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Obesity and Sex Interact in the Regulation of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, for which a number of genetic, environmental, and lifestyle risk factors have been identified. A significant modifiable risk factor is obesity in mid-life. Interestingly, both obesity and AD exhibit sex differences and are regulated by sex steroid hormones. Accumulating evidence suggests interactions between obesity and sex in regulation of AD risk, although the pathways underlying this relationship are unclear. Inflammation and the E4 allele of apolipoprotein E have been identified as independent risk factors for AD and both interact with obesity and sex steroid hormones. We review the individual and cooperative effects of obesity and sex on development of AD and examine the potential contributions of apolipoprotein E, inflammation, and their interactions to this relationship.

Keywords

Alzheimer's disease; β-amyloid; apolipoprotein E; estrogen; inflammation; obesity; sex differences; testosterone

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the leading cause of dementia. The neuropathological hallmarks of AD include neuron loss, accumulation of amyloid-β (Aβ) plaques and hyperphosphorylated tau in the form of neurofibrillary tangles and neuropil threads, and gliosis (Cherry et al., 2014; Glass et al., 2010; LaFerla, 2010; Morris et al., 2014). There is compelling evidence that abnormal Aβ accumulation (Mucke and Selkoe, 2012; Tanzi, 2012) or hyperphosphorylated tau (Iqbal et al., 2010) or both (Zempel and Mandelkow, 2014) are the primary driving force(s) in the pathogenesis as well as strong support for key contributions by activated microglia and

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astrocytes (Cherry et al., 2014; Glass et al., 2010). Regardless of the proximal cause(s) of the neural injury in the AD brain, successful therapeutic intervention will require understanding of the factors that culminate in development of pathology.

The risk of AD is affected by numerous factors. Aging is the single greatest risk factor for AD, with the prevalence doubling every five years after the age of 65 (Hebert et al., 2003). However, the age-related physiological changes that contribute to this effect are uncertain. In addition to aging, AD risk is regulated by genetic factors. A small percentage of AD cases result from autosomal dominant mutations in the Aβ precursor protein, presenilin-1, and presenilin-2. The key consequences of these mutations appear to be increased production of A β and/or a change in the ratio of Aβ species, both of which foster Aβ accumulation (LaFerla, 2010; Tanzi, 2012). The most prevalent genetic risk factor for AD is the E4 allele (apoE4) of the cholesterol transporter apolipoprotein E (Saunders et al., 1993; Strittmatter et al., 1993), which also appears to regulate Aβ accumulation. In addition to apoE, there are a number of single nucleotide polymorphisms in genes that are associated with relatively subtle increases in AD risk. Among these are several genes associated with innate immunity (Tanzi, 2012), pointing to a role of the immune system, and microglia in particular, in AD pathogenesis. As with most diseases, AD risk is also significantly affected by several environmental and lifestyle factors, including education (Ferrari et al., 2014; Sharp and Gatz, 2011), head injury (Breunig et al., 2013), air pollution (Calderón-Garcidueñas et al., 2012), and physical exercise (Brown et al., 2013; Tolppanen et al., 2015). In recent years, an especially interesting risk factor has been obesity (Emmerzaal et al., 2015), which may contribute to links between cardiovascular diseases and AD (Hayden et al., 2006).

As with many disorders, significant sex differences exist in AD risk and development, with women being disproportionately affected by AD. These sex differences are likely to be mediated both via actions of sex steroid hormones, as well as by differences in neurophysiological substrates between men and women. Moreover, several normal age-related changes significantly increase AD risk including (i) estrogen depletion associated with menopause, (ii) age-related decreases in testosterone in men, and (iii) increasing adiposity in men and women. Since both estrogen and testosterone regulate adiposity, there are likely interactions between sex steroid hormones, adiposity, and AD risk that may be expected to exhibit sex differences.

In this review, we consider the individual and interactive effects of these AD risk factors as well as possible mechanisms that may be underlying these relationships. We begin by examining obesity as a risk factor for AD and sex differences in AD development. We then examine how sex differences and obesity interact in the context of AD, before exploring mechanisms underlying this relationship. Though there are likely to be a number of important mechanisms, our review will focus on inflammation, apoE4, and their interaction in the context of sex differences, obesity, and AD.

1. Obesity/metabolic syndrome as risk factors for AD

A. Epidemiological studies

Accumulating evidence over the past several years has identified obesity and related conditions as significant risk factors for the development of AD. Body mass index (BMI) is a commonly used measure of obesity, and though some studies show an association between BMI and AD, with an up to 40% increased risk for obese individuals (Fitzpatrick et al., 2009; Gustafson et al., 2003), others have found no association (Qizilbash et al., 2015; Yoshitake et al., 1995) (reviewed in Profenno et al., 2010). However, central adiposity may be a more important factor and better predictor of AD risk than BMI (Gustafson et al., 2009; Luchsinger et al., 2012; Whitmer et al., 2008), as visceral fat has been shown to be particularly harmful (Bloor and Symonds, 2014). Central adiposity has been shown to be a risk factor for AD as well as for cognitive impairment (Feng et al., 2013; Gustafson et al., 2009; Luchsinger et al., 2012; Whitmer et al., 2008), and visceral fat deposits are associated with lower brain volumes at middle age (Debette et al., 2010). Importantly, it appears that obesity at midlife is a particularly strong risk factor for onset of AD in late life (Emmerzaal et al., 2015; Fitzpatrick et al., 2009; Meng et al., 2014; Profenno et al., 2010; Xu et al., 2011). Intriguingly, the association between obesity and AD risk diminishes with age. Weight loss and low BMI are actually associated with increased risk of AD in older adults, whereas a higher BMI may be protective at advanced ages (Besser et al., 2014; Emmerzaal et al., 2015; Fitzpatrick et al., 2009; Hughes et al., 2009; Profenno et al., 2010). In fact, one study found that overweight and obese older adults were protected against AD, mild cognitive impairment (MCI), and vascular dementia (Doruk et al., 2010). One interpretation of these findings is that obesity at midlife may serve as a triggering factor for AD neuropathology, the effects of which do not become apparent until onset of clinical dementia later in life.

