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Etiology and Pathophysiology/Obesity Prevention

A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment

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Summary

Recent research suggests that increased adiposity is associated with poor cognitive performance, independently of associated medical conditions. The evidence regarding this relationship is examined in this review article. A relatively consistent finding across the lifespan is that obesity is associated with cognitive deficits, especially in executive function, in children, adolescents and adults. However, as illustrated by contradictory studies, the relationship between obesity and cognition is uncertain in the elderly, partly because of inaccuracy of body mass index as a measure of adiposity as body composition changes with aging. This review further discusses whether obesity is a cause or a consequence of these cognitive deficits, acknowledging the possible bidirectional relationship. The possible effects of increased adiposity on the brain are summarized. Our investigations suggest that weight gain results, at least in part, from a neurological predisposition characterized by reduced executive function, and in turn obesity itself has a compounding negative impact on the brain via mechanisms currently attributed to low-grade systemic inflammation, elevated lipids and/or insulin resistance. The possible role of cognitive remediation treatment strategies to prevent and/or treat obesity is discussed.

Keywords: Adiposity, body mass index, cognition, cognitive impairment, obesity.

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Introduction

Obesity, defined by accumulation of excess adipose tissue, has become a worldwide epidemic with dramatic consequences for health because of its association with increased heart disease, hypertension, diabetes, stroke and cancer (1,2). While some of these medical comorbidities are themselves associated with adverse cognitive effects (3–6), recent research suggests that adiposity has a specific association with cognitive function. Obese rats have been shown to perform worse on learning and memory tasks compared with rats of normal weight (7,8). Notably, non-obese rats fed a high-fat diet have also been shown to be cognitively impaired compared with those fed normal chow (9–13). In humans, recent investigations across the lifespan have examined whether obese individuals have cognitive deficits compared with their normal-weight counterparts. Childhood and adult obesity is increasing dramatically and if obese individuals show early impairment of cognitive performance this could lead to a larger and even more devastating epidemic: that of earlier onset dementia. Midlife obesity is already a risk factor for dementia in the elderly (14–18). While there is a focus on improving cognition and function in the elderly, in an obese individual there may be

greater impediments to improvement. With the substantial increase in obesity, a significant decline in cognitive performance could have further functional implications, not only for the individual but for society in general.

The evidence regarding the relationship between obesity and cognition across the lifespan is reviewed in this article. We first summarize and discuss the findings of the association in childhood and adolescence (age 4 to 18 years), in adulthood (age 19–65 years) and in the old (age 65–99 years). There is also evidence that poor performance in cognitive function in children predicts future increase in body mass index (BMI), suggesting a bidirectional relationship. The effects of weight loss and high-fat diets on cognition will be briefly discussed. In addition, this review will examine the effects of obesity on the brain via neuroimaging methods, with mention of potential biological mechanisms for this association.

Methods

PubMed, Medline and PsycInfo were searched for words such as 'obesity', 'adiposity', 'overweight', 'body mass index', 'weight', 'waist circumference' or 'waist to hip ratio' paired with 'cognition', 'cognitive function' or 'cognitive performance'. Studies that used the Mini-mental state examination (19) were excluded because (i) it is of relevance as a screening measure only in the elderly; (ii) it is not a sensitive or specific measure of integrity for particular cognitive domains and (iii) the score is affected by education and cultural factors (20). Any additional articles meeting inclusion criteria but not identified by search were crosschecked. Articles were scanned to ensure that the association between obesity and cognition was examined.

In this review, we selected only articles that measured both obesity and cognition, with primary aim to identify the relationship between these two constructs. That is, other articles examining obesity with another condition, such as hypertension, were not included in this review (unless hypertension was included as a covariate). The literature on metabolic syndrome was also excluded for four reasons (i) the clinical construct metabolic syndrome has multiple definitions with different criteria and obesity is the main factor we are interrogating; (ii) a review of cognitive dysfunction in metabolic syndrome was published in 2007 (21) (although most studies included in the present review were published after 2007); (iii) metabolic syndrome cannot be diagnosed in children under 10 years old and (iv) metabolic syndrome and its relationship to cognition have usually been examined in the middle aged or elderly.

In these studies obesity was defined primarily by BMI (kg m^{-2}) of 30 or above in adults (unless otherwise stated), and above the 95th percentile for age and height in children. High waist-to-hip ratio or high waist circumference was also used as a measure of adiposity in a few studies.

Cognitive function refers to the processing, integration, storage and retrieval of information. Cognitive function includes perception, attention, memory and executive function. Executive function, the most consistent deficit found in the obese, encompasses a diverse range of cognitive processes facilitating initiation, planning, regulation, sequencing and achievement of complex goal-oriented behaviour and thought (22,23), which in turn may impact on eating behaviour. Executive function has been usually measured by tasks such as the Wisconsin Sorting task, the Stroop task or the Trail Making test, which measure switching and cognitive flexibility, and the Iowa gambling task, which measures inhibition and rule acquisition. However, working memory has also been suggested to be part of executive function (24). Cognitive dysfunction or impairment has been usually estimated by statistically significant deficits in test performance compared with healthy controls or normative data.

Results

Cognitive deficits in obese children and adolescents (aged 4–18 years)

Nine cross-sectional studies were found which examined obesity and cognitive function in children and adolescents (see Table 1). Some studies were population-based whereas others reflected a clinically obese population. Obesity was defined using standard growth curves (weight above the 95th percentile classified as obese) and compared with normal weight. Alternatively, using a linear regression model, an increasing BMI was associated with lower cognitive function, suggesting a linear relationship. All cross-sectional articles were published within the last 5 years, highlighting this as a developing area. Findings have been relatively consistent, with eight of the nine studies showing significantly poor cognitive indices in obese individuals compared with those of normal weight.

Cognitive deficits in obese children and adolescents were found most consistently in tests of executive function (25–28), while some studies also found deficits in short-term memory (29) (an aspect of executive function (24)), global functioning (30,31) and verbal abilities (32) compared with normal-weight adolescents. It has been suggested that impairment in verbal abilities in young age could lead to impairment in executive function (33). The study that did not report an association between high weight and poor cognitive function used standard growth curve of BMI in a regression model to predict cognitive function (34). This study was limited in that only 10% of participants were overweight. It is likely that the negative effects of adiposity on cognition in children and adolescents are only detected over a threshold, i.e. only in the obese.

Probably one of the best studies showing the clear association between elevated BMI and cognitive dysfunction in

Table 1 Nine cross-sectional studies of the association between obesity and cognition in children and adolescents (4–19 years old)

Reference	How was obesity measured?	Study population and ascertainment	Controls	Cognitive tests	Covariates/exclusions	Results
Azurmendi *et al.* (2005) (32)	BMI as a continuum	60 boys and 69 girls aged 5 years – school children	Multiple regression analyses	Matrices, verbal abilities, affective labelling, display rules, false beliefs	None	Negative relationship between BMI and verbal abilities, especially evident in girls
Miller *et al.* (2006) (30)	>150% of ideal body weight	12 early onset morbidly obese (EMO individuals aged 4–22 years [mean: 10.9 years]) – clinic setting	21 Normal-weight siblings; 17 Prader–Willi Syndrome	Woodcock–Johnson test of cognitive abilities and achievement, overall cognitive ability score	Sex	Overall cognitive ability score was significantly lower in the EMO compared with control siblings, but significantly higher compared with Prader–Willi syndrome. EMO subjects also had lower thinking ability, cognitive efficiency, phonemic awareness & working memory (**executive function**) than controls.
Cserjé'si *et al.* (2007) (27)	BMI = 27.16 kg m^{-2}	24 (12 obese) boys, mean age 12 years – school children	Age matched normal-weight boys	Digit Span memory task, Raven's progressive matrices, semantic verbal fluency, D2 attention endurance test, Wisconsin sorting card	None	Obese children performed worse on the Wisconsin sorting card test (**executive function**) and D2 attention endurance task despite similar intelligence and memory capacity to that of the control group
Mond *et al.* (2007) (26)	BMI > 19.8 kg m^{-2} for boys and BMI > 19.7 kg m^{-2} for girls	9,415 children aged 4.4–8.6 years (4.3% of girls and 2.4% of boys were obese) – population-based	Non-obese	Standardized test to assess motor development, development of speech, cognitive development, and psychosocial development	Age, nationality, year of recruitment, location and duration of kindergarten	An association between obesity and impairment in gross motor skills was found in the entire sample after controlling for covariates. When separated by gender, obese women were impaired in their ability to focus attention continuously during the examination (**executive function**) compared with normal-weight girls.
Gunstad *et al.* (2008) (34)	Standard BMI growth curves mean BMI = 26.21 kg m^{-2}	478 (45 overweight) children/adolescents aged 12.46 years (range 6–19 years) – population-based	Compared with other weight groups	Digit Span backward, Trial Making Test B, Verbal recall; Animal fluency; finger tapping	Age and education Exclusion: mental illness or family history of mental illness, neurological injury and any significant medical condition	No associations were found between BMI and cognitive function

