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The relationship between obesity and cognitive health and decline

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The relationship between obesity and cognitive impairment is important given the globally ageing population in whom cognitive decline and neurodegenerative disorders will carry grave individual, societal and financial burdens. This review examines the evidence for the link between obesity and cognitive function in terms of both the immediate effects on cognitive performance, and effects on the trajectory of cognitive ageing and likelihood of dementia. In mid-life, there is a strong association between obesity and impaired cognitive function. Anthropometric measures of obesity are also associated with reduced neural integrity (e.g. grey and white matter atrophy). Increasing age coupled with the negative metabolic consequences of obesity (e.g. type 2 diabetes mellitus) are likely to significantly contribute to cognitive decline and incidence of dementia. Stress is identified as a potential risk factor promoting abdominal obesity and contributing to impaired cognitive function. However, the potentially protective effects of obesity against cognitive decline in older age require further examination. Finally, surgical and whole diet interventions, which address obesity may improve cognitive capacity and confer some protection against later cognitive decline. In conclusion, obesity and its comorbidities are associated with impaired cognitive performance, accelerated cognitive decline and neurodegenerative pathologies such as dementia in later life. Interventions targeting mid-life obesity may prove beneficial in reducing the cognitive risks associated with obesity.

Obesity: Dementia: Cognitive performance: Cognitive decline

Ageing and cognitive decline

In 2011, 17·5 % of the European population was aged 65 years or older and this is expected to rise to 30 % by 2060[1]. The increasing life expectancy across the world necessitates urgent public health action aimed at preserving the physical and mental health status and autonomy of the elderly via optimal control of chronic diseases and a focus on the various dimensions of quality of life (physical, psychological, social). Ageing is accompanied, for a significant proportion of the population, by cognitive decline which is the primary risk factor for the development of neurodegenerative disorders, including Alzheimer's disease (AD)[2]. The 2015 World Alzheimer Report estimated 46·8 million cases of dementia in 2015 and projects that this number will double every 20 years[3], underscoring the magnitude of this problem in terms of social and economic aspects, including towering costs of disease management, caregiver burden, loss of income and loss of productivity for the patient and the caregiver, and palliative and terminal care. Therefore, preserving normal cognitive capacities for as long as possible, along with improving knowledge about the preclinical phase in order to identify and target at-risk asymptomatic individuals, are urgent public health challenges[4,5].

There is a genetic component to dementia[6]. ApoE is the strongest risk factor for late onset AD. ApoE encodes three common alleles (ε2, ε3, ε4). ApoEε4 is associated with increased AD risk in a cumulative fashion such that one ApoEε4 allele increases AD risk 3-fold, and

Abbreviations: AD, Alzheimer's disease; IGT, impaired glucose tolerance; MDP, Mediterranean dietary pattern; T2DM, type 2 diabetes mellitus; WHR, waist-to-hip ratio.

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two ApoEε4 alleles increase AD risk 12-fold. The presence of the ApoEε4 allele is associated with decrease in age at AD onset, whereas ApoEε2 is associated with decreased risk for AD and later age at onset. Other factors may also contribute to the development of dementia and factors which are modifiable require examination so that we can make health and lifestyle interventions to reduce the burden of dementia in the face of a globally ageing population.

Curative treatments or therapies aiming to at least decelerate cognitive decline are rather inefficient. At present, neuroscientists working in the field of AD indicate strong doubts that a cure will be found soon[7]. When significant cognitive loss has already taken place, the respective neuronal networks are likely irreversibly compromised and their replacement, if it were to become technically feasible, would not restore the individual's intellectual identity. Thus, prevention of cognitive decline is the only sensible approach to meet the challenge of an ageing and dementing population[7–9]. The onset of cognitive decline is evident from as early as 45 years of age with a 3·6 % decline in mental reasoning demonstrated in men and women aged 45–49[10]. Evidence of such early decline highlights the importance of promoting healthy lifestyles in middle age, at the latest, in order to slow the trajectory of age related cognitive decline.

