A life-course approach to the aetiology of late-onset dementias

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Substantial progress has been made in the understanding of the neurobiology of dementias, but comprehensive causal models are not available. Genetic and environmental factors probably interact to determine vulnerability to the dementias. The life-course approach to age-related diseases, when systematically applied to the dementias, provides opportunities to identify the nature and timing of environmental contributions. We discuss the relevance of the fetal origins of adult disease hypothesis to the dementias. Associations between the dementias (most often described as Alzheimer's disease) and ischaemic heart disease, obesity, hypertension, hyperlipidaemia, and non-insulin-dependent diabetes mellitus are set against associations between dementias and childhood intelligence, low educational attainments, low socioeconomic status, occupation, and lifetime dietary history. Biological mechanisms that explain how fetal development might influence the risk of adult disease may be relevant to many age-related diseases including the dementias and, possibly, to the biology of ageing.

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Introduction

Gene–environment interactions in dementias

The amyloid hypothesis continues to provide the most useful model of Alzheimer's disease (AD) aetiology.[1] Although the current focus on molecular approaches to AD has been worthwhile, many clinical scientists believe that AD is best explained by interactions between environmental and genetic factors, this explanation is consistent with a major causal role for non-inherited factors in age-related disease. The ultimate strategy will be to discover interventions to prevent the diseases of old age, including dementia syndromes, by combining genetic and environmental methods of research.

Life-course approach

A life-course approach considers factors that act during development and ageing, which might influence disease onset. It aims to identify periods (so-called critical periods; panel) during which an individual is at greatest risk of damage if exposed to a putative risk factor acting alone or in combination with other factors. The life-course approach to common diseases of late onset has not yet been applied to AD.[2,3] However, if done so, it could help disentangle the genetic and environmental factors that contribute to differences in dementia incidence. There are few studies on the possible developmental origins of stroke, hypertension, and ischaemic heart disease (IHD), which are factors associated with increased dementia risk, even though models of AD onset suggest that there are important antecedents acting from conception.[4] Life-course methods seek to identify when exposures have their greatest effect and how accumulation of exposures could have additive effects over the life course. Exposures are not necessarily independent: insults can be inter-related, or exposure to one factor might increase the chance of subsequent exposure to another and so set off a chain of events leading to disease. Ben-Shlomo and Kuh[5] have reviewed key conceptual issues that are basic to the life-course approach and of much relevance to the dementias.

Panel: **Fetal source of late life pathology**

Programming

This term is used to describe fetal adaptive responses to a suboptimum intrauterine environment that lead to lasting, irreversible, adverse consequences for the adult. These consequences may lead to structural changes in specific organs or the dysregulation of physiological regulatory systems, but these changes are not invariable.

Critical periods and imprinting

Early undernutrition can induce permanent impairment of growth, whereas later undernutrition produces only a temporary setback. When a metabolic system is permanently changed by early undernutrition, the phenomenon is termed metabolic imprinting. The recent term developmental plasticity is applied to disease-relevant metabolic changes and sometimes subsumes these interrelated processes.

Ageing and dementia

AD lies within a heterogeneous domain of age-related dementia syndromes that merge with lesser forms of cognitive decline. Precise boundaries between AD and other common dementias are poorly defined, and the specificity of any environmental risk factor is unknown. Likewise, the relation between ageing and dementia syndromes is unclear. Dementias could be age related, developing alongside brain changes that accumulate over time. Alternatively, dementias could be age dependent, and rely intimately on biological ageing to progress. Shared environmental risk factors could imply a pathogenesis common to many dementia syndromes, or susceptibility shared between most dementias such that an environmental contribution to dementia risk might act by increasing rates of normal brain ageing rather than hastening a dementing process (figure 1).

