Commentary

Cardiovascular disease prevention and the rise in dementia

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Introduction

Published data suggest that an increase in dementia might be an unintended consequence of successful cardiovascular disease prevention policies. The risk of developing both coronary heart disease (CHD) and Alzheimer’s disease, the commonest cause of dementia, is increased in people with a common genetic trait, namely inheritance of an allele (ε4) encoding apolipoprotein (apo) E4, who comprise almost 30% of the UK population. Under normal circumstances, ε4 carriers die earlier than the remainder of the population but by reducing their risk of CHD and prolonging life, statin therapy may increase the prevalence of Alzheimer’s disease. Existing data provide little evidence that statins or any other therapy prevent cognitive decline, which has made screening for the risk of Alzheimer’s disease hard to justify. However, the inexorable rise in dementia suggests that this needs to be reappraised.

Changing life expectancy

Life expectancy has advanced rapidly in Britain during the past 30 years. Between 1980–82 and 2005–07, it increased by 8.9% in men and 6.1% in women, average ages of death rising to 77.2 and 81.5 years, respectively (Figure 1), and the trend is continuing. A major contributory factor has been the concomitant reduction in mortality from cardiovascular disease in the UK, which accounts for 36% of total mortality. Half of the former is from CHD, a quarter from stroke and it is the main cause of death before the age of 75 years. Coronary mortality peaked in 1970 and has fallen gradually ever since, decreasing between 1981 and 2000 in men and women aged <75 years in the UK by 62% and 45%, respectively; there has also been a 23% reduction in deaths from stroke before the age of 65 years. Figure 2 illustrates the decline in cardiovascular mortality in England.

It has been estimated that the major modifiable risk factors, namely raised serum cholesterol, smoking and high blood pressure, account for 45%, 29% and 22%, respectively, of all myocardial infarcts. Life-style-related reductions in the prevalence of these risk factors have occurred during the past decade: hypercholesterolaemia decreased in men and women by 6% and 7.5%, smoking by 14% and 18% and hypertension by 5% and 12%, respectively. There were also changes in the treatment of cardiovascular disease over the same period: percutaneous coronary interventions tripled, prescriptions for anti-hypertensive and anti-platelet drugs increased 4- to 5-fold and prescriptions for lipid-regulating drugs, mainly statins, increased by 2000%.

Longevity and dementia

One of the most socio-economically and medically challenging consequences of the increasing longevity of the population is the accompanying increase in the prevalence of dementia. This age-related disorder currently affects about 750,000 people in the UK, which is projected to rise to 1 million in 2021 and 1.7 million in 2051. Table 1 shows the results of a meta-analysis of European population-based studies performed in the 1990s, the EURODEM study. This demonstrates the progressive increase
in the incidence and prevalence of dementia with increasing age, especially in women. Alzheimer’s disease is the underlying cause in 62% of cases, vascular dementia (vascular cognitive impairment) in 17%, mixed Alzheimer’s and vascular dementia in 10% and several rarer disorders account for the remainder. More than 95% of those with Alzheimer’s disease, the commonest cause of dementia, are >65 years of age. The projected increase in the frequency of this condition is in marked contrast to the decreasing mortality from cardiovascular disease. So, too is the fact that at any given age women are more prone to dementia than men but less prone to cardiovascular disease. This implies that the two disorders have different aetiologies and suggests that preventive measures for cardiovascular disease may have little effect in preventing dementia due to Alzheimer’s disease. However, there is some evidence that combined angiotensin-converting enzyme (ACE) inhibitor and statin therapy can prevent post-stroke vascular dementia.

### Table 1  Incidence and prevalence rates of dementia from the EURODEM meta-analyses for European studies (reproduced from reference 5)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Annual Incidence/100</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>60–64</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>65–69</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>70–74</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>75–79</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>80–84</td>
<td>2.8</td>
<td>3.4</td>
</tr>
<tr>
<td>85–89</td>
<td>3.9</td>
<td>5.4</td>
</tr>
<tr>
<td>≥ 90</td>
<td>4.0</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Figure 1. Life expectancy at birth in the UK. From period life tables, 1980–82 to 2007–09 (reproduced from Ref. 1).

