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Review

A life course of adiposity and dementia☆

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Abstract

Adiposity, commonly measured as body mass index (BMI), may influence or be influenced by brain structures and functions involved in dementia processes. Adipose tissue changes in degree and intensity over the lifespan, and has been shown to influence brain development in relationship to early and late measures of cognitive function, intelligence, and disorders of cognition such as dementia. A lower BMI is associated with prevalent dementia, potentially due to underlying brain pathologies and correspondingly greater rates of BMI or weight decline observed during the years immediately preceding clinical dementia onset. However, high BMI during mid-life or at least approximately 5–10 years preceding clinical dementia onset may increase risk. The interplay of adiposity and the brain occurring over the course of the lifespan will be discussed in relationship to developmental origins, mid-life sequelae, disruptions in brain structure and function, and late-life changes in cognition and dementia. Characterizing the life course of adiposity among those who do and do not become demented enhances understanding of biological underpinnings relevant for understanding the etiologies of both dementia and obesity and their co-existence.

Keywords: Obesity; Dementia; Alzheimer; Overweight; BMI; Adipose

Contents

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1. Introduction

Overweight and obesity are increasing at epidemic proportions around the world (Ford et al., 2002). The prevalence of overweight and obesity is over 50% among adults in the United States and Europe (Flegal, 2005; Visscher et al., 2000). The highest prevalence has been observed among women age 50 and above (Flegal, 2005), however this is changing as men, and children, are becoming increasingly more overweight and obese as well (Li et al., 2007; Schokker et al., 2007). Women experience the most Alzheimer's disease, which will continue to increase as women live to older ages. One of the most rapidly growing age groups is 85 years and older. At 85, dementia incidence approaches 10% (Aevarsson and Skoog, 1996), and prevalence, 30% (Borjesson-Hanson et al., 2004), with subsequent prevalence estimates as high as 50% at age 95 (Borjesson-Hanson et al., 2004). Alzheimer's disease is expected to reach epidemic proportions between 2010 and 2050, when the number of people with the disease is projected to more than double.

There have been several prospective or nested epidemiologic reports (Barrett-Connor et al., 1996; Buchman et al., 2005; Gustafson et al., 2003; Kivipelto et al., 2005; Nourhashemi et al., 2003; Rosengren et al., 2005; Stewart et al., 2005; Whitmer et al., 2005; Chiang et al., 2007; Whitmer et al., 2007) evaluating BMI in relationship to dementia (Table 1). Most (Gustafson et al., 2003; Hayden et al., 2006; Kivipelto et al., 2005; Rosengren et al., 2005; Whitmer et al., 2005; Chiang et al., 2007; Whitmer et al., 2007) have shown a high BMI to be risky for dementia when measured at least approximately 10 years prior to a clinical diagnosis. Other studies have reported a decline in body weight in the years preceding a dementia diagnosis (Barrett-Connor et al., 1996; Buchman et al., 2005; Knopman et al., 2007; Luchsinger et al., 2007; Stewart et al., 2005), or protective effect of high BMI within 5 years of dementia onset (Luchsinger et al., 2007; Buchman et al., 2005), helping to explain cross-sectional reports of low BMI or underweight being related to dementia (Faxen-Irving et al., 2005; Hogan et al., 1997; Knopman et al., 2007; White et al., 1998; White et al., 1996). One study has shown underweight to be a risk factor when measured 10–20 years prior to dementia onset (Knopman et al., 2007). Therefore, among some individuals, weight loss may be a potential preclinical marker for Alzheimer's disease, and therefore a potential susceptibility phenotype. In addition, low body weight or low BMI has also been shown to predict mortality among demented (Bo et al., 2003). Data on obesity and cognitive impairment is less clear. This has been reviewed previously (Gustafson, 2006).

Biological plausibility for a link between high adiposity indices and dementia is relevant for understanding disease etiology, and to form bases for prevention efforts to decrease disease and health care burden. Adipose tissue may contribute to cognitive decline and dementia in a variety of ways. Higher levels of adiposity or adiposity-related cues leading to cardio- and cerebrovascular disease, may begin as early as during fetal development (Finch, 2005). Second, adipocyte or adipocyte-associated hormones and cytokines may cross the blood-brain barrier and influence health of the brain. Third, basic differences in brain structure and function may influence both whole body adiposity (for example, in terms of acquisition and maintenance) and brain health, and their interaction with each other over the life course. For example, adults with higher adiposity may have a susceptible brain leading to higher adiposity due to basic underlying differences in structure and function of the brain, upon which an interplay of adipose-derived and -related hormones and vascular events occurs. Later, in dementia, areas of the brain involved in energy homeostasis, and learning and memory, are also most susceptible to age-related cognitive decline.

2. Adiposity and developmental origins

Our love affair with fat begins *in utero* — moving forward with time from basic need to evolution of taste preferences and anthropometric characteristics. The relationship between adiposity and health of the aging brain is a lifelong process. The fetal origins, or Barker, hypothesis, was first described in *the Lancet* by Barker and Osmond (1986). This report was based on a geographical analysis of England and Wales, showing that areas of high adult rates of ischemic heart disease in 1968–78 were also those with high infant mortality rates in 1921–25. This contrasted the generally accepted notion that heart disease belonged to affluent social classes. It was suggested that neonatal and postnatal factors, such as nutrition, influenced later adult disease by acting against a background of developmental plasticity (Barker, 1990) or adaptive biological responses enhancing survival (Bateson et al., 2004). While this plasticity has been advantageous from an evolutionary standpoint, it may not continue to be within the context of too rapid environmental change, as has been observed over the last 100 years globally in relationship to obesity, diet, and aging (Gluckman and Hanson, 2006; Gluckman et al., 2005). Indigenous populations in the United States and developing nations around the world, for example, are reaping adverse obesity consequences of generations of beneficial evolution – a thrifty genotype adaptation – that has become maladaptive due to nutritional excess and environmental change (Knowler et al., 1983). In contrast, it is not clear how parallel 20th century trends such as a drop in the mean age of menarche over time (Elmquist and Flier, 2004; Frisch and McArthur, 1974), steady increases in intelligence quotient (IQ) scores, increasing birth weights, and improved and more education for larger proportions of the population, will influence establishment of a cognitive substrate that can counteract potential late-life declines adult health and cognition (Biro et al., 2005; Shenkin et al., 2004).