Obesity is associated with increased risk for the development of metabolic syndrome and type 2 diabetes (T2D), both of which are also independent risk factors for AD (Biessels et al., 2006; Samaras and Sachdev, 2012; Strachan et al., 2011). In addition, both obesity and T2D are risk factors for MCI (Samaras and Sachdev, 2012), and obesity is also linked with cognitive impairments in the absence of dementia (Benito-León et al., 2013; Gustafson et al., 2003; Mazzoccoli et al., 2014). In particular, central adiposity is a risk factor for cognitive decline, as increased visceral adipose tissue is associated with decreased performance on verbal memory and attention tasks, and with lower hippocampal volume (Isaac et al., 2011). Additionally, obesity can impair cognition even in children and young adults (Khan et al., 2014; Reinert et al., 2013; Schwartz et al., 2013; Yau et al., 2012). Thus, there are likely to be two independent pathways; one by which obesity impairs cognition and another pathway by which it promotes AD pathogenesis, that in turn impairs cognition in late life. Interestingly, while the relationship between higher visceral adipose tissue and lower cognitive performance is true in individuals under 70 years of age, this association does not exist in those over age 70 (Yoon et al., 2012), again indicating a protective effect of increased weight at older ages.

Obesity and related metabolic syndromes increase the risk of vascular dementia to an even greater extent than the risk of AD (Hayden et al., 2006; Whitmer et al., 2007; Xu et al., 2011; Yoshitake et al., 1995). Many vascular components are associated with AD neuropathology, including blood brain barrier disruption (Bell, 2012; Bell and Zlokovic, 2009) and cerebral amyloid angiopathy, the accumulation of β-amyloid (Aβ) deposits in the cerebrovasculature (Hultman et al., 2013). In addition, the presence of modifiable vascular risk factors at midlife increases risk of all types of dementia, including AD, later in life (Exalto et al., 2014; Whitmer et al., 2007). As obesity is a major risk factor for cardiovascular disease as well as AD, obesity and vascular factors likely cooperatively contribute to AD pathogenesis.

B. Experimental studies

In agreement with epidemiological findings, experimental studies in animals have demonstrated that obesity and T2D are associated with promotion of AD. First, various animal models of obesity and diabetes exhibit brain changes consistent with early AD pathology (Jayaraman and Pike, 2014). A commonly used approach is the use of high fat diet (HFD) in rodents, which yields diet-induced obesity (DIO). Using this model, our lab and others have shown that DIO in transgenic mouse models of AD increases levels of Aβ (Barron et al., 2013; L. Ho et al., 2004; Julien et al., 2010; Kohjima et al., 2010), a key protein in the initiation and progression of AD (Selkoe, 2011). Tau pathology, the other neuropathological hallmark of AD, is also increased by DIO in a number of strains of transgenic mice (Julien et al., 2010; Leboucher et al., 2013; Mehla et al., 2014; Takalo et al., 2014).

As in the human literature, DIO is also associated with cognitive deficits in animal models independent of underlying AD-related pathology. That is, rodents show impairments on a number of cognitive tasks following HFD, without apparent changes in Aβ accumulation (Davidson et al., 2013; Granholm et al., 2008; Hsu et al., 2014; Kanoski and Davidson, 2011; Kanoski et al., 2010; Knight et al., 2014; Stranahan et al., 2008). In fact, even a short 9-day exposure to HFD can cause cognitive impairment in rats (Murray et al., 2009).

In addition to DIO, genetic and pharmacological manipulations that model diabetes also increase AD-related neuropathology. For example, the BBZDR/Wor rats, a strain genetically prone to T2D, have greater neuronal loss and Aβ pathology than do BB/Wor rats, which are genetically prone to Type 1 diabetes (Li et al., 2007) Further, treatment with streptozotocin (STZ), which kills pancreatic β-cells, is commonly used to induce type I diabetes in animal models. STZ has been found to increase Aβ in both mouse (Currais et al., 2012; Jolivalt et al., 2008; Wang et al., 2010) and rat (Yang et al., 2013) models, as well as increase tau phosphorylation in brain (Jolivalt et al., 2008; Kim et al., 2009; Planel et al., 2007). Transgenic mouse models of obesity include leptin deficient mice (ob/ob) and leptin receptor deficient mice (db/db). Even in the absence of HFD, these transgenic mice show cognitive impairments and Aβ pathology (Li et al., 2012; Ramos-Rodriguez et al., 2013), as well as increased tau phosphorylation (Li et al., 2012; Kim, et al., 2013; Ramos-Rodriguez et al., 2013). Moreover, endothelial cells cultured from db/db mice show increased susceptibility to the toxic effects of Aβ (Carvalho et al., 2014). Interestingly, the antidiabetic

drug metformin has been shown to reduce AD-like pathology in db/db mice, though it did not improve cognition (Li et al., 2012).

Notably, crossing the genetically obese and diabetic ob/ob and NSY mice with an AD transgenic mouse increases cognitive impairment and diabetic outcomes (Takeda et al., 2010), and is associated with severe cerebrovascular pathology (Niedowicz et al., 2014) without affecting Aβ pathology (Niedowicz et al., 2014; Takeda et al., 2010). These studies suggest that adverse metabolic outcomes can be exaggerated in the presence of AD, but genetically induced metabolic outcomes do not necessarily increase AD pathology. Interestingly, complementary findings in an AD transgenic mouse with DIO also suggest that metabolic disturbance may not be the driving force in promotion of AD pathogenesis (Barron et al., 2013). In summary, a number of studies in animal models have demonstrated increased AD-like pathology in the presence of diet- and pharmacologically-induced as well as genetically-induced obesity and metabolic disturbances. Moreover, the literature suggests that dietary components may be important in regulating AD pathology, even in the absence of obesity and metabolic syndromes.