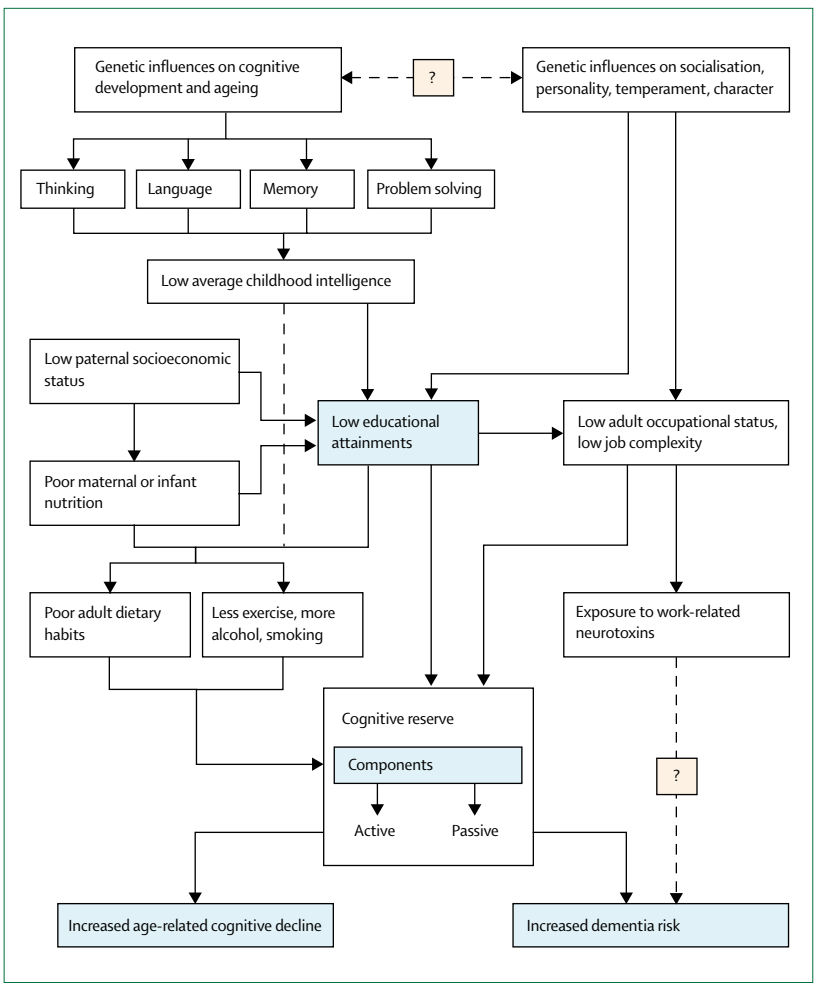

Figure 1: **Environmental influences on cognitive development and age-related cognitive decline**
The directional arrows are shown as influences on progression to decline or dementia. This progression is mediated through an hypothesised cognitive reserve, also shown in the lower part of the figure. The possible contributions to progressive age-related cognitive decline of accelerated ageing are not shown, but are discussed in the text.

Social neuroscience and the ageing environment

Social neuroscience connects social, psychological, and neurobiological processes that are relevant to understanding how environmental factors contribute to late-onset dementias. We propose a scheme of neurobiological, social, and psychological factors that create a cognitive spectrum ranging from successful cognitive ageing to the dementia syndromes, including AD (figure 2). The many underlying issues were set out by the US National Research Council[6] in their assessment of research approaches to the ageing mind, which showed how ageing neurons influence cognitive structures and processes, with a net result modified by the behavioural context within which elderly people seek to adapt. The ageing brain could also possess the potential to adapt itself in response to intrinsic brain ageing and to modify its environment. An environmental association with brain ageing and dementia might exemplify reverse causality (eg, cross-sectional nutritional studies in late life in which dietary choices reflect social and cognitive change of ageing, and not vice versa).

Fetal origins of adult disease

The life-course approach includes all environmental influences on development and ageing. The fetal origins of adult disease (FOAD) hypothesis proposes causal associations between a disadvantageous early fetal environment (indicated by low birthweight for date) and later IHD, hypertension, obesity, and insulin resistance. Support for the FOAD hypothesis comes from associations between historical infant or neonatal mortality rates and rates of diseases (such as hypertension and stroke) in adults at the same time in the same area.[7] Relations between disease incidence and neonatal mortality led to the hypothesis that maternal health was a possible source of these differences. Many international comparisons have established restricted early growth as a correlate of increased risk of IHD, hypertension, impaired glucose tolerance, non-insulin-dependent diabetes mellitus (NIDDM), and obesity. A focus of current work on the FOAD hypothesis is to understand how fetuses can be programmed by suboptimum intrauterine environments (panel). These later responses are made at molecular, cellular, metabolic, neuroendocrine, and physiological levels relevant to individual differences in risk of adult disease, and, possibly, to ageing.[8,9]

Hales and Barker[10] postulate that the underlying mechanisms are adaptive to a later, poor nutritional