Adipose tissue stores of a developing fetus contribute to short- and long-term health (Kind et al., 2006). Enhancing postnatal survival are fetal fat stores that increase dramatically between 35 and 40 weeks gestation, and postnatal fat stores up to age 5 years (Cunnane and Crawford, 2003). The importance of fetal fat accumulation has long been known, as premature babies are at higher risk of slower neurological development and smaller brain size, and fatty acids released from white adipose tissue after birth are a major source of energy for the newborn (Medina and Tabernerno, 2005). Thus, adipose tissue, both as total fat and individual fatty acids, is important in fetal and postnatal brain development.

Higher birth weights have been related to both obesity and higher intelligence or cognitive reserve. Related to obesity, there are two primary observations. The first is that a high level of neonatal adiposity relates to higher childhood and adult BMI. The second is that low neonatal adiposity leads to compensatory effects on appetite and leptin and insulin sensitivity, which

Table 1
Prospective and retrospective (nested) epidemiological studies of adiposity and dementia

Study population	Baseline age (years)	Years of follow-up	Baseline BMI (kg/m^2)	Dementia assessment	Number of demented/ total *n*	Risk ratios for dementia
Prospective studies						
Gerontological and Geriatric Population Studies, H70 (Sweden) (Gustafson et al., 2003)	70	18	25.8 (3.8)	Neuropsychiatric interview, key informant interview, medical record review	93/382	In women with dementia between 79 and 88 years, for each unit (kg/m^2) increase in BMI: At age 70 years, RR=1.13 (1.04–1.24) RR for AD=1.36 (1.16–1.59) At age 75 years, RR=1.13 (1.04–1.24) RR for AD=1.35 (1.19–1.53) At age 79 years, RR=1.15 (1.05–1.26) RR for AD=1.23 (1.10–1.37)
Primary Prevention Study (Sweden) (Rosengren et al., 2005)	47–55	28	25.5 (3.3) among nondemented	Primary+secondary dementia hospital discharge diagnoses	254/7148	In men, the risk of dementia by BMI level: BMI<20: RR=2.43 (1.10–5.29) 20.00<BMI<22.49: RR=1.00 27.50<BMI<29.99: RR=1.72 (1.03–2.88) BMI≥30.00: RR=1.98 (1.10–3.56)
Kaiser Permanente (USA) (Whitmer et al., 2005)	40–45	27	10%≥30 36% 25≥BMI<30; 53% 18.6≥BMI<25; 1.3%<18.6	ICD-9 criteria	713/10,276	In women and men, the risk of dementia by BMI level: BMI>30: RR=1.74 (1.34–2.26) 25≥BMI<30: RR=1.35 (1.14–1.60) Highest fifth of subscapular skinfold thickness: RR=1.72 (1.36–2.18) Highest fifth of triceps skinfold thickness: RR=1.59 (1.24–2.04) In women only, the risk of dementia by BMI level: BMI>30: RR=2.07 (1.49–2.89) 25≥BMI<30: RR=1.55 (1.22–1.97)
Cardiovascular Risk Factors, Aging, and Dementia, CAIDE (Finland) (Kivipelto et al., 2005)	51	21	26.6 (3.7)	Screening, clinical, and differential diagnostic phases	61/1449	In women and men, the risk of dementia with obesity: BMI≥30: OR=2.09 (1.16–3.77) No significant effect of BMI at lower levels
Personnes Agees Quid, PAQUID Study (France) (Nourhashemi et al., 2003)	≥65	8	24.6 (3.9)	Screening, clinical, and differential diagnostic phases	221/3557	In women and men, the risk of dementia by BMI level: BMI<21: RR=1.48 (1.08–2.04) with inclusion of all dementias over 8 years; RR=1.19 (0.72–1.96) when individuals developing dementia within 5 years of baseline were excluded No effect of baseline high BMI
Rancho Bernardo Study (USA) (Barrett-Connor et al., 1996)	50–79	20	25.0	Screening, clinical, and differential diagnostic phases	60/299	Women and men developing AD experienced a greater decline in body weight (≥5 kg) compared to those not developing dementia; men who developed AD had a higher average baseline body weight
Honolulu Asia Aging Study, HAAS (USA) (Stewart et al., 2005)	45–66	32	23.9 (2.7)	Screening, clinical, and differential diagnostic phases	112/1890	In men: During the last 6 years of follow-up, mean age- and education-adjusted weight loss with incident dementia was −0.58 kg (95% CI −0.53 to −0.19), compared to −0.22 kg/y (95% CI: −0.26 to −0.18) among men not developing dementia No effect of baseline BMI

(continued on next page)

Table 1 (*continued*)