A confounding factor is the rising prevalence of obesity in Europe[11], which is associated with impaired glucose tolerance (IGT), subsequent type 2 diabetes mellitus (T2DM) and low grade inflammation, culminating in metabolic syndrome, all of which are associated with cognitive impairment in the short- and long-term[12–15]. Therefore, obesity and its comorbidities are risk factors associated with impaired cognitive performance and cognitive decline.

Obesity and cognitive function

The relationship between obesity and an increased risk of mortality and somatic morbidity is well documented[16]. An association between obesity and cognitive health is receiving increasing recognition. Mid-life obesity is a significant risk factor for developing AD and vascular dementia in later life[17,18]. In addition to an increased risk of an accelerated trajectory of cognitive ageing (discussed later), evidence suggests early to mid-adulthood obesity may have an immediate detrimental impact on cognitive functioning.

A negative association between anthropometric measures of obesity (e.g. BMI, waist circumference) and a number of cognitive domains has been reported. For example, obesity is related to impaired performance on tasks of episodic memory. Verbal learning, indexed by delayed recall and recognition of words, is impaired in those with higher *v.* lower BMI[19,20]. Similar deficits are demonstrated for visual modality episodic memory tasks[21]. Impaired working memory performance has also been demonstrated in overweight and obese young adults compared with healthy weight controls[22]. However, some studies report no difference in memory performance between obese and non-obese individuals[23].

Performance detriments are additionally evident in non-memory related cognitive domains. For example, impaired psychomotor[19] and selective attention[24] performance have been reported in obese cohorts; although not consistently[25,26]. Performance decrements in the executive functions of concept formation and set-shifting, measured by performance on the Wisconsin card sorting test, are also shown in obese cohorts relative to normal weight comparison groups[27,28].

Decision-making impairments exist across disordered eating populations; for example, anorexia nervosa[29] and bulimia[30]. A number of studies have reported that decision-making performance is also altered in obese populations. Performance on the Iowa gambling task suggests morbidly obese individuals have a reduced capacity to maximise an immediate reward or programme a delayed reward[31]. Obese individuals also show impaired performance on additional tasks that require the delay of gratification (e.g. Delayed discounting task[32]). Impaired processing of inter-temporal choices may contribute to poor diet choices in obese individuals (e.g. an increased sensitivity to the immediate reward of consuming highly palatable, energy dense foods while discounting the negative health and metabolic consequences in the long term). Such suboptimal decision-making processing can be considered a significant risk factor in an obesogenic environment in which effortful control of energy intake is critical for the maintenance of a healthy body weight.

A negative relationship between obesity and cognitive performance has not been consistently found, both within and across cognitive domains. Inconsistency in the evidence may be due to the potential moderating influence of a number of obesity-associated comorbidities known to adversely impact upon cognitive performance. This includes T2DM, hypertension, hypercholesterolaemia and insulin resistance, which may co-occur in individuals. Two recent systematic reviews[33,34] of the effects of obesity on cognitive performance in adults (aged 18–65 years) concluded that while there is evidence of impaired cognitive function in obese populations, there is insufficient evidence to date to confirm that these impairments are independent of obesity-related comorbidities and demographic variables (e.g. age, education). This lack of clarity is largely due to many studies failing to adequately control for potential confounding comorbidities

Effects of obesity on the brain

Brain imaging studies suggest that obesity is associated with neural atrophy. Structural alterations in the neural architecture of obese individuals have been reported. For example, elevated BMI is linked to decreased brain volume[35], independent of age and morbidity[36]. Increased BMI is also associated with grey matter atrophy in the temporal, frontal and occipital cortices, hippocampus, thalamus and midbrain[37], and reduced integrity of white matter throughout the brain[38]. It is important to note that it is not always possible to

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disentangle the contribution of obesity to these structural impairments from the effects of ageing and obesity-related comorbidities (e.g. hypertension, metabolic oversupply/dysregulation). However, obesity can be considered a considerable risk factor for reduced neural integrity.