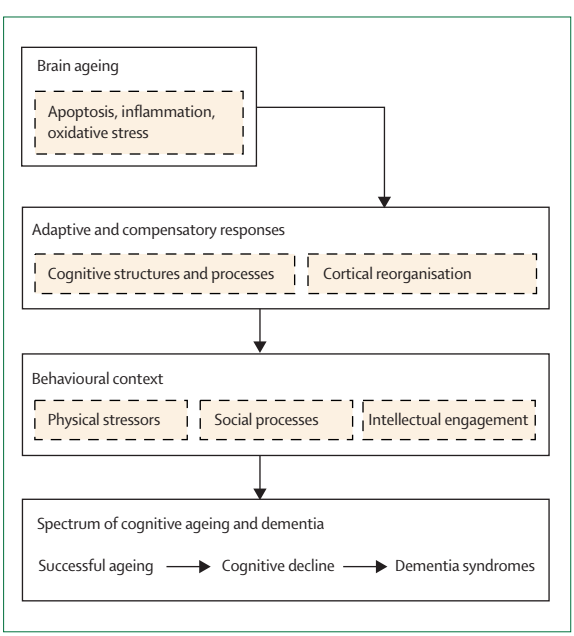

Figure 2: **Multiple levels that modify the clinical expression of dementia**
A much simplified summary of underlying brain changes (including compensatory responses) within which dementia syndromes arise. The contributions of health, social support, personal control of lifestyle or occupational demands on cognitive function in late life are left unspecified under the broad term of behavioural context.

environment, which is predicted by poor maternal nutrition. They propose that when the intrauterine environment is deficient, the fetus can make an adaptive response by favouring the growth of critical body organs while denying others. Mismatching between the fetal and adult nutritional environments is thought to have a major influence on the pathogenesis of the metabolic syndrome.[11] From a psychosocial perspective, the consequences for adult health of abnormal fetal development predict that, in addition to the ill-effects of these intrauterine conditions, children from poorer backgrounds are more likely to receive an energy-dense but nutrient-poor diet, and to be exposed to passive smoking, inferior medical care, and fewer educational opportunities. This combination of fetal and childhood adversities can, in turn, lead to fewer job openings, longer hours of work, limited choices for recreation, and, possibly, to greater exposures to toxic hazards at work.

Associations between adult diseases and dementia

In the next three sections we descibe the evidence for disease associations with dementia. These associations did not define necessary preconditions for the development of dementia. Instead, they point to shared risk factors present in early life that may lead to either dementia or the metabolic syndrome, or both (figure 3).

Cardiovascular disease and hypertension

The FOAD hypothesis arose from ecological studies of associations between infant mortality and incidence rates of adult IHD in the same geographical areas of England and Wales.[7] Methodological concerns were countered by large international studies that followed up individuals into adulthood.[12,13] The association between increased IHD mortality and lower birthweight became widely accepted,[14–17] although twin studies were less convincing.[18] Critics of the strength and directness of the association have questioned the role played by the development of obesity in those of low birthweight and its direct contribution to the pathogenesis of IHD.[12] There are now many excellent comprehensive accounts of this topic, leaving little doubt of an inverse relation between low birthweight and raised systolic blood pressure. However, as sample sizes have increased, the strength of the association is less than initial estimates.[19–21]

Many longitudinal studies, started in the 1960s and 1970s, began to reveal long-term associations between risk factors for IHD, and IHD and subsequent dementia nearly 20 years later. Most studies supported a positive association between systolic blood pressure and incidence of AD in old age,[22–25] but some did not.[26] The epidemiological evidence suggests that relations between blood pressure and AD and between blood pressure and cognitive ageing are not simple, and are probably best represented by a J-shaped curve by which low blood pressure is linked to later AD and higher blood pressure to increased risk of atrial fibrillation, embolic stroke, and vascular dementia.[27] When other risk factors for atherosclerosis are included in the prediction of dementia, there are positive associations between these and later AD.[28]