Study population	Baseline age (years)	Years of follow-up	Baseline BMI (kg/m^2)	Dementia assessment	Number of demented/ total *n*	Risk ratios for dementia
Religious Order Study (USA) (Buchman et al., 2005)	77.1	Average 5.6	27.4 (5.4)	Physician exam, NINCDS-ADRDA criteria for AD	151/832	In women and men: Risk of dementia per one unit decline in BMI from baseline: RR=0.94 (0.91–0.98) Risk of dementia by one unit less BMI at baseline: RR=0.73 (0.63–0.85) Similar result when excluding those developing AD during first 4 years
Cache County study of Memory in Aging (USA) (Hayden et al., 2006)	≥65 years	2–5 (average 3.2)	18.7% of nondemented with obesity, BMI≥30	Screening, clinical, and differential diagnostic phases; DSM-IIIR criteria, via consensus of psychiatrist, neurologist, neuropsychologist, cognitive neuroscientist AD: NINDS-ADRDA VaD: NINDS-AIREN criteria	141/3123 (AD and VaD only)	In women and men: The risk of all dementias with BMI≥30: RR=1.76 (1.03–2.88) The risk of AD with BMI≥30: RR=1.93 (1.05–3.36) In women only, the risk of AD with BMI≥30: RR=2.23 (1.09–4.30)
Kaiser Permanente (USA) (Whitmer et al., 2007)	40–45	21–42	10%≥30 BMI>30, 9%; BMI 25–29, 36%; BMI 18.5–24.9, 55%; BMI<18.5, 1.35%	ICD-9 criteria	609/10,136 477 AD; 132 VaD mutually exclusive diagnoses	In women and men, the risk of AD for: BMI≥30: RR=3.10 (2.19–4.38) BMI 25–29: RR=2.09 (1.69–2.60) In women and men, the risk of vascular dementia for: BMI≥30: RR=5.01 (2.98–8.43) BMI 25–29: RR=1.95 (1.29–2.96)
Washington Heights-Inwood community of New York City (USA) (Luchsinger et al., 2007)	>65 years	5 years	26.68 (5.09) Waist circumference: 92.32 (36.34)	DSM-IV criteria, via consensus of neurologists, psychiatrists, and neuropsychologists AD: NINDS-ADRDA VaD: within 3 months of stroke	181/893	In women and men, BMI in 3rd quartile, 26.3–29.6 compared to 1st quartile (BMI<23.4): RR for all dementias=0.6 (0.40–0.90) RR for AD=0.5 (0.30–0.90) Waist circumference: Increasing HR by waist circumference quartile for dementia with stroke, $p=0.03$ Age<76 years: U-shaped relationship between BMI and all dementias; waist circumference in 4th quartile, >97 cm compared to 1st quartile (≤83 cm): RR for all dementias=2.3 (0.90–5.8) RR for AD=5.1 (1.00–26.40) Weight loss: RR for all dementias=1.9 (1.20–2.90) RR for Dementia with stroke=4.90 (1.90–12.90)
Kaiser Permanente (USA) (Whitmer et al., in press)	42.5	36	30.7 (4.5) among those with central obesity; 24.2 (3.0) among those with no central obesity	ICD-9 criteria	1049/6583	In women and men, the risk of dementia by BMI and central obesity level: BMI 18.5–24.9, no central obesity: RR=1.00 BMI 18.5–24.9, no central obesity: RR=1.89 (0.94–3.81) BMI 25.0–29.9, no central obesity: RR=1.82 (1.57–2.12) BMI≥30, no central obesity: RR=1.81 (1.19–2.76) BMI 25.0–29.9, central obesity: RR=2.34 (1.82–3.02) BMI≥30, central obesity: RR=3.60 (2.85–4.55)

Table 1 (*continued*)

Retrospective (nested) studies	Baseline age (years)	Years retrospective	Baseline BMI or body weight (median)	Dementia assessment	Number of demented/ total *n*	Risk ratio for all dementias
Multiple Risk Factors for Major Diseases (MRMD) and Cancer Screening Program (CSP) Studies, (Taiwan) (Chiang et al., 2007)	≥30 years	8–20	Among all demented, 30.6%≥25.5; Among controls, 22.5%≥25.5	National Health Insurance Database, Taiwan, followed by clinical confirmation by psychiatrists or neurologists;ICD-9 and DSM-IV	157/785 (1:4 case-control match on age, time of enrollment, sex, and residential township)	In women and men, J-shaped relationship between BMI and all dementia: BMI<20.5: RR=1.84 (1.02–3.33) 20.5<BMI<22.9: RR=1.00 23.0<BMI<25.4: RR=1.87 (1.08–3.23) BMI≥25.5: RR=2.44 (1.39–4.28) Between BMI and AD: BMI≥25.5: RR=2.33 (1.06–5.10) Between BMI and vascular dementia: BMI<20.5: RR=4.28 (1.55–11.84) 20.5<BMI<22.9: RR=1.00 23.0<BMI<25.4: RR=2.73 (1.05–7.13) BMI≥25.5: RR=4.62 (1.62–13.20) Stratification by smoking status showed effects of BMI≥25.5 among smokers
Rochester Epidemiology Project, USA (Knopman et al., 2007)	40–99 years, based on age of demented (93.9%> 70 years)	21–30	Women controls: 141 lb Men controls: 168 lb	Medical record reviewal using DSM-IV criteria and all available information	481/962 (1:1 case-control match on age and sex)	In women and men, the odds of dementia by BMI level 9–10 years before dementia: 1st BMI quartile: OR=3.59 (1.51–8.55) In women: 1st BMI quartile: OR=3.42 (1.66–7.04) In men: 1st BMI quartile: OR=0.59 (0.17–1.98)

results in rapid postnatal growth, and higher childhood and adult body mass index (Vickers et al., 2000). Data from the Helsinki Birth Cohort Study suggest that lower birth weight is related to accelerated BMI and body weight accrual between age 2 and 11 years and subsequently higher risk of coronary events (Barker et al., 2005). The relationship between birth weight and adult obesity appears to be U-shaped, with both lowest and highest quintiles of birth weights linked to obesity. This type of relationship is also observed for type 2 diabetes mellitus (Rich-Edwards et al., 1999), indicating potentially different type 2 diabetes mellitus phenotypes (Newsome et al., 2003), as well as higher coronary heart disease mortality, glucose intolerance (Hales et al., 1991), and insulin resistance (Phillips et al., 1994), all risk factors for dementia (Brook et al., 2001; Craft, 2007; DeMichele et al., 2002; Suwaidi et al., 2001; Williams et al., 2002; Yki-Järvinen and Westerbacka, 2000; Zhang and Reisin, 2000).