Table 1 *Continued*

Reference	How was obesity measured?	Study population and ascertainment	Controls	Cognitive tests	Covariates/exclusions	Results
Li *et al.* (2008) (29)	Overweight BMI: >95th percentile for age and height	2,519 children (overweight: 360) aged 8–16 years old (mean = 12); – population-based	Compared between weight groups in a regression analysis	WISC-R (block design, digit span), wide range achievement test (reading and arithmetic), global functioning	Age, gender, ethnicity, education, marital status of the family head, family income, dwelling, hours watching TV, exercise, sports, health status, blood pressure, heart rate, iron deficiency, psychological and social variables	After including all covariates, overweight children performed significantly poorly in the digit span test, a test of attention and working memory, and in global functioning. When dichotomizing the z-scores and performance below 2 was classified as poor, results showed that overweight children performed significantly poorly on block design, a measure of general mental ability and visuospatial organization, after controlling for confounding variables.
Lokken *et al.* (2009) (25)	BMI > 99% for their gender and age (extremely obese)	25 adolescents aged 12–19 years (mean 16.2 years) with mean BMI of 54 kg m^{-2} (range 35–78 kg m^{-2}) – clinic setting	79 adolescents served as normative data	Wide range achievement test (reading subset), Wechsler (vocabulary and matrix reasoning), digit span, continuous performance task, verbal interference, switching of attention, maze task, go-no-go test	None, no differences in cognition in those with and without sleep apnoea, no correlation of cognition with depression	Obesity was associated with poor cognitive performance, especially in the area of **executive function**
Miller *et al.* (2009) (31)	BMI > 95% before the age of 4 years	17 EMO individuals aged 4–22 years (mean: 10.9 years) – clinic setting	15 Normal-weight siblings 16 Prader–Willi Syndrome	Woodcock–Johnson test of cognitive abilities and achievement, overall cognitive ability score	None	Overall cognitive ability score was significantly lower in the EMO compared with controls. No significant difference between those with early onset obesity compared with Prader–Willi syndrome.
Verdejo-García *et al.* (2010) (28)	Used BMI, classified according to Obesity Task Force criteria	8 overweight and 19 obese adolescents aged 13–16 years – recruited for treatment	34 healthy adolescents aged 13–16 years	Stroop test, letter number sequencing, similarities, zoo map, five digit test, Trial Making Test A and B, revised strategy application test, Iowa Gambling Task	Age	Overweight and obese adolescents show poorer performance on tests of **executive function** – inhibition, flexibility and decision making

Underlined references did not find an association between obesity and cognition or found opposite associations than expected.
BMI, body mass index; EMO, early morbid obese; WISC, Wechsler Intelligence Scale for Children.

children is a study by Li *et al*. as it included over 2,000 children and an impressive number of covariates (29). This study found that overweight children (BMI > 95% of recommended age and height) performed significantly poorly on the digit span test, a test of working memory and attention, and in global functioning.

Cognitive deficits in obese adults (aged 19–65 years)

Fifteen cross-sectional and four prospective studies examined the relationship between obesity and cognitive performance in adults aged 19 to 65 years (see Table 2). The evidence is highly consistent with 14 out of the 15 cross-sectional studies showing a negative association between obesity and cognition, 11 of these consistently finding a deficit in the area of executive function (35–51).

The first cross-sectional account of an association between increased adiposity and poor cognitive performance (44) found that obese army men had significantly lower cognitive test scores than the normal-weight men. However, because social class is positively associated with cognition (52) and negatively associated with BMI (53), the authors re-analysed the data in six levels of socioeconomic status (45). Cognitive test scores increased with parental social class in both groups. Within each social class, however, the obese group had lower test scores than the normal-weight group, supporting the idea that obesity, not socioeconomic class, is more strongly related to poor cognitive function. This is in fact consistent with recent data by the US Department of Health and Human services (54) showing only a small association of income and education (both estimates of socioeconomic status) with obesity in women but not in men. A recent review article on socioeconomic status and obesity (55) also found this.

Other cross-sectional studies suggest that higher BMI is associated with poorer performance on tests of global cognitive function, memory and language (46–50) and motor skills (46,51). The one study that did not find a cross-sectional association between obesity and cognition was comprised of 108 participants aged 40 to 66 years, only 21 of whom were obese (56). The limited number of obese subjects in this sample may have contributed to the lack of significant results. The other 14 studies found a negative association between adiposity and poor cognitive performance, although most studied a younger sample.

Four prospective studies investigated the possible impact of obesity on cognitive function and cognitive decline. In Cournot *et al*.'s (47) 5-year longitudinal study, higher BMI at baseline was associated with cognitive decline, but no relationship was found between change in BMI and decrease in cognitive function. Another prospective study found an increase in waist-to-hip ratio from early to late midlife predicted a lower performance in tests of executive function (43). Other prospective study found that a higher BMI in midlife is a risk factor for cognitive decline (42), especially in the area of executive function. Gunstad *et al*.'s (50) prospective data showed that higher waist-to-hip ratio was associated with slower performance in the Trial Making Test B, a measure of executive function, as age increased. Memory also declined over time as a function of weight gain. However, contrary to the above findings, waist circumference and BMI were associated with faster performance on the Trail Making Test A, a test of processing speed, as age increased.

In summary, the findings in adults, 19 to 65 years, are similar to that of children and adolescents, with overweight and obesity being associated with low cognitive performance. Although obese individuals also presented with deficits in language, motor and memory domains, these deficits were most consistently found in the executive function domain. Obesity also predicted cognitive decline, but changes in weight itself did not consistently predict changes in cognition. Before discussing the mechanisms and possible bidirectional relationships, the association of obesity and cognition in the old will be reviewed.

Cognitive performance in obese old adults (aged 66–95 years)

The literature on the relationship between obesity and cognition in the old is more complex than in children, adolescents and adults. Seven cross-sectional and three prospective studies were found within this age group and these are described in Table 3. Cross-sectional studies up to the mean age of 72 years show that obesity is negatively associated with cognition (46,57–62), whereas the two studies with a mean age above 73 show the opposite association, with obesity being positively associated with cognitive performance (46,62).

Prospective studies show similar results to cross-sectional studies, findings being somewhat age dependent and contradictory. One study showed that obesity does predict cognitive decline (63). The other two studies found that obesity either predicted higher cognitive performance (64) or less decline in cognitive function (65). Weight loss was associated with poor cognitive performance in the old (66). The possible mechanisms that could account for these findings are described in the discussion section below.