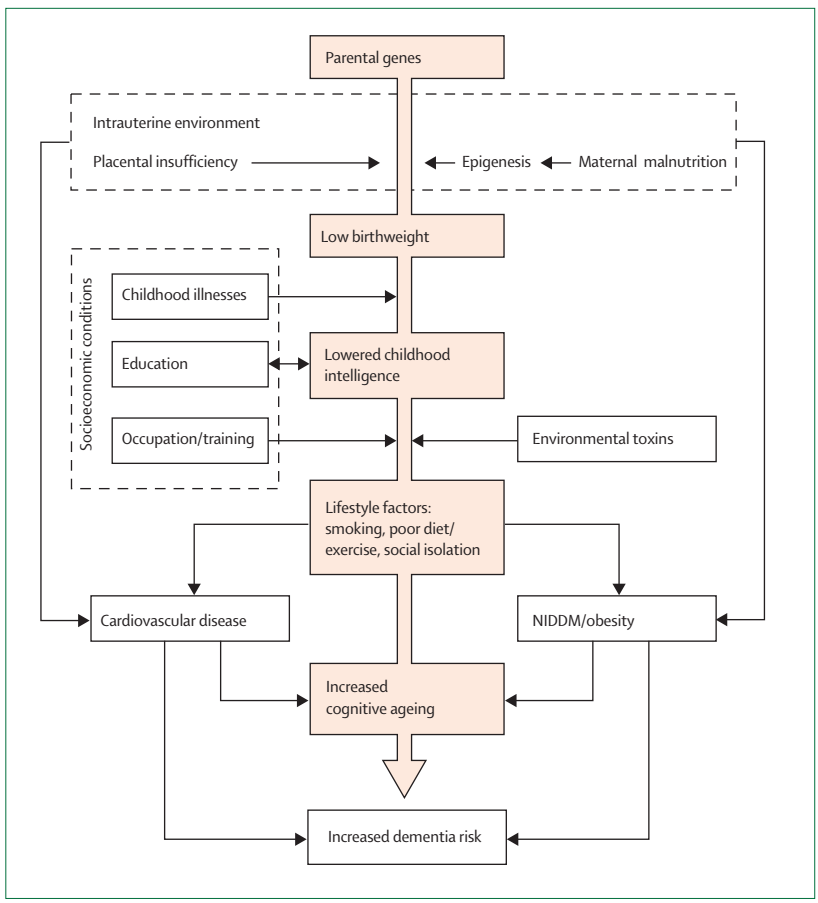

Figure 3: **Summary of possible associations between adult diseases and the risk of dementia**
Pathways are shown by directional arrows between a malnourished intrauterine environment and an increased risk of cognitive ageing and progression to dementia. Factors present from early life (figure 1) are shown in the upper part of this figure. These contribute to the risk of suboptimum cognitive development, fewer learning opportunities, and poor lifestyle choices. These factors precede the clinical onset of cardiovascular disease, non-insulin-dependent diabetes mellitus (NIDDM), and the metabolic syndrome. The risk of these diseases is associated directly with impaired fetal nutrition. There are alternate pathways from fetal malnutrition to increased cognitive ageing and dementia. Low average childhood intelligence is a major influence on lifestyle choices, educational attainments, and occupational opportunities, and, downstream from these, on morbidity and mortality from cardiovascular disease, NIDDM, and metabolic syndrome.

Non-insulin-dependent diabetes mellitus

Low birthweight is associated with impaired glucose tolerance and NIDDM in later life.[29–32] Craft and Watson[33] reviewed the actions of insulin in brain ageing and AD, addressing the specificity and generalisability of insulin's diverse roles. In normal brain function, insulin seems to be involved in memory formation or retrieval, or both. These actions seem to be independent of the global effects of insulin on neuronal glucose metabolism, but there may be region-specific

differences. In early AD, hyperinsulinaemia and reduced efficiency of insulin-mediated glucose suggest that some form of insulin resistance is present in AD.[33–35] Epidemiological investigations of dementia and NIDDM show that both these conditions are highly prevalent in elderly people and often co-exist.[36–44] Inclusion of NIDDM with other cardiovascular risk factors in studies of dementia suggests that complex interactions exist between NIDDM with hypertension[33,37] and the *APOE* genotype.[43] The underlying biology seems intricate with likely interactions between increased formation of cytokines and advanced glycation end-products eventually triggering oxidative stress, amyloidogenesis, and neuronal death.[44]

The metabolic syndrome

Insulin resistance (with or without glucose intolerance), raised blood pressure, raised triglyceride concentration, small LDL particles, low HDL cholesterol, central or abdominal obesity, and pro-thrombotic and pro-inflammatory states comprise key elements of the metabolic syndrome.[45] Because these factors are so firmly linked to the risk of vascular disease, they broadly reflect the net effects of cardiovascular risk on progression to AD. Their involvement with the so-called pro-inflammatory phenotype and increased risk of atherosclerosis supports this interpretation.[46,47] Data from a follow-up study of elderly people, beginning in old age, have suggested that increased risk of cognitive decline is mediated by increased activation of inflammatory processes.[48] There is also some support for increased inflammation in AD. Weaknesses in the argument that the metabolic syndrome is linked to AD are seen in the finding that hyperlipidaemia does not invariably accompany AD.[49] More complex interactions between cardiovascular risk factors seem to be at work. In brain atrophy studies, homocysteine and folate concentrations, hyperlipidaemia, hyperglycaemia, and hypertension seem to contribute to cognitive decline and progression to dementia.[50,51] Intensive, multifactorial longitudinal studies will be needed to unravel the distinct contributions of these variables.