In relationship to intelligence or the establishment of cognitive reserve (Milgram et al., 2006), higher birth weight for gestational age has been positively related to childhood IQ score at ages 7–11 years (Lawlor et al., 2006b; Richards et al., 2001, 2002; Shenkin et al., 2001), and even adult cognition (Bergvall et al., 2006; Richards et al., 2002), crudely or after adjustment for socioeconomic, family, and maternal characteristics. Most of the studies reporting on birth weight and intelligence have taken place in Europe, with birth cohorts spanning 60 years, from 1921 to 1981 (Bergvall et al., 2006; Lawlor et al., 2006b; Richards et al., 2001, 2002; Shenkin et al., 2001). Interestingly, despite improvements in nutrition, education, and socioeconomic environments during the 20th century, a positive linear association between birth weight and childhood IQ is observed across cohorts. While, low birth weight is associated with a variety of unhealthy maternal characteristics including smoking, alcohol intake, low energy intake, inadequate weight gain during pregnancy, and low pre-pregnancy weight (Ashdown-Lambert, 2005). In those studies that can adjust for these factors, birth weight remains positively related to intelligence. Lower birth weights have also been related to future psychiatric disorders (Batstra et al., 2006).

Not only is birth weight important, but birth length; and birth length is highly correlated with adult height. Data from the British 1946 survey suggest that while birth weight is the strongest predictor of cognitive score at age 8 (compared to height and weight at age 8), the relationship between birth weight and height at age 26 is even more related to cognitive score at age 26. Verbal memory was especially influenced by adult height. Longer adult body height has been related to lower dementia risk (Beeri et al., 2005; Kim et al., 2008). While birth weight has often been looked at as an indication of adverse adult disease, birth length, or the partitioning of weight and length has not often been reported. This is critical from an etiologic standpoint, as birth weight is a function of fat, protein, and mineral mass, while length is an indication of physical maturation, and indicates other physiological processes, such as the influence of growth hormones.

3. Adiposity interplays with intelligence during adolescence and adulthood

While higher birth weights and early nutritional status may influence measures of childhood IQ and even adult cognition, potential surrogates for cognitive reserve, it is difficult to understand the direction of the relationship between obesity and intelligence during adolescence and adulthood (Fig. 1). Various questions could be posed such as, ‘Does obesity interfere with

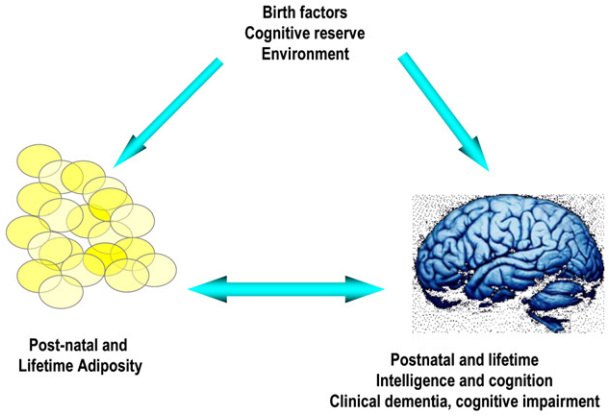

Fig. 1. Interrelationships among birth factors, and later obesity, intelligence, cognition, and dementia.

intellectual development?' or 'Does level of intelligence influence the development of obesity?' In prospective studies, the most common question has been the latter.

The effects of adiposity on brain health in late-life perhaps cannot be completely evaluated without considering cognitive reserve or level of intelligence. However, measurement of this parameter is infrequent or unavailable in many epidemiologic studies of dementia, and level of education is often used as a surrogate marker. Education is inversely related to higher dementia risk, however problematic to assess in earlier cohorts who experience a narrower range of total formal education. Intelligence may be the single largest influencer of whether someone practices good health behaviors, such as eating properly and maintaining a healthy body weight (Gottfredson, 2004). Lower childhood IQ score is related to later adiposity, smoking behavior, high blood pressure, cardiovascular disease, and mortality (Chandola et al., 2006). Childhood IQ has been related to the subsequent development of obesity and related adverse sequelae in the National Child Development Survey, a longitudinal study in the United Kingdom; and the Aberdeen Children of the 1950s cohort in Scotland, each including almost 10,000 men and women (Chandola et al., 2006; Lawlor et al., 2006a). These studies are particularly important, due to their long follow-ups. In the United Kingdom, lower IQ measured at 11 years was related to obesity 31 years later, even after adjustment for numerous other factors, such as childhood height, BMI at 16 years, pubertal development, parents' BMI, birth weight, father's occupational social class, sports activity, and sweets consumption. Among those with an IQ in the lowest tertile, risk for obesity was doubled among women and 60% higher in men. In Scotland, there was a strong age- and sex-adjusted inverse relationship between IQ score at age 7 and adult BMI measured at age 45–52 years (Lawlor et al., 2006a). However, in both studies, if educational attainment was considered, childhood IQ was not related to obesity risk.

Postnatal weight change, as well as adult weight and height attainment, has also been related to cognition. While birth weight and length may be positively related to childhood IQ, data related to postnatal growth shows divergence. In the British 1946 birth cohort, it was shown that weight gain after age 15 was related to lower cognition at age 26, but that height continued to be related to better cognition (Richards et al., 2002). Consideration of education did not alter these findings. In a Danish study of draft board registrants (Halkjaer et al., 2003), a mean decrease in BMI after age 19 among non-obese men, was related to a higher mean intelligence score at age 19; and intelligence score was protective for the development of obesity. However, adjustment for education overwhelmed the latter findings (Halkjaer et al., 2003). Also in the Danish study, among juvenile-onset obese men, higher intelligence was related to a greater decrease in BMI after age 19, which disappeared with consideration of education; and education was protective for the persistence of obesity. Fig. 2 illustrates these hypotheses.