C. Dietary components affect AD risk

Studies in both human and animal models suggest that particular dietary constituents may be important in modulating AD risk. For example, trans and saturated fatty acids are associated with higher risk of AD and MCI (Barnard et al., 2014; M. C. Morris and Tangney, 2014). In rodents, a diet high in saturated fatty acids was found to be more detrimental than a high cholesterol diet (Takechi et al., 2013). Other rodent studies have shown that trans and saturated fatty acids lead to a particularly robust increase in Aβ (Grimm et al., 2012; Oksman et al., 2006). Conversely, diets with high omega 3 polyunsaturated fatty acids are associated with decreased Aβ levels (Hjorth et al., 2013; Julien et al., 2010; Lebbadi et al., 2011; Zerbi et al., 2014), and one study found that a diet low in fat and high in oleic acid was able to reduce Aβ levels and pathology in transgenic mice (Amtul et al., 2010). In addition, the high sucrose and fructose contents of Western diets are also associated with cognitive impairment in humans (Francis and Stevenson, 2011) and increased Aβ (Lakhan and Kirchgessner, 2013; Moreira, 2013; Orr et al., 2014), and tau pathology (Orr et al., 2014) in rodents. Even in the absence of HFD, 10% sucrose water increased Aβ in a mouse model of AD (Cao et al., 2007), and a high fructose diet impaired spatial memory in rats (Ross et al., 2009). Thus, diets high in saturated fatty acids, sucrose, and fructose may contribute to AD pathogenesis, whereas diets high in certain types of fatty acids may be protective.

2. Sex differences in AD risk

The prevalence of AD is greater in women than in men, which holds true even after controlling for the fact that women have an increased lifespan (Li and Singh, 2014). Moreover, apolipoprotein E ε4 allele (ApoE4), the strongest genetic risk factor for AD, has a greater effect in women than it does in men such that a single copy of ApoE4 increases risk about 4-fold in women without significantly affecting AD risk in men (Payami et al., 1994). Similarly, ApoE4 increases rates of conversion from cognitively normal to MCI and from

MCI to AD significantly more in women than in men (Altmann et al., 2014). Interestingly, in transgenic mouse models of AD, female mice are also more affected by AD in that they develop more severe AD-like neuropathology (Carroll et al., 2010; Hirata-Fukae et al., 2008; Schäfer et al., 2006), and have greater cognitive impairments (Blázquez et al., 2014; Carroll et al., 2010).

Several lines of evidence indicate that some of these sex differences in AD risk can be attributed to sex steroid hormones. That is, sex steroid hormones are protective against AD in both sexes, and age-related loss of both estrogens in women (Manly et al., 2000; Pike et al., 2009) and of androgens (Hogervorst et al., 2001; Moffat et al., 2004; Paoletti et al., 2004) in men, have been shown to increase AD risk. Moreover, low brain and circulating estrogen in women (Rosario et al., 2011; Yue et al., 2005) and testosterone in men (Rosario et al., 2011; 2004) have been associated with increased AD risk (Pike et al., 2009). Likewise, our lab and others have demonstrated similar relationships in animal models, such that in a mouse model of AD, androgen depletion in males (McAllister et al., 2010; Rosario et al., 2006) and estrogen depletion in females (Carroll et al., 2007) increases AD-like pathology, changes that are reversed by androgen and estrogen treatment. Collectively, human and rodent data suggest that the age-related depletion of sex steroid hormones, which diminishes beneficial activational effects of hormones in adult brain, places the brain at increased vulnerability for development of AD. Interestingly, emerging data also suggest that organizational effects of sex steroids hormones in the developmental sexual differentiation of the brain may confer greater risk in the female brain (Carroll et al., 2010).

3. Sex differences in obesity

A. Epidemiological studies

Rates of obesity are fairly similar between the sexes, at roughly 33% of men and 36% of women in the US being obese (Ogden et al., 2014). However, sex differences exist in the way that obesity manifests itself and in obesity-related complications. For example, some studies have found that rates of metabolic syndrome are somewhat lower in women (Hadaegh et al., 2013; Pradhan, 2013), and that women are protected against some but not all obesity-related complications (Syme et al., 2008). Yet, over a timespan of about 20 years, the prevalence of metabolic syndrome has increased most significantly among young women aged 20–39 years (Pradhan, 2013). Moreover, increases in BMI are positively associated with inflammation in women, but not men, suggesting that relative increases in BMI may be more harmful in women (Ahonen et al., 2012). In addition, one study found that obese adolescent girls have higher free fatty acid flux than do obese boys, which predicts development of insulin resistance (Adler-Wailes et al., 2013).

A number of studies have demonstrated that premenopausal women are protected against obesity, but that this protective effect is lost at menopause (Bloor and Symonds, 2014; Meyer et al., 2011; Sugiyama and Agellon, 2012). Some of these sex differences may be attributed to the way in which men and women store fat; that is, women tend to deposit excess fat in the lower body, whereas men develop mainly visceral fat deposits (Bloor and Symonds, 2014). Subcutaneous fat in the lower body has a greater capacity to store lipids and undergo tissue remodeling, which may contribute to better metabolic outcomes in

premenopausal women (Bloor and Symonds, 2014). However, these sex differences diminish after menopause, suggesting a role for sex steroid hormones (discussed below).

Sex differences have also been found in brain responses to obesity. For example, men and women differ in the way they respond to food cues, suggesting that women have lower cognitive control of brain responses to food stimulation (Wang et al., 2009). In concordance with this finding, obese women have greater activation of brain regions regulating cognition and emotion in response to high calorie foods (Geliebter et al., 2013). Moreover, men have higher hypothalamic-pituitary-adrenal axis activity to suppress food intake after consuming a meal (Martens et al., 2012), demonstrating that responses to food intake also exhibit sex differences. Finally, the adverse effects of obesity on the brain may be exaggerated in women, as one study found that although both sexes had axonal degeneration with obesity, only obese women showed a positive correlation between BMI, serum leptin levels, and myelin degeneration (Mueller et al., 2011). In summary, though there are no sex differences in rates of obesity, there appear to be significant differences in obesity-related outcomes and in brain responses between the sexes.