Life-course factors and late-onset dementia

From fetal malnutrition to dementia

The FOAD hypothesis is of value when applied to some age-related diseases. However, the question remains as to whether this hypothesis can be usefully applied to dementia or, specifically, to AD (figure 4). There seem at least three plausible pathways from FOAD to dementia: (1) FOAD acts directly on brain during embryogenesis making dementia more likely; (2) FOAD acts indirectly on brain through a pathway that leads to adult cardiorespiratory disease and hyperglycaemia, and then to dementia in old age; or (3) FOAD acts by increasing rates of ageing causing age-dependent disorders to arise prematurely.

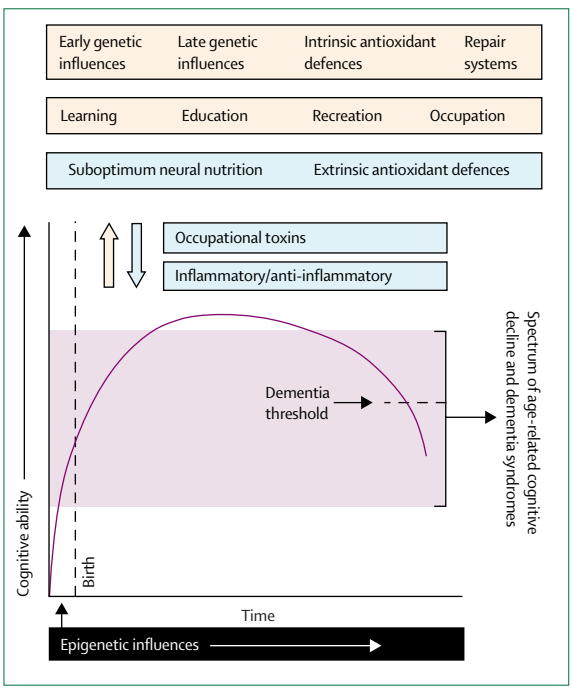

Figure 4: **Life chart of environmental contributions to dementia**
The approximate temporal relations of major environmental influences on the development of late-onset dementia are shown.

Birthweight, cognitive development, and brain ageing

A newborn child is defined as small for gestational age when it is more than 2 SD below the weight expected in the reference population. Babies with low birthweight are at increased risk of neurological abnormality, including failure to attain optimum mental ability in childhood. However, many babies of low birthweight are of short gestational age and subject to many harmful influences. When studies are corrected for gestational age, there is a slight but significant positive association between birthweight and childhood cognitive ability.[52] This association is largely independent of parental social class. No studies on birthweight and brain ageing were identified for this review.

Childhood socioeconomic status and dementia

In 1116 elderly residents of Alameda County (California, USA), self-reported cognitive function was lower than expected in those who had experienced sustained economic hardship.[53] This association remained after adjustment for age, sex, and prevalent disease. In a community-based case-control study, larger family size and less affluent, urban residence were associated with increased AD risk.[54] In a study of 496 men (age 58 years or 64 years) from eastern Finland, parental socioeconomic status and sons' cognitive ability in late adulthood were linked even after adjustment for education.[55] A case-control study of 239 patients with AD found that AD cases were more likely to have experienced a disadvantaged childhood than controls,

and that this effect was most marked in the presence of the apolipoprotein E ϵ4 allele (*APOE* ϵ4).[56]

Studies of childhood deprivation and adult disease are confounded by marked intergenerational continuities in hardship.[57] This is relevant when considering those social processes that influence the risk of detection of clinical AD; cognitively impaired individuals with the greatest social resources may be less likely to present to services.[58] Everson-Rose and colleagues[59] reported that in a population-based sample of 4398 people aged older than 65 years, socioeconomic status in early life was weakly related to mental ability in late life, but not to cognitive decline. Support for this finding comes from the Religious Orders Study,[60] which found no association between childhood social circumstances and subsequent cognitive decline or AD in a prospective study of 859 elderly Catholic clergy. On the basis of these two well-designed studies, the claim that social advantage protects against AD seems unwarranted.