Figure 2. Fall in death rate from coronary heart disease, stroke and other diseases of the circulatory system in people below the age of 75 years in England between 1970 and 2002 (reproduced from BHF Coronary heart disease statistics at www.heartstats.org).
Pathogenesis of Alzheimer’s disease

As reviewed recently, the twin pathological hallmarks of Alzheimer’s disease are the accumulation in the cerebral cortex of plaques consisting of extracellular deposits of amyloid-β (Aβ) peptide, and intracellular accumulation of neurofibrillary tangles containing hyperphosphorylated tau (p-tau), a microtubule assembly protein. These changes are accompanied by loss of neurons in the temporal lobes and a progressive decline in cognitive function.

Risk factors for vascular dementia include diabetes, hypertension, smoking and obesity but their role in Alzheimer’s disease is unclear. In contrast, there is good evidence that genetic factors are involved. Three genes are implicated in early-onset Alzheimer’s disease, amyloid precursor protein (APP) and two presenilin genes (PSEN 1 and PSEN 2). Mutations in any of these genes can result in an imbalance between Aβ production and clearance that leads to a build up of Aβ. The likelihood of developing late-onset Alzheimer’s disease is markedly influenced by the apoE genotype, which accounts for 20–30% of the risk. ApoE is a constituent of plasma very low-density lipoprotein (VLDL) and VLDL remnants, where it acts as a ligand for the apoB,E or low-density lipoprotein (LDL) receptor. There are three common isoforms, apoE2, apoE3 and apoE4 encoded by three alleles, ε2, ε3 and ε4. More than 55% of the UK population are homozygous for ε3, roughly 25% are heterozygous for ε3 and ε4, ~3% are homozygous for ε4 and most of the remainder are heterozygous for ε2. Less than 1% are homozygous for ε2 but analysis of apoE genotypes or phenotypes is often performed in lipid clinics because homozygous inheritance of apoE2 can cause a form of mixed dyslipidaemia characterized by accumulation of VLDL remnants (type III).

Compared with individuals homozygous for ε3, possession of one ε4 allele increases the risk of late-onset Alzheimer’s disease by 2- to 4-fold, whereas homozygosity for ε4 increases the risk almost 15-fold. Life-time risks of developing Alzheimer’s disease by the age of 85 years are 7–10% in ε3/3, 20–30% in ε3/4 and 50–60% in ε4/4; the higher values in each instance relate to females. Mechanisms invoked for the increased risk associated with the ε4 allele include interaction between apoE4 and Aβ, and apoE4-mediated inhibition of neuronal repair and remodelling. Other genes implicated in late-onset Alzheimer’s disease include Sortilin-related receptor 1 (SORL 1) and clusterin (CLU). The latter, also known as lipoprotein J, forms complexes with Aβ in the cerebrospinal fluid that can penetrate the blood–brain barrier.

Reitz et al. concluded their review by advocating screening in middle age to detect those at high risk of Alzheimer’s disease. This conflicts with the opposition to screening voiced by the UK National Screening Committee’s Appraisal of Alzheimer’s disease. However, the latter’s scientific credibility is undermined by its misstating that there are four common apoE alleles (there are only three) and that homozygous inheritance of apoE4 occurs in ~1% of the normal population (the correct value is close to 3%).

Statins, apoE genotype and cardiovascular disease

A large meta-analysis of clinical trial data has confirmed the efficacy of statins in lowering LDL cholesterol and reducing the incidence of CHD and strokes. For each millimole per litre decrease in LDL, coronary mortality was reduced by 19% and total mortality by 12%. A subsequent meta-analysis showed that the greater the reduction in LDL cholesterol, the greater was the reduction in the risk of vascular events. Absolute reductions in major cardiovascular events were roughly twice as great in persons with pre-existing CHD as in those without disease, and a recent systematic review concluded that there was only limited evidence that statins were cost-effective in primary prevention, urging caution regarding their use in people at low risk.