B. Experimental Studies

Experimental work in animal models has confirmed the existence of sex differences in obesity. Most studies have demonstrated that female rodents are protected against metabolic impairments associated with DIO. For example, despite similar inflammatory cytokine expression in adipose tissue, female mice had less infiltrating macrophages, later onset of glucose homeostasis impairments, better insulin sensitivity, and less fat deposition in the liver than did male mice (Medrikova et al., 2012). In another study, obese male mice had increased levels of inflammatory cytokines and macrophage infiltration in adipose tissue, whereas obese female mice had an increase in anti-inflammatory T cells in adipose tissue (Pettersson et al., 2012). Female rodents have greater expandability of adipocytes which may allow them to maintain insulin sensitivity in response to HFD (Amengual-Cladera et al., 2012; Medrikova et al., 2012). Additionally, female adipocytes have greater insulin sensitivity and lipid production, and higher levels of proteins involved in glucose and lipid metabolism (Macotela et al., 2009). Adipocytes of castrated male mice have increased insulin sensitivity and lipogenesis, whereas adipocytes from ovariectomized female mice have decreased lipogenesis (Macotela et al., 2009), pointing to the role of sex steroid hormones in sex differences in adipose tissue properties.

Females also appear to be protected against the adverse effects of HFD on the brain; male mice developed more metabolic and cognitive impairments and had alterations in hippocampal synaptic plasticity that female mice did not (Hwang et al., 2010). Moreover, in one mouse model of diabetes, the NSY mouse, 98% of males become diabetic by 48 weeks of age, versus only 31% of females (Ueda et al., 1995), and another study found that though both sexes became obese, only male rats lacking the leptin receptor developed T2D (Moralejo et al., 2010).

However, the opposite has also been demonstrated, in that female rats had a greater increase in body weight, despite having lower energy intake than males (Nadal-Casellas et al., 2012). Furthermore, obese female rats had reduced insulin signaling in brown adipose tissue, while

males had increased mitochondrial function, which may have served to suppress oxidative damage and reduce insulin signaling impairments (Nadal-Casellas et al., 2012). Though a few studies have shown greater detrimental effects in females, the majority of research suggests that female rodents are protected against some aspects of obesity and related complications. As discussed below, evidence suggests that sex steroid hormones may be particularly important in regulating these sex differences.

C. Estrogens and Obesity

Sex differences in obesity may be partly accounted for by sex steroid hormones, and estrogens have a multitude of roles in obesity and metabolic syndrome. As mentioned previously, sex differences in fat storage are diminished after menopause, with postmenopausal women showing a shift from subcutaneous to visceral fat deposition (Brown and Clegg, 2010; Meyer et al., 2011; Shi and Clegg, 2009; White and Tchoukalova, 2014). A number of findings point to the role of a loss of estrogen in this shift after menopause. For example, aromatase is required for the conversion of androgens to estrogens, and both male and female mice lacking aromatase have increases in adiposity and insulin resistance (Jones et al., 2000; Takeda et al., 2003), which can be reversed by estrogen treatment (Takeda et al., 2003). Moreover, the main source of estrogens in postmenopausal women is the adipose tissue, where androgens are converted into estrogens. Interestingly, aromatase activity in adipose tissue increases with age as well as with obesity (Meyer et al., 2011). Estrogens also have a number of important roles in insulin homeostasis, including increasing the release of insulin from the islet of Langerhans, preventing β-cell apoptosis and improving insulin's action (Meyer et al., 2011).

The effects of ovariectomy (OVX) and estrogen replacement in rodent models highlight the importance of estrogen in regulating adiposity, body weight, and metabolism. For instance, OVX mice were shown to have pancreatic beta cell dysfunction that could be reversed by hormone replacement (Bailey and Ahmed-Sorour, 1980). Both male and female aromatase knockout mice have a number of metabolic disturbances that can be restored with estrogen replacement (Simpson et al., 2005). Furthermore, one study found that estrogen replacement and exercise had additive beneficial effects in reversing the metabolic disturbances associated with OVX and HFD (Zoth et al., 2010). Thus, loss of ovarian hormones causes metabolic disturbances in both the presence and absence of HFD, which can be reversed by estrogen replacement.

In addition to its effects peripherally, estrogen signaling in brain is required for energy homeostasis. Specifically, estrogen receptor α (ERα) signaling is important in this regard, as both male and female mice knocked out for ERα have increased adiposity and metabolic disturbances even on a regular chow diet (Heine et al., 2000). Moreover, ERα signaling in hypothalamus appears to be especially crucial, as blocking ERα only in the ventromedial hypothalamus causes obesity, hyperphagia, and hyperglycemia in rodents (Musatov et al., 2007). Thus, estrogen has roles in adiposity, insulin homeostasis, body weight, and energy homeostasis.

D. Testosterone and obesity

Just as depletion of estrogens at menopause in women is associated with increased risk of obesity and metabolic syndrome, so too is the age-related decline of androgens in men. Low testosterone levels are associated with insulin resistance, metabolic syndrome, and development of T2D (Kapoor et al., 2007; 2005; Stellato et al., 2000; Zitzmann, 2009). Obesity, T2D, and metabolic syndrome are also associated with low testosterone levels in pre-pubertal (Mogri et al., 2013) and young men (Chandel et al., 2008; Goncharov et al., 2008).