Discussion

Obesity and cognition in children, adolescents and adults

The studies on obesity and cognition in children, adolescents and adults provide substantial evidence that obesity is positively associated with cognitive deficits, independent

Table 2 Fifteen cross-sectional and four prospective studies on the association between obesity and cognition in adults aged 18 to 65 years

Reference	How was obesity measured?	Study population and ascertainment	Controls	Cognitive tests	Covariates/exclusions	Results
Cross-sectional studies						
Sorensen *et al.* (1982) (44)	BMI ≥31 kg m^{-2}	1,806 obese men and 2,719 normal-weight men aged 18–21 years – population-based cohort	Normal-weight controls	Danish intelligence test named BPP-53: four subsets concerning letter matrices, verbal relations, number series, and figure analysis	Time and place of examination	Obese men had significantly lower scores than normal-weight men on all test scores, including tests of **executive function**
Chelune *et al.* (1986) (37)	Morbid obesity, more than 100% overweight	44 obese adults (mean age = 33 years) – obesity clinic setting	Normative data	WAIS, TMT A and B, category test – non-verbal measure of new concept formation and high cognitive problem solving	None	24% and 21% of obese patients had TMT A and B scores (respectively) that fell within the impaired range. 50% of the patients were impaired in the Category test. All tests of **executive function**.
Etou *et al.* (1989) (51)	BMI mean = 39.2 kg m^{-2}	26 (13 obese adult onset) women (age ranged 21–49 years) – obesity clinic setting	13 normal-weight women	Psychomotor (tap test, transfer coordination test, traverse speed test), time cognition (time judgment estimation, and reproduction) – both as self-cued or externally cued	Matched on intelligence, age, height and education	Obese women showed impaired manual coordination in tapping, dexterity and responsiveness tasks. In the time cognitive test, speed of the obese subjects was much longer when they were self-cued as opposed to externally cued.
Davis *et al.* (2004) (38)	BMI > 25 kg m^{-2}	15 overweight or obese (mean age = 28.5 years) – obesity clinic setting	26 normal-weight individuals	Iowa gambling task: a decision making test measure of executive function	Emotional over-eating	Participants with high BMI performed poorly on the Iowa gambling task, a test of **executive function**
Ward *et al.* (2005) (56)	BMI > 30.0 kg m^{-2} No participant above 260 pounds	108 participants aged 40–66 years (mean age of 54.2 years), 21 obese participants – community sample	Compared BMI in a stepwise linear regression analysis	WAIS, RAVLT, TMT A and B	Age, BMI, family history of AD, APOE genotype, total cholesterol, systolic and diastolic BP, gender, education	No associations between BMI and cognitive performance were found
Gunstad *et al.* (2007) (41)	BMI > 25 kg m^{-2}	408 adult participants aged 20–82 years (separated young: 20–50 years, vs. old: 50–82 years). Only results for the young are presented – population-based cohort.	Normal-weight adults	Attention (digit span forward, choice reaction time, TMT A), executive function (span of visual memory, verbal interference, TMT B, maze errors)	Estimated intelligence, years of education, sex, and self-reported measures of anxiety, depression and stress	Overweight and obese individuals performed worse on tests of **executive function** compared with normal-weight individuals
Roberts *et al.* (2007) (35)	BMI = 25.7–30.1 kg m^{-2}	10 overweight women aged 18–55 years – volunteers	50 healthy normal weight	Set shifting (Wisconsin sorting task, perseverative errors, TMT, Brixton task, CatBat task, haptic illusion task), detail focus (Rey complex figure, the group embedded figure task)	None	Moderate to strong effect sizes are seen for the tasks measuring detail focus with the overweight having lower scores. Small effect sizes are seen for the set-shifting tasks, measure of **executive function**.

Table 2 *Continued*

Reference	How was obesity measured?	Study population and ascertainment	Controls	Cognitive tests	Covariates/exclusions	Results
Boeka and Lokken (2008) (36)	Average BMI = 51.18 kg m^{-2} (range 35–80 k m^{-2})	68 patients seeking surgical treatment of obesity, average age 41 years – obesity clinic setting	Normative data, Bonferroni correction used 0.006	TMT A and B, Wisconsin sorting test, verbal fluency (controlled oral word association test and animal naming test), verbal learning (California verbal learning test-II), reading ability (Wide range achievement test), WAIS (similarities, block design, digit span, and digit symbol), Rey complex figure test	Matched for age and education	Obese individuals performed worse on measures of **executive function** compared with normative data. No significant differences emerged between obese individuals with and without comorbid medical conditions of hypertension, type II diabetes, and obstructive sleep apnoea on the tasks of executive function.
Dore *et al.* (2008) (49)	WC and WHR	917 individuals aged 23–98 years (mean age 62 years) – population-based cohort	Compared within weight groups in a regression analysis	Global composite, verbal memory, visuospatial organization, scanning and tracking (TMT A and B, digit symbol, symbol search), working memory (digit span forward and backward, letter number sequence, control oral word associations), abstract reasoning (similarities from WAIS), MMSE	Age, education, gender, examinations, smoking, cholesterol, prevalent CVD, CRP, systolic blood pressure, depression, glucose and physical activity	WC was inversely related to global composite, scanning and tracking, and abstract reasoning (**executive function**) after controlling for all covariates except physical activity. Only similarities remained inversely related when also including physical activity. WHR was inversely related to global composite, visuospatial organization and working memory, after controlling for all covariates except physical activity. When physical activity was included as a covariate these associations disappeared.
Fergenbaum *et al.* (2009) (39)	BMI > 30.0 kg m^{-2}	207 individuals aged 19–65 years (median = 39) – community setting	Compared within weight groups in a regression	Clock drawing test, TMT A and B	Age, sex, hypertension, CVD, diabetes, insulin resistance, smoked	Results found that obese individuals had low cognitive performance on **executive function** (as measured by the TMT B). Higher risk was found in women.
Nilsson and Nilsson (2009) (46)	BMI > 25 kg m^{-2} for men, BMI > 23.8 kg m^{-2} for women WHR > 0.8 for women, WHR > 1 for men	2,675 participants aged from 35 to 90 years divided by middle-age (35–55 years); young old (60–70 years) and old-old (75–90 years), and by male and female. Only results for the young and middle age are presented in this table – population-based cohort.	Normal-weight participants	Vocabulary test, memory tests (episodic and semantic), fluency tests, Wechsler block design test, immediate and delayed free recall test	Education (as age and sex were independent variables) Secondary analyses: excluded demented, those who suffer high blood pressure, diabetes or stroke	The overweight performed worse on semantic memory compared with normal weight. Before the exclusion: All overweight (WHR) performed worse on the block design test, a test of motor function, than normal weight. Overweight (BMI) middle-age participants also performed worse on block-design test than the normal weight.
Lokken *et al.* (2010) (40)	Average BMI = 49.24 kg m^{-2}	169 morbidly obese adults with mean age of 42 years – obesity clinic setting	Age and education matched normative data	Wide range achievement test (reading subset), Wechsler (similarities, block design, digit span, digit symbol), Wisconsin sorting card test, Rey complex figure test	Age and education matched normative data	Obese individuals scored significantly lower on the Wisconsin sorting card test and on the Rey complex figure test (measures of **executive function)** compared with normative data

Table 2 *Continued*

Reference	How was obesity measured?	Study population and ascertainment	Controls	Cognitive tests	Covariates/exclusions	Results
Prospective studies						
Cournot *et al.* (2006) (47) Cross-sectional and Prospective (5 years)	Quintiles of BMI were used	2,233 participants (291 obese) aged 32, 42, 52 or 62 years at baseline – population-based cohort	Quintiles of BMI (each group was comprised of 445 people)	Word list learning, immediate and delayed free recall, WAIS (digit symbol substitution test), selective attention test	Age, sex, education, diabetes, systolic blood pressure and perceived health score	Higher BMI was associated with poor cognitive performance (all tests, including tests of **executive function**). Higher BMI at baseline was associated with higher cognitive decline. No association between changes in BMI and cognitive function.
Wolf *et al.* (2007) (43) Prospective (12 years)	WHR: top quartile BMI = 30 kg m^{-2}	1,814 participants aged 40–70 years (mean age: 52.6 years) at the baseline – population-based cohort	BMI < 30 kg m^{-2}, WHR, quartiles 1–3	Visual reproductions (immediate and delayed), paired associates (immediate and delayed), logical memory (immediate and delayed)	Variables were regressed on age and educational attainment	Upper quartile on WHR in midlife predicted poor performance on **executive function** and visuomotor skills 12 years later. No significant difference of BMI > 30 kg m^{-2} versus BMI < 30 kg m^{-2} on cognitive function.
Sabia *et al.* (2009) (42) Cross-sectional and Prospective	BMI > 30.0 kg m^{-2}	5,641 Caucasian individuals aged 25 years at baseline and then measured again every few years – population-based cohort	Compared within weight groups in a regression analysis	MMSE, short-term verbal memory, executive function (AH4-I for reasoning, verbal and semantic fluency)	Age, sex, education, smoking, weekly alcohol consumption, frequency of fruit and vegetables, moderate activity per week, MIA, angina, stroke, diabetes, cholesterol and blood pressure	Obese had lower MMSE, memory and **executive function** than normal-weight individuals. These associations were stronger when individuals were old (e.g. 44 or 61 years) than when they were 25 years. An increase on BMI predicted lower performance on **executive function** tests. Similar results were encountered with underweight participants.
Gunstad *et al.* (2010) (50) Cross-sectional and Prospective	BMI, WC and WHR	1,703 individuals aged 19–93 years (mean age 55.5 years) – population-based cohort	Compared within weight groups in a mixed effects regression analysis	Global cognitive function (MMSE, blessed information-memory-concentration test), attention and executive function (WAIS digit span forward and backward, TMT A and B), memory (verbal learning test, Benton retention test, prospective memory test), language (letter and category fluency, Boston naming test), visuospatial (card rotations test)	Excluded if they had stroke, dementia, myocardial infarction, atrial fibrillation. Controlled for age, sex, education, hypertension, glucose diabetes, anti-lipid medication.	High BMI, WC and WHR were associated with poorer performance on global cognitive function, memory and language. Higher WHR was associated with slower performance in the TMT B, a test of **executive function**, as age increased. Memory declined over time as a function of increasing weight. WC and BMI were associated with faster performance on the TMT A as age increased.

