are associated with the risk of premature mortality or the chance of surviving to old age. The most robust evidence comes from very large studies or combining smaller studies through systematic review and meta-analysis, and investigating heterogeneity and confounding. Where available we have drawn on this type of evidence in our review. We acknowledge that our review is not comprehensive, and potentially important factors, such as reproductive function, have not been included.

While many of the effects of these pre-adult characteristics on mortality risk are small, they may provide important clues to aetiology. Together these small effects accumulate and can lead to significant individual and subgroup variation in longevity and mortality, especially when adult characteristics are also taken into account. Further research needs to explore whether improvements to mortality prediction can be achieved by combining lifetime risk profiles, in a similar way in which adult factors are already combined to provide CHD risk profiles.

From the evidence available, relative effects would appear to be similar in men and women and across social groups. Treatment effects across these

groups are also generally stable. For example, statins reduce cholesterol by just as much in smokers as non-smokers, and in all other groups equally, suggesting how similar we all are biologically. These similar relative effects may hide differing absolute effects because of differences in underlying prevalences of risk factors and disease. Thus, women live longer than men and tend to experience CVD mortality rates similar to men approximately 10 years later so absolute risk levels in women that would indicate the need for secondary prevention treatment (by statins for example) are lagged by 10 years in women compared to men.

Importantly, all-cause and many cause-specific mortality rates remain considerably higher in those who came from lower rather than higher socioeconomic groups in childhood as well as in adult life. In part this excess risk appears to be due to increased lifestyle risk factors, such as smoking and poor diet, and in part due to lower access to some preventive and health promotion intervention. Targeting interventions for these groups may be appropriate.

Of the risk factors explored, the secular trends are most worrying for obesity. Over the last 15 years the percentage that are obese has risen from 11 to 17% in children and from 15 to 24% in adults (Statistics on obesity, physical activity and diet, 2009; Foresight programme of the Government Office of Science, 2007). The consequences of these trends on morbidity and mortality are not altogether clear as other CVD risk factor levels in the population (such as blood pressure and lipid profiles) have been improving (Gregg *et al.*, 2005), despite obesity being a risk factor for these risk factors at the individual level. For example, a Swedish study showed that obese men now in their fifties have much lower other risk factors than obese men over 40 years ago (Rosengren, 2009).

Researchers are now more likely than before to investigate healthy ageing rather than focus only on disease-specific mortality and morbidity. For example, a new interdisciplinary research collaboration has recently received cross research council funding[1] to study lifetime and common determinants of three aspects of healthy ageing: physical and cognitive capability (the ability to undertake the physical and intellectual tasks of daily living), psychological and social wellbeing, and underlying biological ageing processes.[2]

With the steady increase in life expectancy, indicators of the health of individuals need to extend beyond mortality risk to encompass a broader range of indicators such as individual changes in function, disability onset or duration, disease progression, survival after diagnosis and quality of life. Similarly, indicators of the health of populations, and subgroups within a population, should encompass cohort changes in function and disability-free

[1] See www.newdynamics.group.shef.ac.uk

[2] See 'Healthy Ageing across the Life Course' (HALCyon) at www.halcyon.ac.uk).

life expectancy, disease incidence, survival after diagnosis and quality of life. We hope this review will encourage actuaries and epidemiologists to apply the insights gained from a life course perspective on individual risk to explain population trends and differences by cohort, gender and socioeconomic groups and identify areas where early and targeted interventions to improve long-term survival should be considered.

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