There appears to be a bi-directional relationship between testosterone loss and obesity, such that low testosterone levels predispose to obesity, and obesity causes decreases in testosterone levels (De Maddalena et al., 2012; Grossmann et al., 2014). In accord with this idea, weight loss has been found to increase testosterone levels. For example, free testosterone levels increase in men after bariatric surgery and are associated with improved insulin and glucose sensitivity (Botella-Carretero et al., 2013), but men with low testosterone levels are at an increased risk of regaining weight (Wang et al., 2013). Conversely, testosterone supplementation can also lower risks of obesity and metabolic syndrome as long-term testosterone replacement in older men is often associated with reduced body weight, waist circumference, and BMI, and with a reduction in symptoms of metabolic syndrome (Yassin et al., 2014). Additionally, our lab has shown that loss of testosterone in male rodents exacerbates effects of DIO, whereas testosterone replacement protects against DIO-induced hyperglycemia and hyperinsulinemia (Jayaraman et al., 2014).

One mechanism by which obesity may contribute to testosterone loss is via excess adipose tissue. Levels of aromatase, which converts testosterone to estradiol, are high in adipose tissue (Meyer et al., 2011). Thus, increased adiposity would result in increased activity of aromatase and thereby increased metabolism of testosterone to estrogens (Blouin et al., 2006). Additionally, male mice maintained on HFD have decreased testosterone levels associated with apoptosis of Leydig cells in the testes and reduced testicular weight and function (Zhao et al., 2014). Thus, it is likely that both, increased metabolism of testosterone in adipose tissue and decreased testosterone production in the testes, are mechanisms by which obesity drives testosterone loss. Consistent with this possibility, obese men placed on caloric restriction have increased serum testosterone levels, due to both an improvement in testicular function and a decrease in the conversion of testosterone to estrogens in adipose tissue (Schulte et al., 2014). Moreover, testosterone inhibits adipogenesis, as testosterone supplementation has been found to inhibit pluripotent stem cells and pre-adipocytes from becoming adipocytes (White and Tchoukalova, 2014). These studies point to the existence of a vicious cycle in which low testosterone and obesity interact to promote development of both conditions.

4. Interactions between sex differences, obesity, and Alzheimer’s disease

A. Epidemiological studies

Although few studies have explored sex differences in the effects of obesity on AD risk, available evidence suggests that the adverse effects of obesity on cognition and AD risk are

stronger in women than in men. One study found that only in women did obesity increase risk of AD, and diabetes increase risk of vascular dementia (Hayden et al., 2006). In contrast, Whitmer and colleagues found no sex differences in the association between BMI and AD risk (Whitmer et al., 2007). Many studies controlled for sex rather than examining sex differences (Debette et al., 2010; Exalto et al., 2014; Ho et al., 2010; Hughes et al., 2009; Isaac et al., 2011), suggesting that sex differences may be more prevalent than the literature currently reflects. Sex differences have also been demonstrated in the effects of obesity on blood brain barrier disruption (a risk factor for AD), with overweight and obese women, but not men, showing increased disruption (Gustafson et al., 2007). Interestingly, greater blood brain barrier disruption at old age correlates with availability of sex steroid hormones at middle age (Gustafson et al., 2007).

Independent of AD, sex differences are observed in the effects of obesity on age-related cognitive decline. Specifically, in contrast to the finding that obesity increases AD risk only in women; obesity, hypertension, and high adiposity were associated with cognitive decline in men but not in women (Elias et al., 2003; Kanaya et al., 2009). In addition, sex differences have been found in effects of obesity on brain structure, with obese men having gray matter loss and alterations not found in obese women (Taki et al., 2008). In contrast, increases in BMI have been associated with temporal lobe atrophy in women (Gustafson et al., 2004), and obesity is linked with myelin degeneration in women but not men (Mueller et al., 2011). Though the factors underlying the observed sex differences are unclear, the greater prevalence of vascular risk factors in men may indicate that men are more susceptible to the effects of obesity on vascular outcomes. In summary, findings on sex differences in the effects of obesity on AD, cognition, and brain structure are mixed, and future studies should address the role of sex in these relationships.

B. Experimental studies

The literature on sex differences in obesity and AD risk in experimental models is extremely limited, but studies have generally shown that male mice may be more sensitive to the effects of dietary manipulations. Our own lab has demonstrated that although both male and female AD transgenic mice become obese on HFD, only males exhibit significant ectopic fat accumulation, hyperglycemia, and hyperinsulinemia (Barron et al., 2013). Despite differential effects of HFD on metabolic outcomes, both males and females have increased Aβ deposition (Barron et al., 2013), suggesting that AD-related pathology is accelerated by other obesity-induced effects, perhaps including inflammation.

Though not directly related to AD risk, other studies in animal models have demonstrated that neural effects of obesity are generally more pronounced in males. For example, obese male mice have learning and memory impairments and reductions in synaptic plasticity that are not present in female mice (Hwang et al., 2010). Additionally, male mice have been shown to be more sensitive to the beneficial effects of diet. That is, male mice fed a rodent diet supplemented with phyto-nutrients and fish oils had improved working memory and hippocampal mitochondrial function, whereas female mice did not show improvements with diet supplementation (Wolf et al., 2012). A major limitation in our understanding of this issue is that most studies use only male rodents to examine dietary effects on brain changes

and AD outcomes; thus, sex differences in obesity and cognitive decline/AD risk may be far more prevalent than currently assumed.

5. Mechanisms underlying sex differences in obesity and Alzheimer's disease

A. Apolipoprotein ε 4

A.1. Apolipoprotein ε 4 and Alzheimer's disease—Apolipoprotein E is a cholesterol transporter that has three isoforms that vary by a single amino acid: apoE ε2, ε3, and ε4, with the ε4 allele (apoE4) being the strongest genetic risk factor for AD (Corder et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993). Only ~12% of the general population are apoE4 carriers (de-Andrade et al., 2000), yet its frequency increases to ~50% in AD patients (Ward et al., 2012). Moreover, the onset of AD occurs earlier in apoE4 carriers (Corder et al., 1993), and ~40% of healthy middle-aged versus ~8% of non-carriers have Aβ accumulation (Lathe et al., 2014; Liu et al., 2013). Apart from increasing AD risk, apoE4 is associated with greater cognitive decline over a 6 year period in healthy middle-aged adults (Blair et al., 2005). ApoE4 is also linked with greater AD-like pathology in mouse models, where it has been shown to potentiate oligomerization of Aβ (Belinson and Michaelson, 2009), and accelerate and worsen Aβ plaque formation (Youmans et al., 2012).