In addition to structural and morphological alterations in the obese brain, neural imaging studies show altered functional activity. This includes decreased regional blood flow to the prefrontal cortex in healthy adults with elevated BMI[39]. Significantly reduced functional activity in cortical areas associated with episodic memory (hippocampus, angular gyrus and dorsolateral prefrontal cortex) is associated with both obesity and insulin resistance[21]. Obese individuals also demonstrate lower working memory task related activation in the right parietal cortex[26].

Obesity has been associated with an increase in brain age, in respect of cerebral white matter atrophy, where the greatest degree of atrophy has been identified in middle-age, equating to an estimated increase in brain age of 10 years. Importantly, middle-age may represent a critical period for brain ageing, where vulnerability to obesity is particularly acute compared with later life[40]. Indeed, white matter atrophy has been identified as starting in middle-age[41]. The action of proinflammatory cytokines is a possible mechanism for these changes in white matter volume[40]. Adipose tissue secretes adipokines[42], manifesting either pro- or anti-inflammatory properties[43]. Importantly, in obesity, there is a reduction in adiponectin[44], which is known to protect against inflammation, cell proliferation and supports energy metabolism[45], and upregulation of other adipokines, leading to a chronic inflammatory state and metabolic disease[46]. Consequently, a host of microphysiological changes occur, which facilitate white matter abnormalities[47].

Age, obesity and risk of dementia

The relationship between obesity and later cognitive decline is far from clear. There is increasing evidence that higher adiposity, both in respect of BMI and central obesity, in mid-life is a risk factor for subsequent impairment in cognitive functioning[18,48,49], and has been identified as a modifiable risk factor for cognitive decline and impairment[50]. However, obesity in later-life seems to offer a level of protection against cognitive decline, with some studies demonstrating slower decline in the obese compared with those of a normal weight[51,52].

Associations between age and risk level for later dementia show that obese individuals admitted to hospital between ages 30 and 39 years showed a 3·5 increased relative risk ratio for AD and vascular dementia in later life. This relative risk reduced in a stepped fashion up to age 70 years in those obese on admission but was still associated with a greater risk of subsequent dementia compared with non-obese controls. The risk of later vascular dementia was reduced in those obese from age 80 years onwards[53]. It has been estimated that being obese at ages 40–45 years increases risk of later dementia by 74 % relative to those of a normal weight[18]. Therefore, mid-life obesity increases risk of dementia in later-life while greater BMI at increased age may attenuate this risk. Thus, classification of obesity in septuagenarians appears to confer protection from dementia[54]. Obesity has been associated with the lowest odds ratio for dementia relative to diabetes, hypertension and dyslipidaemia in mid-(45–65 years) and late-life (above 65 years). However, the odds ratio is higher for mid-life relative to later-life obesity (2·0 and 0·8, respectively)[55]. In a recent systematic review and meta-regression analysis of longitudinal studies examining BMI in mid-life and risk of dementia in late life, being obese but not overweight in mid-life was found to lead to an increased risk of subsequent dementia[56]. Furthermore, a review of empirical research found that the relationship between obesity and risk of dementia was most consistent when obesity was assessed during mid-life and cognition was assessed in later-life, and in studies where there were longer follow-up periods[55].

Importantly, the association between obesity and dementia has been shown to vary as a function of adiposity measure, the outcome of interest and the age at which an individual is classed as obese[53,57,58]. Indeed, using BMI as a measure of adiposity is problematic given that BMI fails to distinguish muscle from adipose tissue and does not indicate distribution of adiposity[59]. Longitudinal studies have the benefit of following cohorts of individuals over prolonged periods of time, making them an ideal approach for observing disease development[60] and identifying patterns, correlates and possible causes of changes that occur with age[61]. In one such study, individuals aged 65 years and over were followed for 5 years to assess the prospective association between adiposity, weight change and dementia, as a function of age. Importantly, findings were adjusted for sample demographics and ApoE ε4. BMI between 26·3 and 29·6 kg/m^2 was related to a lower risk of dementia including AD compared with BMI <23·4 kg/m^2. Waist circumference >97 cm was associated with an increased risk of dementia associated with stroke. However, age mediated the effects of BMI and waist circumference. In individuals below age 76 years BMI between 23·4 and 29·6 kg/m^2 was associated with lower risk of dementia, with a higher risk for those with BMI outside this range. In individuals over age 76 years, risk of dementia decreased with increasing BMI. Waist circumference >97 cm was associated with a higher risk of dementia and AD in those below age 76 years, but this relationship disappeared for those aged over 76 years. Weight loss was related to increased dementia risk relative to those who remained weight stable. However, those that gained weight had a higher risk of dementia associated with stroke[57].