Underlined references did not find an association between obesity and cognition.
AD, Alzheimer's disease; APOE, Apolipoprotein E; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; WAIS, Wechsler Adult Intelligence Scale; WC, waist circumference; WHR, waist-to-hip ratio; MIA, myocardial infarction; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trial Making Test.

Table 3 Seven cross-sectional and three prospective studies of the association between obesity and cognition in old adults aged 66 to 99 years

Reference	How obesity was measured	Study population	Controls	Cognitive tests	Covariates/exclusions	Results
Cross-sectional studies						
Kilander *et al.* (1997) (61)	BMI > 28.6 kg m^{-2}	504 men aged 69–74 years (mean age 72.2 years) – population-based cohort	BMI < 28.6 kg m^{-2}	Total cognitive score: sum of the 13 results: WAIS (digit span forward and backward, block span forward and backward, vocabulary), Claeson-Dahl's test (verbal learning and retention), Rey complex figure, verbal fluency task, Trial Making Test A, B, C and D	Age, sex, stroke, education and occupation	Obesity and smoking were related to impaired cognitive function, independent of stroke, education and occupation
Elias *et al.* (2003) (57)	BMI > 30 kg m^{-2}	551 men and 872 women aged 55–88 years (mean age 66 years) – population-based cohort	Non-obese controls	Logical memory, immediate and delayed recall, visual reproductions, paired associate learning, digit span forward and backward, similarities and word fluency	Age, education, level of occupation, alcohol consumption, mean cigarettes per day, cholesterol level and type II diabetes	Obese men performed significantly worse on logical memory (immediate and delayed), visual reproductions, digit span backward and word fluency. An effect on total test score was also significant. A marginal effect was seen for similarities. No significant results were found for obese women.
Kuo *et al.* (2006) (62)	BMI > 30 kg m^{-2}	2,684 individuals aged 65–94 years (mean age approx 73 years) – population-based cohort	Bonferroni correction to 0.0033	Memory (three tests), reasoning (three tests), speed of processing (two tasks)	Age, race, sex, study site, education, smoking, history of diabetes, stroke, myocardial infarction, hypercholesterolemia, blood pressure	Overweight participants had better performance on a reasoning task than normal-weight participants. Overweight and obese participants performed better on the visuospatial speed of processing than normal weight.
Waldstein and Katzel (2006) (59)	BMI > 30 kg m^{-2} WC > 102 cm for men, WC > 88 cm for women	90 individuals aged 54–81 years (mean age 66.2 years) – community sample	Multiple regression models	WAIS (digit forward, digit backward), immediate and delayed recall or verbal and non-verbal memory. Trial Making Test A and B. Stroop test, grooved pegboard, judgment of line orientation test, block design	Age, education, gender and any other measures that correlated with DV. Excluded those with cardiovascular disease, diabetes, neurological disease, stroke, or major medical disease	Higher WC and BMI were associated with low scores in the Grooved Pegtest and Stroop test, measures of motor and **executive function**. This effect was mediated by diastolic and systolic blood pressure.
Gunstad *et al.* (2007) (41)	BMI > 25 kg m^{-2}	408 adult participants aged 20–82 years (separated young: 20–50 years, vs. old: 50–82 years). Only results for the old are presented in this table – population-based cohort.	Normal-weight adults	Attention (digit span forward, choice reaction time, Trial Making Test A). Executive function (Span of visual memory, verbal interference, Trial Making Test B, Maze errors).	Estimated intelligence quotient, years of education, sex, and self-reported measures of anxiety, depression and stress.	Overweight and obese individuals performed worse on tests of **executive function** compared with normal weight

Table 3 *Continued*

Reference	How obesity was measured	Study population	Controls	Cognitive tests	Covariates/exclusions	Results
Nilsson and Nilsson (2009) (46)	Overweight: BMI > 25 kg m^{-2}, WHR > 1 for men; BMI > 23.8 kg m^{-2}, WHR > 0.8 for women	2,675 participants aged 35–90 years divided by middle-age (35–55 years), young old (60–70 years) and old-old (75–90 years). Only results for the old-old are presented in this table – population-based cohort.	Normal-weight participants	Vocabulary test, memory tests (episodic and semantic), fluency tests, Wechsler block design test, immediate and delayed free recall test	Education Secondary analyses: excluded demented, those who suffer high blood pressure, diabetes or stroke	Overweight (BMI) old-old performed significantly better at the block design test, a test of motor function, than the old-old normal weight.
Walther *et al.* (2010) (60)	BMI > 30 kg m^{-2}	95 women aged 52–92 years (mean age 67 years) – community sample	53 normal weight, 22 overweight and 20 obese	MMSE, WAIS (vocabulary), Trails A (visuomotor speed). Memory factors: logical memory recall, verbal pair associated, face recognition, visual paired associates, long-delay cued recall. Executive factors: Wisconsin card sorting test, mental arithmetic total score, verbal fluency task, digit span backwards, mental control.	None reported for the cognitive scores	Obese women had significantly lower scores in tests of **executive function** compared with normal-weight participants
Prospective studies						
Elias *et al.* (2005) (63) Prospective approx 4–8 years	BMI > 30 kg m^{-2}	551 men and 872 women aged 55–88 years (mean age 66 years) – population-based cohort	Non-obese controls	Logical memory, immediate and delayed recall, visual reproductions, paired associate learning, digit span forward and backward, similarities and word fluency	Age, education, occupation, native language, alcohol, smoking, total cholesterol, diabetes, hypertension. Excluded those with stroke, dementia or cardiovascular disease	Obese men showed decrements on digit span backward, visual reproductions and global composite after correction for multiple covariates. Women also showed decrements on a few cognitive measured but none reached significant after inclusion of covariates.
Sturnman *et al.* (2008) (65) Prospective 6 years	BMI > 30 kg m^{-2}	3,885 participants (2,371 African–American participants) 65 years or older (mean 73.8 years) – population-based cohort	Mixed effect regression model	MMSE, immediate memory and delayed recall, symbol digit test, composite measure of global function was computed by combining the four tests	Age, sex, race, education. Adjusting for comorbid illnesses (stroke, diabetes, hypertension and heart disease) did not change the findings	Cognitive function scores were found to be lower at both the lower and upper ends of BMI, this was especially so for African–American individuals. Higher BMI levels were associated with less decline in cognitive function.
Han *et al.* (2009) (64) Prospective 2 years	BMI > 25 kg m^{-2} For men: WC > 90 cm, WHR > 0.90 For women: WC > 80 cm, WHR > 0.85	721 Asian individuals aged 60–84 years (mean 68 years) – population-based cohort	Regression models and ANCOVA using categorical adiposity parameters	Word fluency test, Boston naming test, MMSE, word list memory, constructional praxis, word delay recall, word recognition, construction recall	Age, sex, education, depression, smoking, hypertension	For men: increased obesity (BMI, WC, WHR) over time, when obese at baseline, was associated with a positive change in cognition. For women: decreased obesity (WHR) over time, when obese at baseline, was associated with cognitive decline.

Underlined references did not find an association between obesity and cognition or found opposite associations than expected.

BMI, body mass index; DV, dependent variable; MMSE, Mini-Mental State Examination; WAIS, Wechsler Adult Intelligence Scale; WC, waist circumference; WHR, waist-to-hip ratio.

of socioeconomic factors, depression and cardiovascular factors. Although it is evident that obesity impacts on different areas of cognitive function, the most consistent findings have been with measures of executive function. Because executive function tends to be associated with domain-specific processes, such as language, motor function and attention, a deficit in any of these could also suggest a mild executive dysfunction. Thus, more research is needed in this area to ensure that obesity is associated solely with an executive dysfunction or with a number of deficits.