ApoE4 is also associated with changes in vascular pathology and in blood brain barrier function. Specifically, AD patients who are apoE4 carriers have greater arteriosclerosis and cerebral amyloid angiopathy (Premkumar et al., 1996; Yip et al., 2005), and though cerebral amyloid angiopathy is rare in the absence of AD, it is found in otherwise healthy homozygous ApoE4 carriers (Walker et al., 2000). Mice expressing human apoE4 have reduced cerebral vascularization at a young age and increased vascular atrophy at old age (Alata et al., 2015). Moreover, apoE4 is associated with increased blood brain barrier permeability and breakdown in both humans (Halliday et al., 2013) and in mouse models (Bell et al., 2012; Nishitsuji et al., 2011). Thus, apoE4 may be acting through several different mechanisms, including regulation of Aβ oligomerization and deposition, and disruption of the vasculature and the blood brain barrier.

Notably, carriers of one apoE4 allele have a ~30% lifetime risk of AD, meaning that a significant proportion of apoE4 carriers never develop the disease (Genin et al., 2011). Thus, apoE4 is neither necessary nor sufficient for AD. Consequently, apoE4 must interact with other risk factors, perhaps including obesity and diabetes, to influence AD risk.

A.2. Apolipoprotein ε4 and obesity—Abundant evidence indicates that apoE4 is a risk factor for several metabolic disturbances and adverse cardiovascular outcomes, including hypertension (Niu et al., 2009), increased systolic blood pressure and carotid artery thickness (Atabek et al., 2012), increased triglyceride and low density lipoprotein cholesterol levels (de-Andrade et al., 2000; Kypreos et al., 2009), decreased high density lipoprotein cholesterol levels (Zarkesh et al., 2012), and higher pancreatic islet amyloidosis in diabetic patients (Guan et al., 2013). Female apoE4 carriers have been found to have increased central adiposity (Oh et al., 2001) and frequency of apoE4 is increased in

metabolic syndrome patients of either sex (Sima et al., 2007). Additionally, among obese men, those with apoE4 have higher insulin and glucose levels (Elosua et al., 2003; Marques-Vidal et al., 2003). In a DIO mouse model, apoE4 was associated with greater metabolic impairments and adipocyte hypertrophy (Arbones-Mainar et al., 2008). However, other studies fail to find a significant relationship between apoE4 and metabolic disturbances including insulin resistance (Meigs et al., 2000; Ragogna et al., 2011). The reason for these discordant findings is unclear, but may reflect the growing appreciation of gene-environment interactions in mediating the effects of apoE4 in aging and age-related diseases (Corella and Ordovas, 2014). For example, deleterious effects of apoE4 on heart disease risk and outcomes are preferentially observed in the context of high saturated fat diets (Corella et al., 2011; Yang et al., 2007).

A number of mechanisms that may underlie the association between obesity and apoE4 have been identified. For example, apoE isoforms have been shown to differentially interact with hormones important in nutrient sensing and homeostasis, including adiponectin (Arbones-Mainar et al., 2008) and leptin (Fewlass et al., 2004). Moreover, apoE acts in the hypothalamus to suppress food intake (Shen et al., 2008), but how this might differ by apoE genotype in not known. Importantly, apoE4 carriers have lower levels of hippocampal insulin degrading enzyme, which is also involved in Aβ clearance (Cook et al., 2003; Du et al., 2009; Edland, 2004). MCI patients with apoE4 have higher levels of the more toxic, lipid depleted Aβ, while all apoE4 carriers have an increase in lipid depleted apoE, which is less effective at clearing Aβ (Hanson et al., 2013). Interestingly, levels of lipid depleted Aβ are increased in the presence of a diet high in saturated fats and glycemic index, and decreased with a low saturated fat and glycemic index diet (Hanson et al., 2013).

As with cardiovascular disease, the combination of obesity and apoE4 may also affect AD outcomes. For example, mid-life obesity (Ghebranious et al., 2011) and high fat and calorie intake (Luchsinger et al., 2002), are associated with greater risk for AD only in apoE4 subjects. Men with both type 2 diabetes and the apoE4 allele have a 5.5 times greater risk of AD, as well as greater AD neuropathology than men with neither risk factor (Peila et al., 2002). Further, the relationship between obesity and diminished cognitive functions appears to be strongest in apoE4 carriers (Zade et al., 2013). Thus, gene-environment interactions between apoE4 and obesity appear to be important regulators of cognitive decline and AD risk.

A.3. Sex differences in apolipoprotein ε4, obesity, and Alzheimer's disease

—ApoE4 is the primary genetic risk factor for late-onset AD. Interestingly, the increased AD risk associated with apoE4 disproportionately affects women: AD risk is increased approximately 4-fold and 10-fold in women with one and two apoE4 alleles, respectively, whereas men show essentially no increased risk with one apoE4 allele and a 4-fold increase in risk with two apoE4 alleles (Payami et al., 1994). Additionally, female apoE4 carriers exhibit a significantly greater risk than male apoE4 carriers of converting to MCI, and from MCI to dementia (Altmann et al., 2014). ApoE4 is also more strongly linked to cognitive dysfunction (Beydoun et al., 2012) and brain atrophy (Holland et al., 2013; Liu et al., 2010) in women. Healthy older female, but not male, apoE4 carriers have decreased default mode network activity that is correlated with cerebrospinal fluid levels of tau protein (Damoiseaux

et al., 2012). Similarly, female but not male apoE4 mice exhibit cognitive impairments (Raber et al., 2002).