Ageing, obesity and impairment in specific cognitive domains

Impaired verbal fluency, memory and performance on global screening measures have also been related to

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obesity; demonstrating an independent relationship between cognitive performance and obesity. Individuals aged 19–93 years were assessed on average 3·1 times, every 2–3 years. On measures of global cognitive function, higher BMI, waist circumference and waist-to-hip ratio (WHR) were associated with poorer performance; poorer performance was seen with increasing age in cases of larger waist circumference and WHR. Executive function was assessed by trail making tests A and B[12]. Both tests measure mental flexibility, speed of processing and visual search[62]. With increasing age, higher BMI and waist circumference were related to quicker performance on trail making tests A[12], where twenty-five numbered circles are connected sequentially[62]. However, higher WHR related to slower performance with age on trail making tests B[12], where numbers and letters are connected in order in an alternate fashion (e.g. 1-A, 2-B, etc.)[62]. Similarly, increasing obesity as identified on all three obesity measures and ageing were associated with declining performance in visual memory. The relationship between verbal functioning and obesity varied depending upon the measure used but did not vary with age. Specifically, poorer performance for letter and category fluency was related to BMI, waist circumference was related to poorer performance for letter fluency and WHR was related to poorer performance for category fluency. Only WHR was associated with visuospatial skills with increasing age, whereby a higher WHR was related to slower decline[12]. Similar relationships have been found between weight change and cognitive performance. In a second prospective study, BMI was calculated across the adult lifetime (early adulthood, and early and late mid-life). Executive function, memory and performance on the mini-mental state examination were examined in late mid-life. Adjusting for age, sex and education, cumulative obesity was related to poorer performance on the mini-mental state examination and in inductive reasoning and verbal fluency (phonemic and semantic) compared with normal weight. The finding for mini-mental state examination performance remained following further adjustment for health behaviours and health measures assessed in late mid-life. Conversely, cognition was also associated with the cumulative effects of being underweight (BMI < 20). Being underweight on two or three occasions was related to lower inductive reasoning, verbal fluency and mini-mental state examination performance also[63]. Being underweight and a reduction in weight may reflect the onset of pre-clinical dementia, which has consequences of lowered food intake and changes in lifestyle[64,65]. This notion of cognitive dysfunction promoting weight loss prior to clinical significance has been supported in a review of nineteen cohort studies[56].

Metabolic consequences of obesity

Adiposity is a risk factor for a range of health conditions including vascular comorbidities, which in themselves increase the risk of dementia. Chronic, low-grade inflammation associated with obesity has been linked to insulin resistance[66]. Proinflammatory cytokines have been suggested to cause insulin resistance in liver and adipose tissue by interfering with insulin signalling. Specifically, both autocrine/paracrine cytokine signalling and endocrine cytokine signalling have been implicated in localised and systemic insulin resistance[67]. Insulin resistance is central to the metabolic syndrome, which has been associated with an increased risk of cognitive decline and dementia[15,68–70]. A number of consequences of insulin resistance have been posited including, but not restricted to, lipid metabolism and mitochondrial dysfunction, white matter atrophy, and synaptic loss and neuro-inflammation[71,72]. Further, the administration of insulin for the treatment of insulin resistance has produced promising results in alleviating cognitive impairment in cognitively healthy and unhealthy samples; however, treatment effects have been found to be modified by dose and ApoE genotype[73]. For example, improvements have been found in areas such as visuospatial and verbal working memory[74,75].