Developmental origins data have led many researchers to hypothesize a link between brain and bone development, since early growth appears to be good for both brain and bone, but bad for cardiovascular disease, diabetes, and obesity. Insulin-like growth factor (IGF) may be a link between brain and bone. Similar to leptin, IGF and IGF receptors, and growth hormone and growth hormone receptors, are located in parts of the brain, such as hippocampus, that are responsible for learning and memory. Early in life, IGFs and growth hormone may play a role in the development of areas of the brain that could explain associations between body size and subsequent measures of cognitive functions (van Dam et al., 2000). This would be in line with observed associations between obesity and late-life brain pathologies and dementia and consideration of differential late-life rates of BMI change in dementia. Obesity could be a risk factor for late-life disease such as dementia in a scenario where a larger body size accompanies and even promotes survival, but then becomes a risk factor for dementia among those who are susceptible due to survivorship to high age. This has also been discussed by others (Ross et al., 2007).

4. Other adult-life adiposity–dementia mechanisms

During mid-life, a number of additional events and mechanisms may occur to further the role of higher adiposity in brain health. Several are discussed here, however this is not exhaustive.

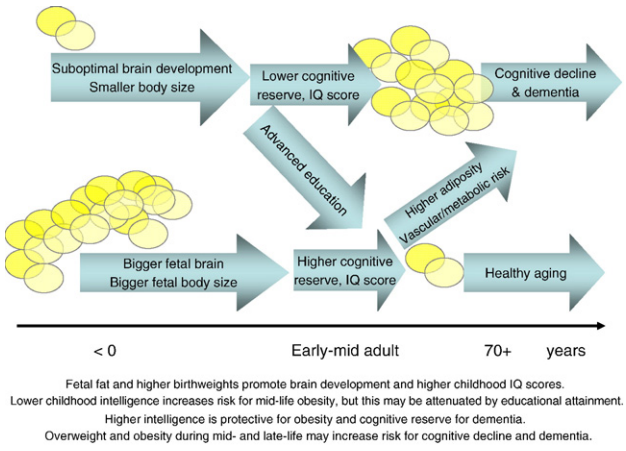

Fig. 2. Adiposity and brain interplay throughout life.

4.1. Deposition of non-adipose tissue fat

It has been known for centuries that non-adipose deposits of triglycerides (also referred to as steatosis or lipotoxicity) may be adversely related to human health (McGavock et al., 2006; Rabkin, 2007). This has been described for various tissues including heart, pancreas, liver, and skeletal muscle, and, as opposed to total fat, may be the primary fat-related cause and correlate of cardiomyopathy, beta-cell failure in type 2 diabetes, and non-alcoholic liver steatosis. When data are combined across studies, BMI is positively correlated with myocardial fat content (Szczepaniak et al., 2003). Accumulation of triglyceride in skeletal muscle, for example, is positively correlated with the severity of insulin resistance, although perhaps not the cause (Pan et al., 1997). Inclusion of more sophisticated imaging techniques in epidemiologic and clinical studies of these types of fat deposits may allow further insight into potential etiological processes related to brain health.

4.2. Activations of the renin–angiotensin system

While, the classical function of the renin–angiotensin system is blood pressure regulation, the renin–angiotensin system may also provide a link between obesity, hypertension, and vascular syndromes, such as type 2 diabetes, and health of the brain (Goossens et al., 2003; Katzov et al., 2004). Human brain and adipose tissue express a full renin–angiotensin system. The adipose renin–angiotensin system is involved in adipocyte growth, differentiation, and metabolism (Strazzullo et al., 2003). The renin–angiotensin system is activated in response to low levels of blood pressure, when angiotensin is converted by renin to angiotensin I, which is subsequently converted to angiotensin II by the angiotensin converting enzyme (ACE). Angiotensin II interacts with angiotensin receptors 1 and 2, to mediate major cardiovascular effects of the renin–angiotensin system, such as increasing blood pressure (Goossens et al., 2003). In the brain, angiotensin II continues conversion to angiotensin IV, which, acting through angiotensin receptor 4 (also known as insulin-regulated aminopeptidase, IRAP) (Albiston et al., 2001; Savaskan, 2005), enhances learning and memory in animal models (Albiston et al., 2001). Thus, the renin–angiotensin system may link vascular health in the periphery, most likely in proportion to the amount of body fat present (Goossens et al., 2003), to dementia processes in the brain (Goossens et al., 2003; Katzov et al., 2004). Larger amounts of body fat increase vasoactivity and expression of vasoactive systems, which leads to increased blood levels of leptin, endothelin, adiponectin, resistin, and numerous other hormones, growth factors, and cytokines through enhanced expression of the genes encoding for these compounds in adipose tissue itself (Barton et al., 2003).

4.3. Actions of leptin

Amount of adipose tissue is positively related to blood leptin levels (Friedman and Halaas, 1998; Lissner et al., 1999), and the CA1 nucleus in the brain is directly affected by adipose-derived hormones, such as leptin. While leptin was deemed the putative obesity hormone in the mid-1990s (Maffei et al., 1995; Zhang et al., 1994), with effects possibly mediated by an impaired blood-brain barrier (Banks, 2003), it did not become the answer to the current obesity epidemic as originally hoped. However, leptin has been shown to have numerous effects on brain development (Harvey et al., 2005) and potentially on brain health in cognition and aging, affecting the function of the hypothalamus, and learning and memory processes controlled by the hippocampus (Davidson et al., 2005). In adults with a recessive mutation in the *ob* gene (homologous to *ob*/*ob* mice), leptin replacement is trophic for the brain, and increases gray matter tissue in the anterior cingulate gyrus, the inferior parietal lobe, and cerebellum (Matochik et al., 2005).