Past researchers have assumed that adiposity itself does not contribute to poor cognitive performance but merely exacerbates cardiovascular disease, which in turn has an impact on cognition. This hypothesis is not supported by the evidence from young samples who are not likely to have cerebrovascular sequelae. It seems that increased adiposity may be a sufficient condition to affect cognitive performance by mechanisms described later in this review. It is also possible that low levels of executive function are a risk factor for an increased BMI and trigger a bidirectional relationship. The studies in support for this hypothesis are outlined in the next section.

Cognitive deficits predict obesity

Two studies support the premise that cognitive dysfunction predicts or causes increased levels of adiposity. One longitudinal study found that low scores on tests of executive function at age 4 predicted a high BMI at age 6 (67). In addition, higher verbal abilities assessed at 4 years old were associated with decreased odds of being overweight at age 6. Another study used a longitudinal birth cohort of 7,990 children which were first assessed at age 7, then at age 11 and finally at 33 years of age (68). Teachers' report of poor hand control and poor coordination at age 7, and actual tests of motor coordination and hand control at age 11, both predicted obesity at age 33, even after adjusting for social class, sex, mother's age, standardized birth weight, maternal smoking during pregnancy, social adjustment score, general motor disability, mental retardation, epilepsy and BMI at age 7.

These studies show that poor performance in executive function and motor function are risk factors for an increased BMI. This suggests that the cognitive deficits may precede obesity. In fact, one study showed that low levels of executive function predicted low fruit and vegetable intake and less physical activity in children (69). To try to understand the possible bidirectional relationship between obesity and cognition, it would important to examine whether a poor diet has an effect on cognition. Equally important would be to examine whether losing weight has any impact on cognition in the obese. The studies assessing change in cognition after weight loss and after a poor diet are described in the next section.

Cognitive performance after diet or weight loss

Research has shown that a 7-d consumption of a high-fat diet (74% kcal as fat) impairs cognitive function, processing speed and attention, in sedentary men (70). Other studies in humans with increased high-fat intake produced similar results (71,72). As described in the introduction, these findings have also been found in rats (9–13). This suggests that the type of diet, rather than obesity, could be responsible for the cognitive deficits.

In addition, other studies have shown that obese individuals who lost a significant amount of weight had an improvement of their cognitive performance, unrelated to improved mood, which could signify that obesity causes the cognitive dysfunction. One study found that obese individuals after an 8-week diet had an average of 7 kg of weight loss and improved scores in working memory (73). Similarly, another study randomized participants with abdominal obesity to two different diets for 1 year. Participants lost an average of 13 kg and showed improvement in short-term memory a year later, with no significant difference between groups (74). Obese individuals who underwent bariatric weight loss surgery had improved memory performance 12 weeks later compared with obese individuals who did not have surgery (75). The three studies mentioned above show an improvement in memory after weight loss, but not an improvement in executive function (although, as said above, working memory has been proposed to be part of executive function) (24). It is possible that persisting deficits in executive function could exacerbate weight regain long term. Contrary to these findings, a study randomly allocated 72 obese women aged around 50 years old to a 15% fat weight-reducing diet or to a no diet condition for 12 weeks (76) and found that weight loss had no significant effect on cognition, even though their depression scores had significantly reduced and individuals had lost between 2 kg and 12 kg, with an average weight loss of 7.9 kg.

These studies show that weight loss has the potential of reversing some negative effects obesity has on cognition. However, because these studies did not measure any biological variables, nor did they control for exercise which has been shown to improve cognition, it is impossible to say whether changes in cognition were modified by the actual weight loss, exercise or change in metabolic or inflammatory factors.

Genetic vulnerability

One last hypothesis that needs to be evaluated is whether obesity and low cognitive performance have a common genetic vulnerability. That is, there could be a gene(s) for both obesity and cognitive impairment triggered by the environment. Research has repeatedly shown a strong

association between attention deficit hyperactivity disorder (77–82) and obesity and has suggested that there are two facets of the same disease (78). Interestingly, low executive function has been shown to be a predictor of inattentive behaviour (83,84), suggesting that executive dysfunction could be a precursor of attention deficit hyperactivity disorder.

Recently, a prospective study showed that the obesity-related gene, FTO, is associated with reduced brain volume in cognitively healthy subjects and with Alzheimer's disease (AD) risk, even after adjusting a wide number of metabolic and cardiovascular factors (85). It is very possible that this or other genetic factors could impact both obesity and cognition, but more research is urgently needed.

Obesity and cognition in the elderly

Studies described above show that obese individuals of 72 years have cognitive deficits compared with age-matched normal-weight individuals, whereas individuals past 72 years appear to benefit from the extra weight. This is possibly because BMI is not a good measure of body composition in the old. However, two possible biological mechanisms may explain these findings. One is that obese men retain more testosterone in their body fat and this in turn helps prevent cognitive impairment (possibly via conversion to oestrogen). In fact, research has shown that decline in testosterone in older men results in functional impairments in the brain (86) as does early oestrogen loss in women. The other mechanism is that higher leptin in participants may protect cognition (87). However, it is also possible that this is a survival effect in an elderly sample. This means that those individuals who are obese at middle age are more likely to die at younger ages compared with individuals with elderly onset obesity, and those who did not die may have survival genes.

Obesity in the old has been reported to be both detrimental and protective; however, it seems that weight change in age may be a better predictor of cognitive decline. In fact, the use of BMI in the elderly needs to be re-examined. For example, while a BMI of 25 may still be a healthy BMI, weight loss in the elderly can be a consequence of neurodegeneration and cognitive decline, thus studies late in life are difficult to interpret. Gender differences are greater and lean mass differences are covert within the same BMI and are magnified with age. Thus, weight maintenance or rather lean mass maintenance (i.e. positive effect of exercise and negative effect of actual weight loss and nutritional deficit) in old age should be encouraged. Weight loss (by calorie restriction alone) should be discouraged, to prevent loss of lean mass. It is important that guidelines that recommend a certain weight range for a specific age range take into account these findings. More research is needed in older people with BMI of 30 or more; however, it seems rapid weight loss should be discouraged. Regular weight bearing activity (walking, Tai Chi, water classes, etc.) will sustain mobility, joint function and improve body composition at the same BMI.

Biological mechanisms, as suggested by research in the elderly or in rats

Three mechanisms in which obesity could impair cognition are suggested in the literature. However, these have only been examined in the elderly or in rats and may not be associated in the young, which is why we urge more research in this area. These mechanisms are not suggested to be independent and there may be significant overlap between them.

Systemic inflammation

Obesity is considered to be a low-grade pro-inflammatory state as numerous studies have reported low-grade elevation of C-reactive protein, tumour necrosis factor and/or serum amyloid A in obese individuals (88–90). C-reactive protein has also been associated with low cognitive performance in obese elderly women (91). Other inflammatory markers have been linked to cognitive impairment (92,93).

Triglycerides

Elevated triglycerides have been found in obese rats and this disrupts leptin transport across the blood-brain barrier (94). Another experiment tested whether triglycerides could be responsible for the impaired learning and memory seen in obese rats by treating obese and normal-weight mice with gemfibrozil, a drug that lowers triglycerides, or a vegetable oil vehicle (7). Gemfibrozil did improve performance of the obese rats compared to the vegetable oil vehicle, but this effect was not found in the normal-weight rats. This study also found that injecting the triglyceride triolein into the brain impaired acquisition in normal-weight mice, compared with those injected with palmitate or saline. Because triglycerides are not consistently elevated in obese humans, future research could easily examine whether having high triglycerides mediates the relationship between obesity and cognition. In addition, this hypothesis could be tested by measuring cognitive performance in non-obese hypertriglyceridaemia.