Type 2 diabetes and cognitive function

Insulin resistance is predictive of subsequent development of T2DM[76]. This may reflect part of a sequential relationship, which features adiposity and hyperinsulinaemia as appearing in a linear fashion prior to the onset of glucose intolerance and T2DM[77].

IGT occurs prior to the development of diabetes and may contribute to cognitive impairments (see[78] for a review). Recent studies have shown that the performance of ostensibly healthy middle-aged women with IGT was impaired in cognitive tasks, which predominantly engage the hippocampus[79]. IGT in later life may confer a greater risk for AD than T2DM[17] because IGT is likely to be untreated and result in longer exposure to glucose excursions. Indeed, higher glucose levels may increase the risk of cognitive dysfunction in non-diabetic individuals[80,81].

T2DM not only increases the risk of subsequent cognitive dysfunction[82,83], but may also lead to an accelerated rate of cognitive ageing[84,85]. T2DM has been associated with reduced performance in a number of cognitive domains including verbal memory, processing speed[86,87], attention[88], spatial working memory[89], verbal fluency[85] and executive function[90]. However, glycaemic control may play a role in determining the extent to which individuals experience cognitive impairment[91,92].

T2DM is an independent risk factor for the development of CVD[93]. Similarly, hyperinsulinaemia and insulin resistance may lead to an increased risk of CVD[94,95]. Cardiovascular risk factors present in mid-life increase the risk of subsequent dementia[96]. Hypoperfusion and microemboli, both a consequence of cardiac disease, have been implicated in the aetiology of dementia[97]. Additionally, multiple lacunar infarctions are common in individuals with diabetes and these have been associated with cognitive decline[98]. Further, T2DM has been associated with global brain atrophy[99], with the rate of loss being greater than that found in normal

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ageing[100], supporting the notion of accelerated cognitive ageing. Moreover, the abnormalities present in insulin resistance in T2DM have also been observed in those with AD[101,102]. As insulin action has been implicated in neuronal and synaptic formation, development, repair and neuroprotection[103,104], this has important clinical consequences.

Since obesity and subsequent T2DM increases the risk of AD by 65 % (relative risk in T2DM is 1·46[60]) and about 80 % of AD patients have problems with glycaemic control, AD has been referred to as type-3 diabetes[61]. It has been proposed that AD is a metabolic disease, mediated by impairments in brain insulin responsiveness, glucose utilisation and energy metabolism, which leads to increased oxidative stress, and inflammation, which worsens insulin resistance[105]. Advanced glycation end-products are also elevated in both T2DM and AD. The relative risk of vascular dementia in those with T2DM is 2·49[83] and its development relates to a history of hypertension and disturbances in cerebral blood flow.

Further evidence for the potential role of insulin resistance in dementia comes from evidence that an increase in enzymes responsible for the generation of β-amyloid, as well as increased levels of β-amyloid in the brain, have been identified following induced insulin resistance in animal studies[106,107]. Additionally, impairments in insulin signalling contribute to impairments and dysfunction in mitochondrial structure and function due to energy deficiency, having consequences for increased reactive oxygen species production[108] and neuropathology in AD[66].

The obesity paradox

It should also be noted that being underweight in middle and old age has recently been associated with an increased dementia risk. The incidence of dementia decreased as a function of increasing BMI. Paradoxically, morbid obesity in adult life was associated with a 29 % lower dementia risk compared to healthy weight[109]. In older adults, current obesity levels have been inversely associated with dementia[110]. This could represent an 'obesity paradox' in which late life weight loss may precede dementia[52] and occur before any presentation of cognitive impairment. A recent retrospective cohort study of almost two million individuals aged over 40 years in the UK, reported that being underweight in middle age and old age carries an increased risk of dementia[109]. This assertion is controversial and, in contrast to the evidence of an association between obesity and dementia, may reflect the tendency to underdiagnose dementia by general practitioners at the time the data were collected, and over or under adjustment for a number of factors such as competing risk of mortality as well as selection bias, and bias in the diagnosis of dementia in those with lower BMI/age[111].