Presence of the leptin receptor in the hippocampus, hypothalamus, amygdala, cerebellum, and brain stem indicates potentially linked regulatory mechanisms (Davidson et al., 2005; Harvey et al., 2005). Recent experimental data show that leptin and adiponectin, another adipose-derived hormone, interact directly with hypothalamic nuclei and regulate energy expenditure and hyperphagic responses (Kishi and Elmquist, 2005; Qi et al., 2004). Leptin, may even shape the hypothalamus in the earliest stages of development and enhance cognition (Harvey et al., 2005). Direct leptin administration has been shown to improve memory processing in mice and enhance *N*-methyl-D-aspartic acid (NMDA) receptors (Harvey et al., 2005). However, other roles of leptin and related adipose-derived factors in the Alzheimer brain are not clear (Fewlass et al., 2004; Olsson et al., 1998; Power et al., 2001). We have explored the influence of leptin on blood-brain barrier (BBB) disturbance, a common occurrence in those with dementia and vascular diseases (Blennow et al., 1990). While leptin was not related to BBB integrity in otherwise healthy women aged 70 years or older, BBB was related to a combination of adiposity markers including being overweight or obese and lower levels of sex hormone binding globulin (SHBG) levels (Gustafson et al., 2007). SHBG is highly inversely correlated with adiposity (Pearson's age-adjusted correlation $r=-0.53$), and may therefore not only reflect sex hormone metabolism differences, but also the influence of specific adiposity depots.

Leptin also plays a role in brain reward systems (Fulton et al., 2006; Fulton et al., 2000). However, cross-sectional studies in obese versus non-obese young adults are unclear. Fasting plasma leptin has been inversely correlated with grey matter volume in areas of the brain in which obese have reduced grey matter in comparison with lean individuals (Pannacciulli et al., 2007).

4.4. Actions of ghrelin

Ghrelin, a stomach- and brain-derived, orexigenic peptide hormone, may interact with leptin to regulate energy balance. Ghrelin is an example of the neurochemical overlap between reward and energy balance regulation systems, and the reward systems have been implicated in addictive behaviors such as compulsive overeating and drug dependence. Ghrelin also appears to activate the cholinergic–dopaminergic reward link, which is associated with reward and motivated behavior, such as food searching (Jerlhag et al., 2006). Interestingly, there is a high degree of co-morbidity between eating disorders and drug and alcohol abuse in humans (Wolfe and Maisto, 2000).

Polymorphisms in the pro-ghrelin gene have been associated with obesity (Ukkola et al., 2002) and methamphetamine dependence (Yoon et al., 2005), while polymorphisms in the ghrelin receptor gene have been associated with bulimia (Miyasaka et al., 2006) and obesity (Baessler et al., 2005).

4.5. Actions of other hormones and neuropeptides

A myriad of other hormones have been related to obesity and the regulation of food intake, as well as concomitant disease states. Examples of these hormones include: insulin, adiponectin, tumor necrosis factor alpha, plasminogen activator inhibitor-1, retinol binding protein, and resistin (Katagiri et al., 2007). Specifically secreted by the gut are those such as cholecystokinin, pancreatic polypeptide, peptide YY, and glucagon-like peptide 1 (Huda et al., 2006); and examples of neuropeptides include neuropeptide Y, galanin, agouti-related protein, and alpha-melanocyte-stimulating hormone (Wilding, 2002). Numerous reviews have been written on these hormones in relationship to their food intake regulatory functions. However, it is unclear for most, as to their role in dementia-related processes. Insulin and insulin resistance are reviewed extensively by others in this issue and will not be discussed here.

4.6. Disruptions in brain structure and function

One approach to understanding how adiposity may influence cognitive and dementia processes over a lifetime is to better understand parallels between brain structure and function in food intake regulation and dementia. Data from our population-based studies in Sweden suggest parallel linear trends in average BMI from mid- to late-life related to the presence of brain changes — higher BMI from mid- to late-life is related to temporal atrophy (Gustafson et al., 2004) and lower BMI from mid- to late-life is related to other neuropsychiatric conditions, such as geriatric depression (unpublished data). In addition, retrospective analyses (Gustafson et al., 2007) indicate that blood-brain barrier integrity is related to a cluster of obesity-related factors 24 years previous. These data are suggestive of inter-individual differences in brain structure and/or function that influence feedback mechanisms and control of food intake. These data also illustrate that while an obesity epidemic is upon us, energy metabolism is highly regulated within an individual at the cellular level over the lifetime (Cota et al., 2007; Shaw et al., 2007).

Superimposed upon a regulated energy metabolism are responder/non-responder phenomena to environmental obesigenic stimuli. For example, observations of stress-related disruptions in eating behavior (Adam and Epel, 2007) show that there are 'stress eaters' who naturally have higher stress reactivity, manifested by higher urinary cortisol and insulin levels and weight gain during stressful periods (Epel et al., 2004). Distinct food preferences, such as high fat foods (Kirschbaum et al., 1993) or more calorie-dense foods, have also been observed among those with greater stress responses. In relationship to adiposity-related dementia susceptibility, there may be those who are 'at risk' based on similar or unidentified mechanisms.

Numerous brain regions are involved in the regulation of energy homeostasis (Schwartz et al., 2000) and the neural regulation of food intake. It was shown 20 years ago, that lesions of the hypothalamic ventromedial nucleus produce obesity, and of the lateral hypothalmic area, leanness (Bray et al., 1990). Imaging studies have shown that there is differential stimulation of specific areas of the brain in fasted versus fed states, as well. Hunger has been contrasted to satiety using PET (Positron Emission Tomography), and is related to significant changes in regional cerebral blood flow in the hypothalamus, amygdala, and insula cortex, as well as greater regional cerebral blood flow in the bilateral striatum, anterior cingulate, thalamus, and brainstem (Hinton et al., 2004); whereas satiety has been related to greater regional cerebral blood flow in the lateral orbitofrontal cortex, bilateral occipital cortex, inferior temporal cortex, and posterior temporal cortex (Hinton et al., 2004). The nucleus accumbens is also an important brain structure regarding taste and visceral functions, and involved in overall control of food intake, receiving information from the amygdala, hippocampus, thalamus and prefrontal cortex related to emotional learning, memory and complex cognition (Kelley, 2004).