Impaired insulin regulation

Insulin helps to regulate brain function and cognitive processes. Data also supports a significant role of insulin in memory. Insulin-sensitive glucose transporters are expressed in the medial temporal region of the brain that supports memory formation (95). Improved memory is induced by raising plasma insulin levels of AD patients (96,97). Recently intranasal insulin administration produced improvements in memory and functioning among

patients with mild cognitive impairment and AD compared with a placebo (97). However, contrary to these findings, higher fasting insulin levels and reduced cerebrospinal fluid-to-plasma insulin ratios, suggestive of insulin resistance, have been observed in patients with AD without apolipoprotein ε4 alleles (98). Individuals with insulin resistance are more likely to suffer from AD (99–102) and those with AD have higher plasma insulin (102). These contrasting results could be explained by the evidence showing that acute hyperinsulinaemia facilitates memory whereas chronic hyperinsulinaemia (usually associated with insulin resistance) may impair it (95,98–102).

Obesity and the brain

Studies have investigated the association of BMI with both grey matter and white matter volume. For example, Walther *et al*. (60) found that, after controlling for hypertension, BMI was associated with decreased grey matter volume in the orbitofrontal cortex, associated with executive function, and right cerebellum, an area that plays an important part in motor function. Other studies have found comparable results in adults of all ages (56,103–106). In addition, BMI has been positively associated with greater white matter volume (60,106), suggesting that obesity may increase myelin. This is another possible mechanism in which old individuals may benefit from obesity. However, BMI has also been associated with large volumes of white matter hyperintensities (107), which may explain why obesity is a risk factor for dementia.

Public health issues

Although obesity is significantly associated with impaired cognition, especially in those individuals aged up to 65 years old, we are still unsure whether these deficits affect the individual and maintain, or exacerbate, the weight. Although prospective research has identified that normal weight is a key factors for longevity with obesity shortening life significantly (2,108), the impact of these deficits on other aspects of health, on the economy and the community in general have not been measured. This review highlights the urgency to invest in novel obesity research and institute informed public health programmes. It is also important to consider the possibility that obesity is, at least in part, a neurological condition, not only a so-called 'lifestyle' disorder. In fact, we propose a common genetic vulnerability for obesity and cognitive impairment which is triggered by lifestyle issues. Potential effective ways of preventing and treating obesity based on this review are discussed in the next section.

Future research and conclusion

Several new directions of research have been suggested by this review article. For example, improving aspects of individual cognitive function may prevent and treat obesity. Cognitive remediation therapy has been shown to be useful to treat cognitive deficits in anorexia nervosa, and in turn correcting these deficits helped individuals gain weight and maintain it long term (109–111). Individuals with anorexia nervosa have cognitive deficits which maintain the disorder. Similarly, we propose that, in the specific domain of feeding behaviour, obese individuals are too flexible, cannot plan a diet, and fail to associate health outcomes with food choices (all aspects of impaired executive function). Although hypothetical, it is possible that cognitive remediation could treat obesity, by helping individuals maintain a healthy lifestyle long term.

In addition, current strategies for obesity prevention (including providing healthier choices, educating parents, encouraging physical activity) have not proved successful in the long term (112,113). Therefore, we propose a new approach, cognitive remediation therapy, designed to improve neurocognitive abilities such as attention, memory and executive function, which may prevent weight gain. Indeed, by increasing the levels of cognitive function this may aid in helping individuals make suitable lifestyle decisions and stop the vicious cycle.

Longitudinal studies are also needed to confirm whether cognition in children and adolescents predicts adiposity in adults, particularly after controlling for covariates such as exercise, socioeconomic status, age, sex, inflammation, nutritional habits, among others. Studies examining the mediating relationships of inflammation, glucose and triglycerides in the relationship between obesity and cognition will also increase insight about the mechanisms.

In conclusion, the evidence supports a hypothesis of an early association between obesity and poor cognitive performance. Although more research is needed to understand the mechanisms and bidirectional relationships between adiposity and cognition, novel treatments aimed at correcting these deficits could be trialled as a test of the hypothesis.

Conflict of Interest Statement

None.

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References

1. Aronne LJ. Epidemiology, morbidity, and treatment of overweight and obesity. *J Clin Psychiatry* 2001; **62**: 13–22.
2. Bray GA, Bouchard C, James WPT. *Handbook of Obesity*. Marcel Dekker Inc: New York, NY, 1998.
3. Battersby C, Hartley K, Fletcher AE, Markowe HJL, Brown RG. Styles W: cognitive function in hypertension: a community based study. *J Hum Hypertens* 1993; **7**: 117–123.

4. Anderson-Hanley C, Sherman ML, Riggs R, Agocha VV, Compas BE. Neuropsychological effects of treatments for adults with cancer: a meta-analysis and review of the literature. *J Int Neuropsychol Soc* 2003; **9**: 967–982.
5. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol* 2008; **7**: 184–190.
6. Manschot SM, Brands AM, van der Grond J, Kessels RPC, Algra A, Kappelle JJ *et al*. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. *Diabetes* 2006; **55**: 1106–1113.
7. Farr SA, Yamada KA, Butterfield DA, Abdul HM, Xu L, Miller NE *et al*. Obesity and hypertriglyceridemia produce cognitive impairment. *Endocrinology* 2008; **149**: 2628–2636.
8. Winocur G, Greenwood CE, Piroli GG, Grillo CA, Reznikov LR, Reagan LP *et al*. Memory impairment in obese zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. *Behav Neurosci* 2005; **119**: 1389–1395.
9. Stranahan AM, Norman ED, Lee K, Cutler RG, Telljohann RS, Egan JM *et al*. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. *Hippocampus* 2008; **18**: 1085–1088.
10. Molteni R, Barnard RJ, Ying Z, Roberts CK, Gomez-Pinilla F. A high-fast, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience* 2002; **112**: 803–814.
11. Greenwood CE, Winocur G. Cognitive impairment in rats fed high-fat diets: a specific effect of saturated fatty-acid intake. *Behav Neurosci* 1996; **110**: 451–459.
12. Winocur G, Greenwood CE. High-fat diets impair conditional discrimination learning in rats. *Psychobiology* 1993; **21**: 286–292.
13. Winocur G, Greenwood CE. Studies of the effects of high fat diets on cognitive function in a rat model. *Neurobiol Aging* 2005; **26**: S46–S49.
14. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT *et al*. Midlife and late-life obesity and the risk of dementia. *Arch Neurol* 2009; **66**: 336–342.
15. Kivipelto M, Ngandu T, Fratiglioni L, Vitanen M, Kareholt I, Winblad B *et al*. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* 2005; **62**: 1556–1560.
16. Gustafson D. A life course of adiposity and dementia. *Eur J Pharmacol* 2008; **585**: 163–175.
17. Whitmer RA, Barrett-Connor E, Quesenberry CP, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ* 2005; **330**: 1360.
18. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology* 2008; **71**: 1057–1064.
19. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.
20. Anderson T, Sachdev P, Brodaty H, Trollor J, Andrews G. Effects of sociodemographic and health variables on Mini Mental State Exam Scores in older Australians. *Am J Geriatr Psychiatr* 2007; **15**: 467–476.
21. Taylor V, MacQueen GM. Cognitive dysfunction associated with metabolic syndrome. *Obes Rev* 2007; **8**: 409–418.
22. Stuss DT, Benson DF. *The Frontal Lobes*. Raven Press: New York, NY, 1996.
23. Luria AR. The frontal lobes and the regulation of behavior. In: Pribram KH, Luria AR (eds). *Psychophysiology of the Frontal Lobes*. Academic Press: New York, NY, 1973, pp. 3–26.
24. Baddeley AD. *Working Memory*. Clarendon Press: Oxford, 1986.
25. Lokken KL, Boeka AG, Austin HM, Gunstad J, Harmon CM. Evidence of executive dysfunction in extremely obese adolescents: a pilot study. *Surg Obes Relat Dis* 2009; **5**: 547–552.
26. Mond JM, Stich H, Hay PJ, Kraemer A, Baune BT. Associations between obesity and developmental functioning in pre-school children: a population-based study. *Int J Obes* 2007; **31**: 1068–1073.
27. Cserje'si R, Molnar D, Luminet O, Lenard L. Is there any relationship between obesity and mental flexibility in children? *Appetite* 2007; **49**: 675–678.
28. Verdejo-García A, Pérez-Expósito M, Schmidt-Río-Valle J, Fernández-Serrano MJ, Cruz F, Pérez-García M *et al*. Selective alterations within executive functions in adolescents. *Obesity (Silver Spring)* 2010; **18**: 1572–1578.
29. Li Y, Dai Q, Jackson JC, Zhang J. Overweight is associated with decreased cognitive functioning among school-age children and adolescents. *Obesity* 2008; **16**: 1809–1815.
30. Miller J, Kransler J, Liu Y, Schmalfuss I, Theriaque DW, Shuster JJ *et al*. Neurocognitive findings in Prader-Willi syndrome and early-onset morbid obesity. *J Pediatr* 2006; **149**: 192–198.
31. Miller JL, Couch J, Schwenk K, Long M, Towler S, Theriaque DW *et al*. Early childhood obesity is associated with compromised cerebellar development. *Dev Neuropsychol* 2009; **34**: 272–283.
32. Azurmendi A, Braza F, Sorozabal A, García A, Braza P, Carreras MR *et al*. Cognitive abilities, androgen levels, and body mass index in 5-year-old children. *Horm Behav* 2005; **48**: 187–195.
33. Fuhs MW, Day JD. Verbal ability and executive functioning development in preschoolers at head start. *Dev Psychol* 2011; **47**: 404–416.
34. Gunstad J, Spitznagel MB, Paul RH, Cohen RA, Kohn M, Luyster FS *et al*. Body mass index and neuropsychological function in healthy children and adolescents. *Appetite* 2008; **50**: 246–251.
35. Roberts ME, Demetriou L, Treasure J, Tchanturia K. Neuropsychological profile in the overweight population. *Therapy* 2007; **4**: 821–824.
36. Boeka AG, Lokken KL. Neuropsychological performance of a clinical sample of extremely obese individuals. *Arch Clin Neuropsychol* 2008; **23**: 467–474.
37. Chelune G, Ortega D, Linton J, Boustany M. Personality and cognitive findings among patients electing gastroplasty for morbid obesity. *Int J Eat Disord* 1986; **5**: 701–712.
38. Davis C, Levitan RD, Muglia P, Bewell C, Kennedy J. Decision-making deficits and overeating: a risk model for obesity. *Obes Res* 2004; **12**: 929–935.
39. Fergenbaum JH, Bruce S, Lou W, Hanley AJG, Greenwood C, Young TK. Obesity and lowered cognitive performance in a Canadian First Nations population. *Obesity* 2009; **17**: 1957–1963.
40. Lokken KL, Boeka AG, Yellumahanthi K, Wesley M, Clements RH. Cognitive performance of morbidly obese patients seeking bariatric surgery. *Am Surg* 2010; **76**: 55–59.
41. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Compr Psychiatry* 2007; **48**: 57–61.
42. Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort study. *Am J Clin Nutr* 2009; **89**: 601–607.
43. Wolf PA, Beiser A, Elias MF, Au R, Vasan RS, Seshadri S. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. *Curr Alzheimer Res* 2007; **4**: 111–116.