Collectively, these findings may go some way to explain the relationship between mid-life obesity and late-life dementia. There is less evidence available to explain the unexpected finding that obesity in late life confers protection against dementia. However, possible mechanisms include larger leg lean mass promoting glucose metabolism[112], which could avoid the pathogenic consequences of increased glucose availability via glucose uptake into muscle.

Stress as contributing risk factor

Stress is experienced when an individual perceives a mismatch between the demands of a stressor and their ability to cope. In homeostatic terms: demand exceeds the regulatory capacity of the organism[113]. The stress response is primarily mediated by two neuroendocrine systems: the sympathetic adrenal–medullary system and the hypothalamic–pituitary–adrenal axis. Activation of these systems ultimately results in the release of corticosteroids (via the sympathetic adrenal–medullary system) and glucocorticoids (via the hypothalamic–pituitary–adrenal axis) which instigate adaptive survival responses to meet the demands of the stressor. While stress responses are adaptive, prolonged, excessive, or repeated response activation can result in a cumulative toll on the organism which accelerates wear and tear on bodily systems[114]. Chronic psychosocial stress drives physiological dysregulation that has been associated with multiple and profound negative effects on human health and well-being, ultimately affecting quality and longevity of life[115,116].

Stress, energy homeostasis and metabolic outcomes

Exposure to stress is associated with both metabolic dysfunction[117] and impairment of cognitive performance[118]. Therefore, stress is a potentially important risk factor contributing to the relationship between obesity and cognitive function. There is considerable neurobiological overlap between stress and energy homeostasis systems. The hypothalamus is sensitive to the negative feedback action of glucocorticoids, and also to energy balance and appetite hormones (e.g. insulin, ghrelin, leptin)[119]. Furthermore, the hypothalamic–pituitary–adrenal axis is sensitive to most central and peripheral neuropeptides involved in energy homeostasis and appetite (e.g. orexigenic neuropeptide Y[120]). Chronic stress also modifies peripheral metabolic and adipose physiology. For example, cortisol (the primary human glucocorticoid) increases plasma levels of leptin and ghrelin and alters the expression of neuropeptides that regulate energy intake[121]. Glucocorticoids also inhibit insulin release and decrease insulin sensitivity promoting metabolic oversupply which contributes to the development of hypertension, central obesity and glucose intolerance, key features of metabolic syndrome[122].

The relationship between psychosocial stress and negative metabolic outcomes is gaining increasing recognition. Chronic stress prospectively predicts abdominal fat accumulation[123], metabolic syndrome[124], and obesity[125]. Stress promotes irregular eating patterns and physical inactivity and can bias food preferences towards high-energy dense food[122]. For example, stress increases

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the intake of sweet high-fat foods[126], fast-food[127], a high-fat diet[128], unhealthy snacking[129,130], binge eating[131] and reduces vegetable intake[132].

Existing metabolic risk may increase vulnerability to the negative effects of stress on body composition. For example, cumulative stress is associated with higher fasted glucose, insulin and insulin resistance in those with high *v.* low BMI[119]. Obese individuals are also more vulnerable to being exposed to elevated glucocorticoid levels. Central obesity is associated with glucocorticoid excess[133], elevated basal cortisol[134], and higher cortisol reactivity to acute stress exposure[135].

Such findings suggest stress promotes an internal milieu and behaviours that increase the risk of metabolic oversupply which have grave long-term consequences for health. Conditions characterised by metabolic oversupply (e.g. obesity and diabetes mellitus) are associated with increased oxidative stress, systemic inflammation, altered gene expression (e.g. shortening of telomeres) and impaired cognitive performance[136].