Studies of the geographical distribution of birth place in AD may be relevant, because area of residence is linked to socioeconomic status. There are some consistent findings from the UK that incident dementia is more likely to be detected in urban than in rural settings.[61] In a study of early-onset AD in Scotland, a non-random distribution of AD cases by place of birth and clinical detection was found, with clusters of cases in some deprived urban areas linked to coal mining.[62] Kinship did not explain this clustering.[63] These findings suggest that during the relevant birth epoch (1910–1925), non-genetic factors contributed to early-onset AD. However, there is no worldwide consistency in these data; for example, in Quebec, Canada, late-onset AD was more common in rural areas than in urban areas.[64] Increased paternal age, which is a marker for lower birth order and dilution of parental care,[65] has been reported as a risk factor for early-onset AD,[62,66] but not late-onset AD.[67–72] Differences between studies are probably attributable to sampling, power, and selection of controls. In summary, there are some ecological studies that suggest a slight association between a disadvantaged childhood and AD, but the largest cohort study[60] did not support this relation. Parental age studies are consistent with this latter view.

Childhood mental ability and AD

Mental ability is a life-long trait that shows substantial stability. The nature of the association between this trait and individual differences in rates of cognitive decline with age and progression to dementia is uncertain. Childhood mental ability scores are rarely available for individuals now at risk of late-onset dementia. The Nun Study[73] examined essays written by novices in US convents who were aged about 22 years, and showed that linguistic density (a proxy for intelligence in early adulthood) could be linked to a lower risk of dementia in old age. Whalley and colleagues[74] compared differences in childhood intelligence scores between controls and two groups of dementia patients: group 1, all Scottish early-onset dementia cases born in 1921;[75] group 2, a local sample of late-onset dementia. Childhood intelligence did not distinguish between children who later developed early-onset dementia and locality-selected matched controls who did not appear as cases in a national survey of early-onset dementia. However, childhood intelligence scores were lower in those who developed late-onset dementia and local people at age 64 years but who had not developed dementia before age 77 years. When biennial comparisons were made, intelligence differences were more common in dementia cases with onset after age 72 years. The relation between dementia risk and childhood intelligence was present across the range of intelligence and was not confined to those with low childhood scores.

Although the general conclusions seem safe, there are caveats. Separately, it was shown that functional independence and health status in old age is, in part, linked to childhood mental ability.[76] The possibility that cognitive ageing is slower in people of higher trait ability (the differential ageing hypothesis) has been tested in several studies but with inconsistent results. For example, Christensen and Henderson[77] found no differences in rates of cognitive decline between elderly academics and manual workers, with the academics maintaining their advantages in old age. However, Deary and co-workers[78] reported a contrary finding, showing that higher initial ability (estimated by the National Adult Reading Test) was associated with slower rates of decline. Differences between these two studies are probably attributable to sampling methods: Christensen and Henderson[77] sampled from the extremes of ability distribution, whereas Deary and colleagues[78] obtained a near-normal population sample.

The burden of dementia alone is possibly insufficient to cause an individual to be recognised as a dementia patient; the additional problems of poor health and limited functional independence in late life, which can be linked to lower childhood mental ability, might be required to cause a dementia threshold to be crossed. Seen in these terms, the clinical dementia syndrome would reflect a decompensation of brain mechanisms that adapt to damage caused by disease and ageing. Against this can be set the competing causes of premature death, many of which are associated with lower childhood mental ability.[79] Selective removal of these individuals from the population at risk of late-onset dementia could partly offset the contribution in late life to health status linked to lower childhood intelligence. Studies of this type are unusual, but will become feasible as individuals grow older in continuing longitudinal studies of cognitive ageing for whom childhood mental ability data are available.[80,81] So far, there is evidence from just two relevant studies that lower childhood intelligence is associated with AD. Of

course, childhood intelligence scores are related to, and possibly determined by, complex processes that include childhood socioeconomic status (figure 1). In this context, an association between lower childhood intelligence and greater AD risk may support a link between AD and lower childhood socioeconomic status.