This attitude contrasts with the proposal to administer a ‘Polypill’ containing a statin, three antihypertensives, folic acid and aspirin to everyone >55 years of age, regardless of their risk status, in the expectation that this will reduce cardiovascular events by 80–90%. The influence of apoE polymorphism on CHD risk in 14 published studies was analysed by Wilson et al., who found that possession of an ε4 allele was associated with a 26% increase in risk compared with individuals homozygous for ε3. Another very recent study involving over 10 000 control subjects found that the frequency of ε4 homozygotes decreased from 2.7% in those below the age of 60 years to 0.8% in those >85 years of age, the corresponding values in individuals with an ε3/4 genotype being 26.8% and 17.5%, respectively. Increased mortality from CHD and Alzheimer’s disease seems the most likely explanation for the observed decrease in the frequency of ε4 carriers with increasing age.

The interaction between apoE genotype and statin therapy was examined in a substudy of the Scandinavian Simvastatin Survival Study (4S). This showed that the risk of death among myocardial infarct survivors with an ε4 allele was more than...
twice that of non-carriers and that this excess risk was abolished by treatment with simvastatin. The corollary of the latter observation is that by offsetting the increased cardiovascular risk and thereby increasing life expectancy, statins might increase the chances of ε4 carriers developing Alzheimer’s disease—unless they also mitigate the risk of the latter.

**Statins and dementia**

Case control and prospective studies have suggested that statins decrease the risk of Alzheimer’s disease by ~40%. The Rotterdam study found that this protective effect was exerted irrespective of whether the statins used were lipophilic and crossed the blood–brain barrier or were hydrophilic and did not, which is counterintuitive. In contrast to these observational studies, an updated Cochrane review of two double-blind randomized, placebo-controlled trials in people at risk of dementia, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) and the Heart Protection Study (HPS), found no evidence that statins, whether hydrophilic or lipophilic, can prevent dementia. A more recent analysis of PROSPER showed that administering pravastatin to men and women aged 70–82 years had no effect on the decline in cognitive function with age and it was concluded that giving statins to the elderly to prevent cognitive decline is a futile exercise. This conclusion has subsequently been confirmed by the negative outcome of randomized, double-blind trials of simvastatin and atorvastatin in subjects with mild to moderate Alzheimer’s disease.

**Implications for public health**

If one accepts the evidence that inheritance of the ε4 allele increases the risk of both CHD and Alzheimer’s disease and that statins mitigate the risk of the former but not the latter, this raises important issues. Treating ε4 carriers with statins has been shown to reduce their mortality but, by improving life expectancy, this would increase their chances of developing Alzheimer’s disease, which are already greater than the remaining 70% of the population. The extent to which this might occur would be enhanced if a statin-containing Polypill was administered to everybody >55 years of age, which is anticipated to increase life expectancy by 11–12 years. This suggests that until such time as Alzheimer’s disease can be treated or prevented the present policy of prescribing statins only to individuals with or at high risk of cardiovascular disease (>20%/10 years) should be maintained.

**Figure 3.** Projected number of hospital admissions for heart failure in men and women over the age of 45 years in England (based on data in BHF Coronary heart disease statistics: heart failure supplement, 2002 edition at www.heartstats.org).

Another debilitating disorder possibly influenced by preventive strategies is heart failure, a common consequence of CHD. Although statins may postpone its onset they appear to be ineffective once the condition has become established. Recent estimates suggest that heart failure affects even more people in the UK than dementia and, like the latter, its prevalence seems to be increasing although it differs in that males are affected more than females (Figure 3). The annual cost to the NHS of treating both these disorders runs into billions of pounds.

Whether existing constraints on screening for apoE genotype should be maintained is questionable. For example, a case could be made for screening people in their mid-sixties with a family history of Alzheimer’s disease, for whom knowing their apoE genotype might influence personal decisions on issues affecting their future. Even more pertinent is the need to identify cognitively normal individuals at high risk who could benefit from therapeutic interventions when these become available, as it is hoped they eventually will.

**Acknowledgements**

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References