44. Sorensen TIA, Sonne-Holm S, Christensen U. Reduced intellectual performance in extreme overweight. *Hum Biol* 1982; **54**: 765–775.
45. Sorensen TIA, Sonne-Holm S, Christensen U. Cognitive deficiency in obesity independent of social origin. *Lancet* 1983; **1**: 1105–1106.
46. Nilsson LG, Nilsson E. Overweight and cognition. *Scand J Psychol* 2009; **50**: 660–667.
47. Cournot M, Marquie JC, Ansiau D, Martinaud C, Fonds H, Ferrieres J *et al*. Relation between body mass index and cognitive function in healthy middle-aged men and women. *Neurology* 2006; **67**: 1208–1214.
48. Gunstad J, Paul RH, Cohen RA, Tate DF, Gordon E. Obesity is associated with memory deficits in young and middle-aged adults. *Eat Weight Disord* 2006; **11**: 15–19.
49. Dore GA, Elias MF, Robbins MA, Budge MM, Elias PK. Relation between central adiposity and cognitive function in the Maine-Syracuse study: attenuation by physical activity. *Ann Behav Med* 2008; **35**: 341–350.
50. Gunstad J, Lhotsky A, Wendell CR, Ferrucci L, Zonderman AB. Longitudinal examination of obesity and cognitive function: results from the Baltimore Longitudinal Study of Aging. *Neuroepidemiology* 2010; **34**: 222–229.
51. Etou H, Sakata T, Fujimoto K, Kurata K, Terada K, Fukagawa K *et al*. Characteristics of psychomotor performance and time cognition in moderately obese patients. *Physiol Behav* 1989; **45**: 985–988.
52. Hackman DA, Farah MJ. Socioeconomic status and the developing brain. *Trends Cogn Sci* 2009; **13**: 65–73.
53. Sobal J, Stunkard AJ. Socioeconomic status and obesity: a review of the literature. *Psychol Bull* 1989; **105**: 260–275.
54. Ogden CL, Lamb MM, Carroll MD, Flegal KM. *Obesity and Socioeconomic Status in Adults: United States 1988–1994 and 2005–2008*. National Center for Health Statistics: Hyattsville, MD, 2010. NCHS data brief no 50.
55. McLaren L. Socioeconomic status and obesity. *Epidemiol Rev* 2007; **29**: 29–48.
56. Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. *BMC Neurol* 2005; **5**: 23.
57. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. *Int J Obes* 2003; **27**: 260–268.
58. Jeong SK, Nam HS, Son MH, Son EJ, Cho HK. Interactive effect of obesity indexes on cognition. *Dement Geriatr Cogn Disord* 2005; **19**: 91–96.
59. Waldstein SR, Katzel LI. Interactive relations of central versus total obesity and blood pressure to cognitive function. *Int J Obes* 2006; **30**: 201–207.
60. Walther K, Birdsill AC, Glisky EL, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. *Hum Brain Mapp* 2010; **31**: 1052–1064.
61. Kilander L, Nyman H, Boberg M, Lithell H. Cognitive function, vascular risk factors and education. A cross-sectional study based on a cohort of 70-year-old men. *J Intern Med* 1997; **242**: 313–321.
62. Kuo HK, Jones RN, Milberg WP, Tennstedt S, Talbot L, Morris JN *et al*. Cognitive function in normal-weight, overweight, and obese older adults: an analysis of the advanced cognitive training for independent and vital elderly cohort. *JAGS* 2006; **54**: 97–103.
63. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Obesity, diabetes and cognitive deficit: the Framingham Heart study. *Neurobiol Aging* 2005; **26S**: S11–S16.
64. Han C, Jo SA, Seo JA, Kim BG, Kim NH, Jo I *et al*. Adiposity parameters and cognitive function in the elderly: application of the 'Jolly Fat' hypothesis to cognition. *Arch Gerontol Geriatr* 2009; **49**: e133–e138.
65. Sturnman MT, Mendes de Leon CF, Bienias JL, Morris MC, Wilson RS, Evans DA. Body mass index and cognitive decline in a biracial community population. *Neurology* 2008; **70**: 360–367.
66. Bagger YZ, Tanko LB, Alexandersen P, Qin G, Christiansen C. The implications of body fat mass and fat distribution for cognitive function in elderly women. *Obes Res* 2004; **12**: 1519–1526.
67. Guxens M, Mendez MA, Julvez J, Plana E, Forns J, Basagana X *et al*. Cognitive function and overweight in preschool children. *Am J Epidemiol* 2009; **170**: 438–446.
68. Osika W, Montgomery SM. Physical control and coordination in childhood and adult obesity: longitudinal birth cohort study. *BMJ* 2008; **337**: 1–5.
69. Riggs N, Chou CP, Spruijit-Metz D, Pentz MA. Executive cognitive function as a correlate and predictor of child food intake and physical activity. *Child Neuropsychol* 2010; **16**: 279–292.
70. Edwards LM, Murray AJ, Holloway CJ, Carter EE, Kemp GJ, Codreanu I *et al*. Short-term consumption of a high-fat diet impairs whole-body efficiency and cognitive function in sedentary men. *FASEB J* 2011; **25**: 1088–1096.
71. Greenwood CE, Winocur G. High-fat diets, insulin resistance and declining cognitive function. *Neurobiol Aging* 2005; **26**: 42–45.
72. Pistell PJ, Morrison CD, Gupta S, Knight AG, Keller JN, Ingram DK *et al*. Cognitive impairment following high fat diet consumption is associated with brain inflammation. *J Neuroimmunol* 2010; **26**: 25–32.
73. Halyburton AK, Brinkworth GD, Wilson CJ, Noakes M, Buckley JD, Keogh JB *et al*. Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. *Am J Clin Nutr* 2007; **86**: 580–587.
74. Brinkworth GD, Buckley JD, Noakes M, Clifton PM, Wilson CJ. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. *Arch Intern Med* 2009; **169**: 1873–1880.
75. Gunstad J, Strain G, Devlin MJ, Wing R, Cohen RA, Paul RH *et al*. Improved memory function 12 weeks after bariatric surgery. *Surg Obes Relat Dis* 2011; **7**: 465–472.
76. Bryan J, Tiggemann M. The effect of weight-loss dieting on cognitive performance and psychological well-being in overweight women. *Appetite* 2001; **36**: 147–156.
77. Altfas JR. Prevalence of attention deficit/hyperactivity disorder among adults in obesity treatment. *BMC Psychiatry* 2002; **2**: 9.
78. Odent M. Attention deficit hyperactivity disorder (ADHD) and obesity: two facets of the same disease? *Med Hypotheses* 2010; **74**: 139–141.
79. Pagoto SL, Curtin C, Lemon SC, Bandini LG, Schneider KL, Bodenlos JS *et al*. Association between adult attention deficit/hyperactivity disorder and obesity in the US population. *Obesity (Silver Spring)* 2009; **17**: 539–544.
80. Cortese S, Bernardina BD, Mouren MC. Attention-deficit/hyperactivity disorder (ADHD) and binge eating. *Nutr Rev* 2007; **65**: 404–411.
81. Levy LD, Fleming JP, Klar D. Treatment of refractory obesity in severely obese adults following management of newly diagnosed attention deficit hyperactivity disorder. *Int J Obes (Lond)* 2009; **33**: 326–334.
82. Cortese S, Angriman M, Maffeis C, Isnard P, Konofal E, Lecendreux M *et al*. Attention-deficit/hyperactivity disorder (ADHD) and obesity: a systematic review of the literature. *Crit Rev Food Sci Nutr* 2008; **48**: 524–537.