The loss of estrogen at menopause appears to increase risk of AD, whereas estrogen treatments may be protective against AD (Pike et al., 2009). However, these relationships may vary depending on apoE genotype. For example, estrogen receptor polymorphisms have been associated with increased risk of AD but only in apoE4-carrying women (Fernandez-Martinez et al., 2013). Further, estrogen-based hormone therapy is associated with memory improvement and slower cognitive decline in non-apoE4 carriers, but not in apoE4-carrying women (Burkhardt et al., 2004; Yaffe et al., 2000). In fact, estradiol may have deleterious effects in the context of apoE4, as female AD patients with high estradiol and the apoE4 allele have an increase in neuropsychiatric symptoms (Xing et al., 2012). Adverse effects of estradiol and apoE4 have also been demonstrated in mice, where estrogen treatment in apoE2 and apoE3 mice reduced Aβ pathology, but increased pathology in apoE4 mice (Kunzler et al., 2014). How estradiol and apoE4 interact is unclear. Estradiol has been shown to increase apoE expression in astrocytes and microglia (Stone et al., 1997; Struble et al., 2007). The particular receptor it acts on may be important, as activation of estrogen receptor α up-regulates apoE expression, while activation of estrogen receptor β down-regulates apoE (Wang et al., 2006). One protective action of estradiol that is compromised by apoE4 is its ability to inhibit pro-inflammatory actions of microglia (Brown et al., 2008). In contrast to evidence that apoE4 may negate or even reverse the neural benefits of estradiol, other reports show that estrogen-based hormone therapy exerts cognitive benefits (Ryan et al., 2009), may reduce AD risk (Rippon et al., 2006), and slows cellular aging (Jacobs et al., 2013) in women with apoE4. Thus, although apoE4 is clearly associated with greater neural risk in women, the role of estradiol in this relationship remains unclear.

Like estrogen loss in women, age-related testosterone depletion in men is a risk factor for development of AD (Pike et al., 2009; Vest and Pike, 2013), and apoE4 interacts with the relationship between testosterone and AD. First, cognitively normal aged men that are apoE4 carriers exhibit significantly lower levels of testosterone than non-carriers (Hogervorst et al., 2002). Second, testosterone levels are inversely associated with hippocampal volume in middle-aged men with apoE4 (Panizzon et al., 2010), but positively correlated with verbal episodic memory (Panizzon et al., 2014). Conversely, one study reported testosterone levels were positively associated with cognitive performance in middle-aged men lacking apoE4, but negatively associated with performance in apoE4 carriers (Burkhardt et al., 2006); however, this study may have been limited by a small sample size. Interactions of androgens and apoE have also been demonstrated in mouse models. Androgens have reduced binding to the androgen receptor in the presence of apoE4 (Raber, 2004). Additionally, apoE4 but not apoE3 mice show cognitive impairments following testosterone depletion (Pfankuch et al., 2005) and pharmacological antagonism of the androgen receptor (Raber et al., 2002). Interestingly, androgen treatment also improves cognitive performance in female apoE4 mice (Raber et al., 2002). Collectively, the limited available data suggest that apoE4 and low testosterone are interactive risk factors for AD. As with estrogen-based hormone therapy in women, it remains unclear whether testosterone treatment in men could mitigate deleterious effects of apoE4. Also uncertain is whether obesity modulates interactions between apoE and sex steroid hormones in men and women.

B. Inflammation

B.1. Inflammation and Alzheimer's disease—Multiple lines of evidence have established inflammation as a key component in the initiation and/or progression of AD pathogenesis (Wyss-Coray and Rogers, 2012). Aging, the most significant risk factor for late-onset AD, is associated with an increase in chronic inflammation (Singh and Newman, 2011). Age-associated increases in pro-inflammatory cytokines can increase Aβ levels, which in turn can activate microglia and astrocytes to perpetuate a cycle of inflammation and Aβ production (Blasko et al., 2004). Indeed, higher levels of circulating inflammatory cytokines are associated with increased risk of developing AD (Tan et al., 2007). In the central nervous system, pro-inflammatory cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) are upregulated in CSF even before detectable Aβ pathology (Avila-Muñoz and Arias, 2014; Eikelenboom et al., 2011). Moreover, higher levels of inflammatory cytokines are associated with greater cognitive decline (Rafnsson et al., 2007) and greater loss of entorhinal cortex volume (Avila-Muñoz and Arias, 2014), as well as greater loss of total brain volume than would be expected for a given age (Jefferson et al., 2007). Cerebral inflammation, independent of other AD pathology markers, predicts early death caused by dementia (Nägga et al., 2014).

The roles of heritability and environmental factors in the association between inflammation and AD have also been demonstrated. Recent genetic evidence links polymorphisms in several components of the immune system as risk factors for AD, including CD 33 (Bertram et al., 2008; Hollingworth et al., 2011; Naj et al., 2011), TREM2 (Kleinberger et al., 2014), clusterin, and CR1 (Harold et al., 2009; Lambert et al., 2009). Further, the production of IL-1β, TNF-α, and interferon γ in response to the pro-inflammatory stimulant lipopolysaccharide (LPS) is greater in children with a parental history of AD (van Exel et al., 2009). Environmental factors that increase inflammation are also implicated in promoting AD. Traumatic brain injury, for example, is associated with increased risk of AD, and chronic neuroinflammation has been suggested as a mediator of this relationship (Breunig et al., 2013). Increased inflammation in response to air pollution is well established, and even children living in highly polluted areas show increased pro-inflammatory cytokines in brain that correlate with Aβ and tau pathology (Calderón-Garcidueñas et al., 2012).

