Obesity

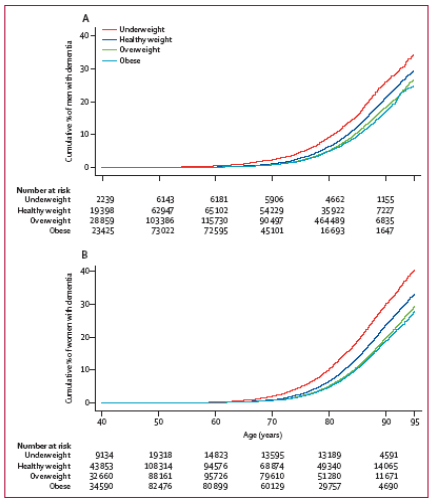
You only need to walk down the high street or wander around the local supermarket to realise the population is getting fatter. It seems to be across the board, children, young adults, the middle aged and some elderly people on mobility scooters, since by that time and a lifetime of obesity, their hip joints and knees are knackered with all the excess weight. By the appearance of some obese people they have certainly worked hard at it over the years - you only have to count the number of booze and crisp aisles in the supermarkets compared to the number of fresh vegetable aisles to get the picture. Apart from all the health issues this fat promotes, cardiac, diabetes, joint wear (orthopaedics) and mental issues, it is reasonable to ask whether an excessive BMI influences the risk of dementia. It seems the answer is not so clear cut.

Typical BMI (weight ÷ height^2) categories are <20 kg/m^2 for underweight; 20–24·9 kg/m^2 for healthy weight; 25–29·9 kg/m^2 for overweight and ≥30 kg/m^2 for obese. Some studies use 18.5Kg as the underweight point. Body mass index (BMI) provides an indirect measure of adiposity, and is strongly correlated with total body fat tissue. Adiposity may influence or be influenced by brain structures and functions, which may be involved in dementing processes. Both obesity and dementia are complex genetic and lifestyle-related disorders.

An understanding of the association of BMI with dementia is a public health priority because the number of people affected by dementia worldwide is expected to rise from 30 million in 2010, to 106 million in 2050. The prevalence of obesity is also increasing worldwide. and in England, doubling between 1993 and 2010. The global burden of obesity in 2008 was estimated to be 1·46 billion overweight adults (BMI ≥25 kg/m2) and 502 million obese adults (BMI ≥30 kg/m^2). However, the association between BMI and risk of dementia is far from clear. Several studies report that being overweight (BMI ≥25 kg/m^2) in mid-life is associated with an increased risk of cognitive impairment and dementia in later life (3,6,8,14) whereas being overweight in later life might be associated with reduced dementia risk (7). This situation has been cited as another example of the so-called obesity paradox (7). Furthermore, low BMI (<20 kg/m^2) is associated with an increased risk of dementia in short-term studies of elderly people (7) and weight loss reportedly occurs before a diagnosis of dementia (5). Inconsistencies might arise because many studies have been quite small with short follow-up durations. A concern for interpretation of the significance of BMI as a dementia risk factor is the lack of consistent adjustment for health and demographic variables as well as factors such as diet, smoking, alcohol and physical activity. It is possible that these other factors interact with or are indirectly influencing the association between obesity and dementia risk. For example, a high-fat, high-calorie diet may increase BMI and dementia risk independently, or affect dementia risk via BMI.

A database analysis of some 41,000 people from 1950 to 2009 who were evaluated for any form of dementia showed that in mid-life, underweight BMI, overweight BMI and Obese BMI were all associated with a risk of dementia in later life (1). Risks were highest for highest for underweight and obese BMI suggesting a U-shaped relationship between midlife BMI and dementia risk. Analysis conducted for men and women separately showed similar patterns to pooled analyses with a suggestion of stronger effects for women than men. For example, obese BMI in midlife was associated with a 3.08 times increased risk of AD for women and a 2.45 times increased risk for men.