Education

There are reported associations between a restricted education and AD.[82] Those with lower educational attainments do less well in late adulthood on cognitive tests, and their lower education may be associated with late-onset AD.[83–85] The strength of the association between dementia and lower educational attainments is inconsistent. For example, in the predominantly well-educated Framingham study population,[86,87] probable AD was detected after the 13-year and 22-year follow-up; demented patients did not differ in their level of education from non-demented individuals. The view that lower educational attainments predispose to dementia, although widely held, was further weakened by Letenneur and colleagues,[88] who completed a pooled analysis of four European population-based studies. The statistical model allowed adjustment for some factors believed to be positively associated with dementia (smoking, sex, and vascular disease). Compared with those who received the most education, women with lower and middle levels of education had greater risks of dementia (lower educated, odds ratio 4·3, 95% CI 1·5–11·9; middle educated, odds ratio 2·6, 95% CI 1·0–7·1). Among men, the odds ratio for dementia did not distinguish between groups by level of education (approximately 1·0). This marked difference between men and women suggests that the reported association between lower educational attainment and dementia may be attributed to some other unknown factor. Gatz and colleagues[89] examined 143 twin pairs who were discordant for dementia, and found that the odds ratio for AD was greater in the least-well-educated twin, suggesting that education and its lifelong correlates could be linked to dementia.

The prevailing model seems secure: there is a positive contribution of education to a hypothetical cognitive reserve that is available to withstand the burden of neurodegenerative pathology,[90,91] and which accounts for individual differences in cognitive impairment in the face of neuropathology that is similar in nature and extent.[92] However, there are at least two large-scale studies that took account of relevant confounders and did not support an overall significant association between lower education and dementia. Education is also an indicator of socioeconomic status, and there are well established health inequalities related to lower socioeconomic status.[93] Inequalities in overall mortality are associated with lower educational attainment and may even increase in old age.[94] The reported association between lower educational attainment and increased dementia, may therefore not be specific for dementia but represent an alternative pathway from social and material disadvantage to increased incidence of age-related diseases, including dementia.

Occupation and lifestyle factors

Occupational attainment is closely linked to both education and childhood mental ability (figure 1), suggesting it may be difficult to establish whether occupation in mid-life (age 40–65 years) influences the incidence of AD in later life, independent of either education or childhood intelligence quotient.[82,95] One hurdle is that many studies lack measures of childhood intelligence. The Scottish Mental Surveys of 1932 and 1947 almost uniquely provide national surveys of childhood mental ability of schoolchildren born in 1921 or 1936, and have yielded valuable insights into this question.[96] A follow-up study of children born in 1921 to age 81 years examined the influence of occupational attainment, education, and head size.[91] Independent of childhood intelligence, duration of childhood education, and level of occupation (adult socioeconomic status) influenced cognitive performance at age 79 years.[91]

Occupation itself might also influence the incidence of dementia. The cognitive complexity of work may be protective,[97,98] although high occupational attainment or increased social resources may make it harder to detect AD.[58] In addition, low adult socioeconomic status (which reflects low occupational attainment) may increase AD incidence, and exposure to neurotoxic agents in the workplace, such as organic solvents, may also be associated with AD. Industries such as lead smelting may produce environmental contamination if badly managed and so expose workers' families to lead, a well-known neurotoxin. Experimental support for the hypothesis that low-level lead exposure in childhood might be associated with AD in later life[99] comes from animal studies that have shown that rat pups exposed to lead show upregulation of amyloid precursor protein (APP) mRNA in later life and increased concentrations of APP.[100] Although exposure to occupational neurotoxins may simply be markers for other factors known to be associated with AD, such as low childhood intelligence, the possibility that such exposures contribute to the incidence of AD in later life cannot yet be excluded.[101] A major challenge in studying the role of neurotoxins in AD is the reconstruction of early-life exposures in a disease that generally presents late in life; the lack of valid biomarkers of long-term exposure to most neurotoxins hinders research in this area.

Diet and lifetime nutrition

Diet, in terms of the adequacy of both energy and specific nutrients, is possibly the best studied environmental influence on brain development and ageing. The influence of different aspects of diet is likely to vary over the life course. In early life, long-chain polyunsaturated fatty acids (especially eicosapentaenoic

and docosahexaenoic acids) are required in large amounts for the rapid brain growth that occurs in the third trimester and postnatal period. Randomised trials in premature infants have shown that long-chain polyunsaturated fatty acids can increase cognitive function at age 7·5–8·0 years.[102] This is consistent with long-term follow-up studies that found that formula feeding was associated with lower cognitive ability in mid-life,[103] and a greater cognitive decline in later life, particularly in those who were below average birthweight.[104] The adverse effects of poor nutrition in early life may be amplified by overnutrition in adult life, as seen in a study of blood pressure.[105] There is some evidence that energy intake in adulthood may be related to subsequent AD[106] or cognitive impairment,[107] consistent with long-term follow-up studies that have found that overweight in mid-life (40–65 years) is associated with increased later AD,[108,109] possibly because of the metabolic sequelae discussed above.