83. Kim J, Whyte J, Hart T, Vaccaro M, Polansky M, Coslett HB. Executive function as a predictor of inattentive behavior after traumatic brain injury. *J Int Neuropsychol Soc* 2005; **11**: 434–445.
84. Brocki KC, Eninger L, Thorell LB, Bohlin G. Interrelations between executive function and symptoms of hyperactivity/impulsivity and inattention in preschoolers: a two year longitudinal study. *J Abnorm Child Psychol* 2010; **38**: 163–171.
85. Keller L, Xu W, Wang HX, Winblad B, Fratiglioni L, Graff C. The obesity related gene, FTO, interacts with APOE, and is associated with Alzheimer's disease risk: a prospective cohort study. *J Alzheimers Dis* 2011; **1**: 461–469.
86. Liverman CT, Blazer DG. *Testosterone and Aging: Clinical Research Directions*. National Academies Press: Washington, DC, 2004.
87. Holden KF, Lindquist K, Tylavsky FA, Rosano C, Harris TB, Yaffe K. Serum leptin level and cognition in the elderly: findings from the Health ABC Study. *Neurobiol Aging* 2009; **30**: 1483–1489.
88. Reinehr T, Stoffel-Wagner B, Roth CL, Andler W. High-sensitive C-reactive protein, tumor necrosis factor alpha, and cardiovascular risk factors before and after weight loss in obese children. *Metabolism* 2005; **54**: 1155–1161.
89. Yang R-Z LM-J, Hu H, Pollin TI, Ryan AS, Nicklas BJ *et al*. Acute-phase serum amyloid A: an inflammatory adipokine and potential link between obesity and its metabolic complications. *Plos Med* 2006; **3**: e287.
90. Yudkin JS, Stehouwer CDA, Emeis JJ, Coppack SW. C-Reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction. A potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999; **19**: 972–997.
91. Sweat V, Starr V, Bruehl H, Arentoft A, Tirsi A, Javier E *et al*. C-reactive protein is linked to lower cognitive performance in overweight and obese women. *Inflammation* 2008; **31**: 198–207.
92. Baune BT, Ponath G, Golledge J, Varga G, Arolt V, Rothermundt M *et al*. Association between IL-8 cytokine and cognitive performance in an elderly general population – The MEMO-Study. *Neurobiol Aging* 2008; **29**: 937–944.
93. Trollor JN, Smith E, Baune BT, Kochan NA, Campbell L, Samaras K *et al*. Systemic inflammation is associated with MCI and its subtypes – the Sydney Memory and Aging Study. *Dement Geriatr Cogn Disord* 2010; **30**: 569–578.
94. Banks WA, Coon AB, Robinson SM, Moinuddin A, Schultz JM, Nakaoke R *et al*. Triglycerides induce leptin resistance at the blood-brain barrier. *Diabetes* 2004; **53**: 1253–1260.
95. Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. *CNS Drugs* 2003; **17**: 27–45.
96. Craft S, Asthana S, Newcomer JW, Wilkinson CW, Matos IT, Baker LD. Enhancement of memory in Alzheimer's disease with insulin and somatostatin, but not glucose. *Arch Gen Psychiatry* 1999; **56**: 1135–1140.
97. Benedict C, Frey WH 2nd, Schiöth HB, Schultes B, Born J, Hallschmid M. Intranasal insulin as a therapeutic option in the treatment of cognitive impairments. *Exp Gerontol* 2011; **46**: 112–115.
98. Craft S, Peskind E, Schwartz MW, Schellenberg GD, Raskind M, Porte D. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype. *Neurology* 1998; **50**: 164–168.
99. Taubes G. Neuroscience: insulin insults may spur Alzheimer's disease. *Science* 2003; **301**: 40–41.
100. Ho L, Qin W, Pompl PN, Xiang Z, Wang J, Zhao Z *et al*. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. *FASEB J* 2004; **18**: 902–904.
101. Razay G, Wilcock GK. Hyperinsulinemia and Alzheimer's disease. *Age Ageing* 1994; **23**: 396–399.
102. Vanhanen M, Koivisto K, Kuusisto J, Mykkänen L, Helkala E-L, Hänninen T. Cognitive function in an elderly population with persistent impaired glucose tolerance. *Diabetes Care* 1998; **21**: 398–402.
103. Gunstad J. Relationship between body mass index and brain volume in healthy adults. *Int J Neurosci* 2008; **118**: 1582–1593.
104. Pannacciulli N, Del Parigi A, Chen K, Le DS, Reiman EM, Tataranni PA. Brain abnormalities in human obesity: a voxel-based morphometric study. *Neuroimage* 2006; **31**: 1419–1425.
105. Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH *et al*. Brain structure and obesity. *Hum Brain Mapp* 2010; **31**: 353–364.
106. Taki Y, Kinomura S, Sato K, Inoue K, Goto R, Okada K *et al*. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity* 2008; **16**: 119–124.
107. Haltia LT, Viljanen A, Parkkola R, Kemppainen N, Rinne JO, Nuutila P *et al*. Brain white matter expansion in human obesity and the recovering effect of dieting. *J Clin Endocrinol Metab* 2007; **92**: 3278–3284.
108. Schneider HJ, Friedrich N, Klotsche J, Pieper L, Nauck M, John U *et al*. The predictive value of different measures of obesity for incident cardiovascular events and mortality. *J Clin Endocrinol Metab* 2010; **95**: 1777–1785.
109. Tchanturia K, Davies H, Campbell IC. Cognitive remediation therapy for patients with anorexia nervosa: preliminary findings. *Ann Gen Psychiatry* 2007; **6**: 14.
110. Tchanturia K, Davies H, Lopez C, Schmidt U, Treasure J, Wykes T. Neuropsychological task performance before and after cognitive remediation in anorexia nervosa: a pilot case series. *Psychol Med* 2008; **38**: 1371–1373.
111. Genders R, Davies H, St Louis L, Kyriacou O, Hambrook D, Tchanturia K. Long-term benefits of CRT for anorexia. *Br J Healthc Manage* 2008; **14**: 15–19.
112. Summerbell CD, Waters E, Edmunds LD, Kelly S, Brown T, Campbell KJ. Interventions for preventing obesity in children. *Cochrane Database Syst Rev* 2005; (20): CD001871.
113. Taylor RW, McAuley KA, Barbezat W, Strong A, Williams SM, Mann JI. APPLE Project: 2-y findings of a community-based obesity prevention program in primary school age children. *Am J Clin Nutr* 2007; **86**: 735–742.