Stress and cognitive function

Stress significantly impacts upon cognitive function acutely and chronically via deleterious effects on neural structures. The acute effects of stress on performance are bidirectional with examples of both enhanced and impaired function. The direction of the effect is mediated by a number of variables, including cognitive domain, proximity of stress to cognitive processes and individual stress responsivity[137,138]. Stress tends to impair cognitive processes that are not directly relevant to the stressor faced. For example, attentional resources needed to process the stressor faced are prioritised. Similarly, priority is given to memory consolidation of information likely to permit future adaptive coping. Cognitive processes extraneous to the immediate threat (e.g. peripheral attention, retrieval of non-stress relevant information) tend to be impaired. Glucocorticoids have been identified as the primary moderator of the acute effects of stress on cognitive function. Glucocorticoids are also associated with impairments to neural integrity in the long term. For example, chronically raised plasma levels are negatively correlated with hippocampal volume and hippocampal-dependent memory deficits in older adults[139]. Evidence also suggests that glucocorticoids exert negative effects upon the integrity and function of neurons in the prefrontal cortex[140].

Stress, obesity and cognitive function

Stress can promote the accumulation of excessive weight, particularly central adiposity, via alterations to energy homeostasis systems and feeding behaviour. Further, obese individuals may be more vulnerable to the cognitive impairing effects of stress due to increased basal and reactive glucocorticoid levels. The combination of increased vulnerability to the deleterious effects of stress, and the risk associated with existing metabolic oversupply that characterises the obese state, suggests obese individuals may be more vulnerable to impaired cognition under conditions of stress. Our laboratory examined the impact of stress exposure on cognitive performance in centrally obese, middle-aged adults. Cortisol responsivity and cognitive performance were assessed after exposure to a laboratory psychosocial stressor or non-stress control in sixty-six high or low WHR adults. Males, particularly of high WHR, tended to exhibit greater cortisol responsivity in response to the stressor. Exposure to the stressor and increasing WHR were associated with poorer performance on tasks of declarative memory; specifically spatial recognition memory and paired associates learning (Cambridge automated neuropsychological test battery[141]). Our findings tentatively suggest a reduction in cognitive performance in those with central adiposity under conditions of acute stress. Therefore, the increased risk of impaired cognition evident in obese populations may be exacerbated by an increased vulnerability to the negative effects of stress.

Can obesity related deficits in cognitive function be reversed?

Weight loss via diet and/or exercise is advisable to reduce obesity and there is some evidence that such interventions may also restore or prevent further decline in cognitive function. Weight loss maintenance requires enduring behaviour change and is likely to be more successful in those who have the cognitive capacity to do this. Some interventions such as bariatric surgery promote rapid loss, while others such as dietary change result in slower body weight reduction. There have been a number of studies which evaluate cognitive function following these interventions.

Bariatric surgery and cognitive function

Interventions which address cerebrovascular risk factors during middle age may be prophylactic for cognitive ageing. One such intervention is bariatric surgery which has been shown to promote rapid improvements in memory and executive function that persist for several years post-operatively[142]. This post-operative improvement in memory performance is not seen in individuals with a family history of AD[143], which suggests that genetic vulnerability or family history may attenuate cognitive recovery post bariatric surgery.

Dietary intervention studies and cognitive function

Whilst the effects of specific nutrients on cognitive performance have been investigated experimentally[144,145], comparatively less is known about the effects of whole dietary patterns which more accurately reflect the complexity of daily eating behaviour as well as the synergistic effects of nutrients in the food matrix.[146]. Experimentally controlled whole diet approaches which reduce postprandial glucose excursions and inflammation by increasing the fibre content of the diet in line with Nordic Nutrition Recommendations have demonstrated cognitive benefits

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within as little as 1 month in middle-aged adults[147]. The Dietary Approaches to Stop Hypertension diet, which is high in fruit and vegetables and low-fat dairy foods and low in saturated fat, showed a positive effect on psychomotor performance in 124 middle-aged adults with hypertension with diet alone[148].

Consumption of a Mediterranean dietary pattern (MDP) rich in olive oil, fruit and vegetables, whole grains, legumes, nuts, low-fat dairy, fish, moderate alcohol (red wine) and low red meat intake has been associated with a reduced risk of pathology and mortality in the general population[149]. This dietary pattern has been identified as a healthy model of eating that should be promoted in non-Mediterranean populations[150,151]. The MDP has also been investigated in relation to cognitive health, decline and dementia. Epidemiological, prospective[152–156], cross-sectional[157–160], and meta-analytic studies[161–163] suggest that adherence to this dietary pattern is associated with less cognitive decline, dementia and AD; although with some disparity amongst the findings[157,164,165].