Studies using MRI (Magnetic Resonance Imaging) have identified a number of brain regions potentially related to adult human obesity. These are prefrontal areas implicated in the regulation of taste, reward, and behavioral processing (Pannacciulli et al., 2006). In obese, decreased gray matter density of the right cerebellum, right frontal operculum, left postcentral gyrus, right and left putamen, and right and left middle frontal gyrus has been observed; whereas lean individuals have decreased gray matter density of the left calcarine, left middle occipital gyrus, left vermis, right middle frontal gyrus, left inferior frontal gyrus, and right cuneus regions. White matter density of the right putamen has also been observed to be lower among lean (Pannacciulli et al., 2006). Therefore, a number of brain regions and processes important for dementia are also important for the regulation of food intake and energy metabolism.

Emotional learning, memory and complex cognition affect eating behavior and are affected in dementia as well. A classic example is memory impairment, the first symptom in Alzheimer's disease, individuals with memory impairments may forget to eat, and thus experience declines in body weight. However, 'body memory' related to food intake in general, may also influence obesity susceptibility. Numerous hypotheses relating memory, a hippocampal function, and control of energy intake, a hypothalamic function, have been brought forward (Davidson et al., 2005; Kelley, 2004; Tracy et al., 2001). One interesting hypothesis relating establishment of body weight set points and feeding behavior to late-life body weight disturbances in Alzheimer's disease, is related to common involvement of hippocampal formations, for example CA1 (*cornu ammonis*). In early Alzheimer's disease, neuropathological lesions appear to be selectively located in medial temporal lobe structures, including the transentorhinal cortex, entorhinal cortex, and CA1 area of the hippocampal formation (Braak and Braak, 1991; Delacourte, 1999), the evidence base for which has been underscored as part of the suggested from the

National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) revisions for diagnosis of Alzheimer's disease (Dubois et al., 2007). The entorhinal cortex within the temporal lobe, is an area of neuropathological, ischemic and other insults in early dementia (Squire and Zola, 1996; Welsh-Bohmer et al., 2001). Temporal atrophy, an early hallmark of dementia and cognitive decline, is a manifestation of neuronal degeneration (deLeon et al., 1996; Visser et al., 2002), and has been related to higher BMI levels 24 years before an atrophy measurement using computed tomography (CT) (Gustafson et al., 2004), and cross-sectionally to lower MRI measures of global brain volume in a study of women and men aged 40–66 years (Ward et al., 2005). Higher BMI has also been shown to predict a higher rate of atrophy progression measured using serial MRI (Enzinger et al., 2005). Central adiposity (high waist-to-hip ratio) has been cross-sectionally related to temporal atrophy using MRI (Jagust et al., 2005).

High BMI may lead to atrophy, or alternatively, some level of atrophy or susceptibility to atrophy may be present among those with a higher BMI due to involvement of common brain structures related to energy metabolism and dementia. Having a smaller temporal lobe volume early on may contribute to dysregulatory events leading to both higher levels of BMI throughout life and/or are reflective of diminished cognitive reserve. This latter scenario has been suggested in a study of children and adolescents using MRI to measure entorhinal cortex thickness in relationship to the primary susceptibility gene for sporadic Alzheimer's disease, apolipoprotein E (APOE) (Saunders et al., 1993; Shaw et al., 2007). Possession of any APOEε4 allele was related to a thinner left entorhinal cortex, with a stepwise increase in entorhinal thickness in the ε3 carriers, followed by those carrying an ε2 allele.

4.7. Adiposity, addictive behaviors and dementia

An area of potential overlap that may help shed light on the adiposity–dementia relationship with consideration for changes in structure and function, is the relationship between obesity and addiction. Is food addiction behind climbing obesity rates? Are certain individuals more likely to be addicted to foods that promote obesity? Is this addiction due to underlying differences in brain morphology and connectivity? Are these differences related to dementia? It has been suggested that obesity, or perhaps better described as one potential corresponding behavior pattern, the 'compulsive consumption of food and inability to restrain from eating despite the desire to do so', be defined as a brain disorder due to its characteristics as an addiction disorder in the forthcoming Diagnostic and Statistical Manual of Mental Disorders—V (DSM-V) (Volkow and O'Brien, 2007). To include obesity, or food addiction and/or overconsumption is in the spirit of pre-existing DSM eating disorders, anorexia nervosa and bulimia disorders, and specific types of obsessive–compulsive disorder, e.g., body dysphoric disorder and anorexia nervosa (Cohen et al., 1997). Interestingly, brain regions affected in or by both addiction and obesity, have also shown to be affected or involved in dementia, as is the proposed network of four circuits in drug addiction and abuse: a) reward, b) motivation/drive, c) memory and learning, and d) control (Volkow et al., 2003). These circuits are directly innervated by the dopaminergic system, and are connected directly and indirectly primarily through glutaminergic projections.

A question herein is also whether early or late alterations in connectivity relate to internal and/or external appetite control and/or food addiction, thus creating a phenotype that is susceptible to both obesity (or disordered eating) and dementia; and whether aspects of dementia etiology, progression, or clinical manifestation, can be better understood from the obesity and addiction literature. Examples of brain regions affected in obesity, dementia, and addiction include: the amygdala, anterior cingulate gyrus, basal forebrain, dorsal striatum, globus pallidus, hypothalamus, hippocampus (CA1 nucleus), nucleus accumbens, orbitofrontal cortex, substantia nigra, posterior cingulate, prefrontal cortex, ventral pallidum, and ventral tegmental area, many of which have been evidenced via imaging techniques, such as PET, MRI or functional MRI (fMRI).