In late adult life, several components of the diet could influence the risk of AD by protecting against tissue damage. For example, antioxidants such as vitamin C, vitamin E, and selenium may protect against damage from amyloid-triggered release of reactive oxygen species.[110] Studies of antioxidant vitamin intake, blood concentrations of vitamins, or supplement use generally support the possibility of a protective effect for these nutrients,[111–114] although some have found no association.[115] B vitamins such as vitamins B6, B12, and folate, which are involved in the conversion of homocysteine to methionine, reduce the risk of hyperhomocysteinaemia, which has been linked to damage of the cerebrovascular epithelium.[116] Many studies support an association between homocysteine concentrations and AD,[117,118] but some do not,[119,120] and a recent study unexpectedly found that high folate intake was associated with a faster rate of cognitive decline.[121] A recent review of the role of dietary factors in AD concluded that, although there is some evidence for an association between diet and AD in adults, the data are mainly derived from observational studies and inconsistent.[122] Although some variation between studies may arise from differences in nutrient intake between populations, a major limitation of all types of observational studies of diet is the possibility of confounding variables, such as socioeconomic status[123] and other behavioural characteristics that influence both dietary intake and cognitive function. Another possibility is that reverse causation, whereby poor cognitive function itself increases the risk of poor nutrition,[124] cannot be excluded in studies of older adults. Intervention studies should provide more robust evidence for nutritional effects, but to date few have been done, and most are of short duration in older adults, which may explain the largely negative results.[125–127] As an alternative, mendelian randomisation, which exploits differences in nutritional status that result from common genetic polymorphisms,[128] may offer new possibilities for exploring life-long effects of nutritional factors on cognitive function.

Biological mechanisms

This review has examined two groups of associations with late-onset dementia. Links are stronger between the first group (cardiovascular disease, NIDDM, and the metabolic syndrome) and age-related dementia, and weaker between the second group (low average childhood intelligence, education, and socioeconomic status) and late-onset dementia. The main issues are whether there are plausible biological mechanisms that explain how developmental exposure influences brain health towards the end of life and whether one or several pathways are needed to explain these associations.

Crucial experiments are lacking on the effects of altering the early life conditions on the ageing phenotype, although there are tantalising clues from the effects of life-long caloric restriction.[129–131] Studies informative to dementia will concentrate on exposures that both modify the development of early neural networks and predict differences in ageing.[132] In this context, the role played by the nervous system on the regulation of lifespan seems most relevant, not least because of the brain's central role in insulin-like signalling and subsequent effects on ageing in mammals.[133]

Possible pathways from adverse developmental exposures to dementia include a chain of events triggered by fetal malnutrition, leading to low birthweight, low average childhood intelligence, low educational attainments, low occupational status, and an unhealthy life style. Acting in combination, the long-term outcome is for these factors to predispose to many age-related diseases including cardiovascular disease, NIDDM, the metabolic syndrome, and dementia. Second, fetal malnutrition may trigger two or more distinct pathways (multiple hits), one affecting neurodevelopment and others perturbing maturation of physiological regulation of blood pressure and glucose metabolism, and thus predisposing to obesity. As yet, there are too few data to distinguish between these pathways, although inflammatory processes may be important.[134] A third possibility, that fetal malnutrition leads to accelerated ageing, is largely unexplored, but might be sufficient to explain proposed associations between fetal development and age-related diseases.

Many plausible biological mechanisms are proposed to explain the association between fetal disadvantage and late-onset disease. Their investigation is only just beginning and has focused largely on the early adult environment. Pathways are also proposed from the intrauterine environment through epigenetic mechanisms involving hypomethylation of key regulatory genes involved in glucose metabolism, although imprinting of other genes is suspected (panel). A single case of hypomethylation of the amyloid

precursor gene in AD is known,[135] and this may prove relevant to understanding other neurodevelopmental and age-related neurodegenerative disorders.[136–138]

Therapeutic pessimism greets the many studies that link childhood adversity to late-onset disease. The reality may be more promising than this. Some epigenetic effects, once identified, may be open to later modification.[139,140] If increased incidence of dementia with age relies on underlying intrinsic ageing processes and these are influenced by fetal development, it is reasonable to assume that some of this developmental contribution is shared with other age-related diseases.

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Authors' contributions

LJW wrote the first draft of the paper. FDD wrote the section on occupational and environmental factors. GM wrote the section on diet, nutrition, and AD and contributed to the section on fetal origins. GM and FDD revised the paper.

Conflicts of interest

We have no conflicts of interest.

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