The Prevencion con Dieta Mediterranea[166] study supplemented older Spanish adults (mean age 67 years) prescribed the MDP with either extra virgin olive oil or mixed nuts and compared cognitive function after 4 years with a non-intervention control who received advice to reduce dietary fat. Better verbal memory was found in those consuming olive oil than controls, and composite memory, frontal and global performance was maintained in both MDP arms relative to the controls whose performance declined over the follow-up period. Although cardiovascular risk was also reduced, no synergistic mechanism of the whole MDP definitively explains the maintenance of cognitive function observed. However, different biological mechanisms have been proposed. These include reduction of vascular risk factors and white matter lesions, metabolic abnormalities (e.g. insulin resistance), oxidative stress, inflammation and advanced glycation end products[161–163].

Limitations of studies examining the association between obesity and dementia

The measure of adiposity employed to indicate obesity influences the relationship found with risk of dementia. The lack of differentiation between muscle and fat tissue in BMI measurement makes this a problematic assessment of body fat[59], which also varies in relation to age and sex. For example, in a cross-sectional validation study, females had a greater percentage of body fat relative to males despite having the same BMI. Furthermore, race, age and race-by-BMI interaction were independently associated with the percentage of body fat for females[167]. The use of self-report data for weight and height at an earlier time of life may be affected by recall bias[110]. Length of follow-up period also makes drawing conclusions regarding risk factors difficult when this is limited. Indeed, in those studies that included a longer follow-up time, the association between obesity and risk of dementia has been found to be most consistent[55].

Heterogeneity in study designs further contributes to the difficulty of forming conclusions about relative risk. In a meta-analysis assessing risk of AD in obesity, diabetes and related disorders, differences in study designs may have contributed to statistical heterogeneity seen in the pooled effect size for obesity. Moreover, no conclusion could be made regarding the effects of the timing of exposure to obesity on risk. Additionally, a lack of adjustment for ApoE status in some studies does not reflect the potential of this to modify the relationship between obesity and dementia risk[168]. Other studies have failed to adjust for other important variables in their analyses including education, cerebrovascular damage and stroke. Also, significant attrition rates are not addressed in some longitudinal studies. Importantly, a meta-regression revealed the association between being underweight in mid-life and risk of later dementia was more likely to have been reported in studies prone to outcome ascertainment bias, selection bias, involving shorter follow-up periods, suffering a greater rate of attrition and where control of potential confounding variables was less adequate[56]. Differences in the diagnostic criteria of dementia and diabetes, in the length of follow-up periods, in the sample sizes and in the recruitment of specific populations have all been reported to contribute to heterogeneity in study findings[169]. Similarly, wide age ranges in respect of study samples and the inclusion of some participants above age 65 years when assessing mid-life exposure further complicates the issues[56]. The lack of inclusion of brain imaging outcomes and autopsy reports means that it is not possible to determine how the severity of subclinical vascular disease features in the risk for dementia with obesity[168]. Cohort effects are also acknowledged in some studies, such as differences in the survival rate due to dementia, obesity-related mortality[17] or perhaps being less vulnerable to the adverse effects of obesity, termed the 'survivor effect'[55].

Conclusions

There is clearly an association between mid-life obesity and cognition and cognitive decline in later life. This is an issue of concern against the background of an ageing population and the failure to stem the rise in obesity. The impact of obesity on cognitive decline and risk of dementia merits further investigation. Investigations into the association between obesity and cognitive health should also consider the contributing effects of psychosocial stress on this relationship. More consistent methodological approaches will likely reduce some of the heterogeneity in the existing data. For example, the selection of an appropriate and reliable measure of obesity, adjusting for important variables (e.g. ApoE status, education, cardiovascular risk) and adequately accounting for attrition. Interventions which reduce obesity are promoted for physical health reasons but the demonstration that weight loss and weight loss maintenance at mid-life can prevent cognitive decline may present a persuasive message to the middle aged who generally fear dementia.

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