Some direct mechanisms relating the aforementioned regions of the brain involved in obesity and addiction to dementia and dementing processes are as follows. First, the nucleus accumbens, involved in overall control of food intake, appears to be a site evidencing higher concentrations of neurofibrillary tangles in aging and Alzheimer's disease (Selden et al., 1994; van Domburg and ten Donkelaar, 1991). Second, in a study comparing Alzheimer's disease, vascular dementia, and normals using PET and voxel-based morphometry, the hypometabolic pattern common to vascular dementia and Alzheimer's disease mainly concerned the posterior parietal, precuneus, posterior cingulate, prefrontal, and anterior hippocampal regions, and linearly correlated with the Mini-Mental State Examination (MMSE) (Kerrouche et al., 2006). Third, *in vivo* brain imaging of people with Alzheimer's disease suggests the presence of functional disintegration in the posterior–anterior brain network from the posterior cingulate cortex to the prefrontal cortex. Using PET, glucose metabolism has shown to be reduced in the posterior cingulate cortex of Alzheimer's disease patients and negatively correlated with MMSE scores and correct responses to an arithmetic task (Ouchi et al., 2004). Fourth, it has been shown using fMRI that patients with Mild Cognitive Impairment (MCI)-amnestic type, exhibit less activity in the posterior cingulate during recognition of previously learned items, and in the right hippocampus during encoding of novel items, despite comparable task performance to the controls. Reduced fMRI signal change in the medial temporal lobe supports prior studies implicating the hippocampus for encoding new information; and reduced signal change in the posterior cingulate is in line with recent research on its role in recognition in normal adults as well as metabolic decline in people with genetic or cognitive risk for Alzheimer's disease (Johnson et al., 2006). Finally, right prefrontal cortex function may be a critical link between 'reflective eating' (eating incorporated with a cognitive component that evaluates body shape, long-term health goals, etc.), addiction and degenerative brain diseases (Alonso-Alonso and Pascual-Leone, 2007). Thus, there are numerous areas of the brain commonly affected

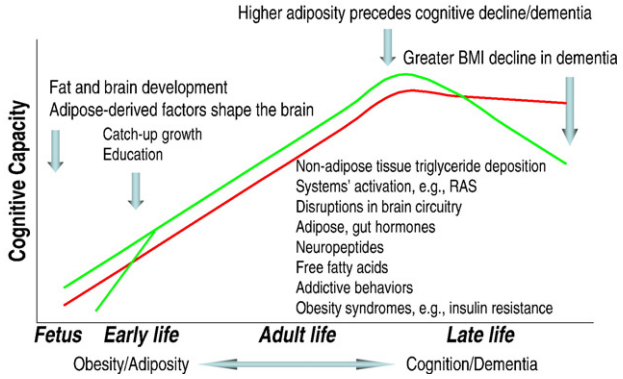

Fig. 3. Mechanisms whereby adiposity may influence cognition and dementia over the life course.

in obesity, addiction and dementia — links between which may provide clues regarding the etiology of these three disorders.

5. Obesity and late-life changes in cognition and dementia

What does the epidemiologic picture of adiposity over the life course in relationship to development of cognitive reserve and dementia, tell us about etiology? Higher fetal and postnatal levels of adiposity contribute to better brain development and sometimes, higher adult adiposity. Lower fetal levels of adiposity and rapid catch-up growth also contribute to higher adult adiposity. Higher adult BMI during mid-life, for example at ages 40–55 (Kivipelto et al., 2005; Rosengren et al., 2005; Whitmer et al., 2005), and during late-life, for example at age 70+ (Gustafson et al., 2003), increase risk for dementia, and are independent of education and other factors. Finally, BMI becomes a dysregulated symptom of underlying dementia processes, as many studies have observed a pronounced anorexia of aging in dementia. This leads to consideration of even earlier variation and potential dysregulation in brain centers responsible for feeding behavior, body weight control, and energy metabolism that may set the course for how adiposity interacts with aging processes and longevity to influence health (Fig. 3). Subsequent, temporal changes in adiposity may be a biomarker for environmental or pathology-induced influences on energy metabolism or adiposity set points that may determine dementia onset, progression, or ultimately death.

6. Public health implications

Effective prevention and control of adiposity are challenges for implementation of public health programs. Overcoming this challenge can be facilitated via knowledge of individual risk. However, this is too often lacking. In the National Health and Nutrition Examination Survey (NHANES), lack of physician-based diagnoses was reported among 22.9% with obesity (BMI $\geq$ 30 kg/m^2), and among obesity-associated disorders, 11.3% with diabetes (fasting plasma glucose > 126 mg/dl), 16.1% with hypertension (systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg), and 37.7% with hyperlipidemia (total serum cholesterol > 200 mg/dl) (Diaz et al., 2004). Being undiagnosed is even higher for certain high-risk groups, such as young, non-White, underinsured adults (Ayanian et al., 2003; Diaz et al., 2004). In addition, even after identification of a problem, there is often inadequate control; for example, 50% of hypertensives and 50% of hyperlipidemics have been observed to be poorly controlled (Qureshi et al., 2001).

Successful prevention of disease depends on the ability to control and/or modify risk and protective factors. In the case of dementia, which is characterized by a long latent period of pathological changes prior to clinical onset of disease, it is often not clear as to when the window of opportunity exists for implementation of adequate or even ultimate prevention and control efforts, but evidence continues to accumulate suggesting that a life course perspective is necessary.

The relationship between adiposity and late-life health of the brain begins early, with critical periods existing during many stages of life including: *in utero*, postnatally, at puberty, early adulthood, menopause, late adulthood, and old age. Maternal and paternal health statuses are therefore, also important. Control over one's health during any given stage both influences and depends on whether he or she survives to the next stage. In addition, the influence of underlying susceptibility phenotypes may relate to manifest dementia phenotypes, reflecting for example, underlying variations in hypothalamic axes, maturation of critical brain structures, and so forth.

How lifetime adiposity influences late-life health of the brain continues to be unveiled. The combined use of enhanced imaging techniques, blood and CSF biomarkers, and genes that complement improved clinical diagnoses, will continue to sober us with complexities, but also propel us forward to enhanced levels of understanding.

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