One substantially larger study has reported an inverse association between BMI and dementia risk in both mid-life and later life. The strength of the association was quite constant even after 15 years of follow-up, including in people 40–55 years of age at the time of BMI measurement (2). These findings question the belief that obesity in mid-life is associated with an increased risk of dementia. Claims that reducing obesity in middle age could help to prevent dementia in older age might therefore be ill founded (1,3,4). If increased weight in mid-life is protective against dementia, the



reasons for this inverse association are unclear. Many different issues related to diet, exercise, frailty, genetic factors, and weight change could play a part. Factors postulated to explain the previously observed protective effect of increased BMI on late-life dementia include low late life blood pressure; high late life cholesterol levels; higher leptin levels; age-related regulatory changes in carbohydrate, lipid, or protein metabolism (5) and increased intake of vitamin E anti-oxidant and vitamin D.

The attached Figure shows the dementia risk as a function of age for various BMI levels (2). A relates to mean and B to women. These curve shapes are what you would generally expect to see for dementia risk as a function of age but plotted by BMI category.

One systematic review suggests that increased BMI is likely to be an independent risk factor for dementia (ie the association between the risk factor of primary interest and the disease outcome is statistically significant) Studies with appropriate exclusion of patients with dementia at the start, enough power, and appropriate adjustment of potential confounding factors support the association between increased BMI and dementia(16). Studies (6) that have younger participants at the start and longer follow-up periods showed even more significant association. BMI is an acceptable measure of body fat in the general population but among older individuals, BMI may underestimate adiposity because lean body mass is replaced by fat on aging. Hence the association of increased body fat to dementia may be weaker among the older participants who may have more body fat in spite of a low body weight. This also implies that the association of BMI to dementia may be more accurately assessed at midlife than in the older years (6). Women with increased BMI are at a greater risk for dementia than men.

Several potential biological mechanisms may explain an association between adiposity (body fat accumulation) and dementia. Firstly , higher BMI is associated with diabetes and vascular diseases, which are related to dementia risk (9). Even allowing for lifespan vascular diseases the association between high BMI and dementia remains significant suggesting that non-vascular pathways might play an important role in the adiposity-dementia association. Secondly, higher adiposity at midlife may reflect a lifetime exposure to an altered metabolic and inflammatory state. Adiposity is one component of the metabolic syndrome which has been related to cognitive decline (10). Further, adipose tissue is the largest endocrine organ and secretes inflammatory cytokines and growth hormones; some of them (such as leptin, interleukin-6, and C-reactive protein) may affect cognitive functioning. Leptin is involved in deposition of amyloid β, and plays a role in neurodegenerative process (11). Studies have reported that early life exposure to an imbalanced nutrition and disadvantaged social status are related to a greater risk of obesity in adult life (12) and dementia in late life (13). Early-life environmental and genetic factors may well contribute to the link between adiposity and dementia.

Finally it is worth considering the converse situation. Studies suggest that increasing **weight loss** per decade from midlife to late life is a marker for MCI and may help identify persons at increased risk for mild cognitive impairment (MCI). Mild cognitive impairment (MCI) is a preceding stage of dementia, approximately 5% to 15% of persons with MCI will progress to dementia per year (15). Therefore, the delay or prevention of MCI could also reduce the public health impact of dementia.

Results of a population-based elderly cohort study show that a higher rate of weight loss from midlife to late life and a lower weight in late life are markers of risk for MCI (15) in the elderly, representing a prodromal stage or an early manifestation of MCI. With regard to causal mechanisms, weight loss prior to cognitive impairment may be related to what has been termed *anorexia of aging*. While the direct cause of this anorexia is not clear, we speculate that the dysfunctional production of certain hormones (cholecystokinin, leptin, cytokines, dynorphin, neuropeptide Y, and serotonin) on dietary intakes and energy metabolism may lead to reduced dietary intakes that affect MCI risk. With regard to reverse causality (a reverse cause and effect), neuropsychiatric symptoms such as depression and apathy, which are predictors of MCI and dementia, may contribute to decreased appetite and weight loss prior to the diagnosis of these conditions.

The association of high midlife weight with MCI may involve effects of obesity on the brain through cerebrovascular disease and metabolic abnormalities (eg, glucose metabolism and insulin signaling). Obesity-related brain pathology is likely includes decreased blood flow ,neuronal injury and death, brain atrophy, cerebrovascular dysfunction, increased levels of β-amyloid precursor protein, increased tau expression, blood-brain barrier dysfunction, inflammation-related pathologies, and dysfunction of microglia and astrocytes (cells in the central nervous system)(16).

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