Activated microglia and astrocytes are found surrounding Aβ plaques in AD, and are associated with increased production of pro-inflammatory factors (Glass et al., 2010). Interestingly, response sites for NFκB, a major upstream regulator of inflammatory cytokine production, have been found in the promoters of genes involved in production of Aβ, and pro-inflammatory cytokines increase the expression of these Aβ-related genes in neurons (Glass et al., 2010; Sastre et al., 2008). LPS increases production of pro-inflammatory cytokines and Aβ in both wildtype mice (Brugg et al., 1995), and in AD-transgenic mice (Sheng et al., 2003). Conversely, anti-inflammatory treatments reduce Aβ production and Aβ plaque deposition (Yan et al., 2003) in rodent models and may have some efficacy in AD prevention (Zandi et al., 2002), although the literature in this area is mixed. The specific role of different components of neuroinflammation in AD pathogenesis is unclear, as some studies have found reduced Aβ pathology in response to increasing microglia (Boissonneault

et al., 2009), whereas others have found that attenuating pro-inflammatory cascades decrease Aβ pathology (Heneka et al., 2013). Thus, some aspects of neuroinflammation appear to be beneficial while others are harmful, indicating a need for more research.

B.2. Obesity and inflammation—Strong links between obesity and chronic inflammation have been established over the last several years (Weisberg et al., 2003; Zeyda and Stulnig, 2009). Not only does obesity appear to drive inflammation, but chronic inflammation can also disrupt metabolic processes to further drive obesity (Thaler and M. W. Schwartz, 2010). For example, healthy men with high levels of pro-inflammatory cytokines in serum had an increased risk of weight gain over a 6 year period (Engström et al., 2003). Conversely, obese subjects placed on a very low calorie diet for 28 days had a decrease in pro- and an increase in anti-inflammatory cytokines (Clément et al., 2004), pointing to the role of diet in the association between obesity and inflammation. In fact, saturated fatty acids have been shown to induce secretion of pro-inflammatory factors in culture (Gupta et al., 2012), whereas polyunsaturated fatty acids improve obesity-associated inflammation (Liu et al., 2013). Inflammation also contributes to insulin resistance (McNelis and Olefsky, 2014), a central feature of the metabolic syndrome. For example, signaling through the inflammatory NFκB pathway can result in insulin resistance peripherally (Arkan et al., 2005), as well as leptin and insulin resistance in the hypothalamus (García-Cáceres et al., 2013). Thus, inflammatory cascades associated with obesity are widely believed to contribute to the relationship between obesity and development of metabolic syndrome and T2D.

Obesity is also associated with central nervous system inflammation. For example, a high fat diet has been linked with a 30% increase in immune cell infiltration into the brain (Buckman et al., 2014). Inflammation in the hypothalamus is a central feature of obesity and high fat diets (De Souza et al., 2005; Milanski et al., 2009; Thaler et al., 2012). In fact, hypothalamic inflammation precedes diet-induced obesity since it is present after even a few days of high fat diet consumption (Thaler and Schwartz, 2010), and neonatally fed mice show preservation of an increased inflammatory response in hypothalamus even in adulthood (Ziko et al., 2014). Furthermore, there are also significant interactions between the hypothalamus and periphery in diet-induced obesity and inflammation. Administering anti-inflammatory antibodies into brains of obese rats led to decreased hypothalamic inflammation, increased leptin sensitivity in hypothalamus, and increased insulin sensitivity in liver, along with restoring liver glucose production (Milanski et al., 2012), demonstrating that manipulating central inflammation has direct effects on the periphery.

A relationship between obesity, inflammation, and cognition has also been established (Freeman et al., 2014). An increase in inflammatory markers in subjects with metabolic syndrome predicted subsequent cognitive decline (Yaffe et al., 2003). Subjects with both metabolic syndrome and high levels inflammation had the worst cognitive performance (Dik et al., 2007). Interestingly, one study found that cognitive performance improved and inflammation decreased after bariatric surgery, though the two did not correlate (Hawkins et al., 2014). Similar findings have been reported in rodent models. For example, levels of the pro-inflammatory cytokine IL-1β correlated with adiposity and cognitive impairment in the db/db mouse model of obesity (Erion et al., 2014). Moreover, treatment with an IL-1β

antagonist prevented obesity-associated cognitive impairments and synaptic dysfunction (Erion et al., 2014). Finally, associations between obesity and inflammation have been shown in the context of neuropsychiatric disorders such as depression, in both humans (Castanon et al., 2014; Soczynska et al., 2010; Viscogliosi et al., 2012), and in mice (André et al., 2014).

Moreover, the hypothalamus has been proposed to play a central role in the relationship between obesity, inflammation, and cognition. That is, inflammatory cytokines and infiltrating immune cells are thought to act in hypothalamus to activate local inflammation. This inflammation then causes synaptic remodeling and degeneration in hypothalamus, thereby affecting any regions to which the hypothalamus projects, including brain regions important in cognition (Miller and Spencer, 2014). Additionally, greater hypothalamic damage was associated with higher levels of inflammatory cytokines and worse cognitive performance in obese subjects (Puig et al., 2015).

Thus, there is strong evidence linking obesity with both peripheral and central inflammation, and with downstream effects including insulin resistance and development of the metabolic syndrome, and cognitive impairments. The short-term inflammatory effects of dietary components are likely to have different effects from the long-term chronic inflammation associated with obesity, though both aspects of the inflammatory cascade are likely important.

B.3. Sex differences in inflammation, obesity, and Alzheimer's disease—The role of inflammation in obesity is observed in both males and females, but there are significant sex differences in obesity-induced inflammatory responses. For example, several studies point to greater inflammation in response to obesity in women than in men (Ahonen et al., 2012; Khera et al., 2009; Mascarenhas-Melo et al., 2013; Petty et al., 2010; Rudnicka et al., 2011). Higher levels of inflammation also correlate more strongly with risk of T2D in women than in men, independent of BMI or adiposity (Thorand et al., 2007). Interestingly, non-diabetic premenopausal women are protected against metabolic disease and inflammation, but this protective effect is lost in the presence of either, T2D or menopause (Mascarenhas-Melo et al., 2013). Thus, it appears that obesity not only induces a greater inflammatory response in women, but higher levels of inflammation are also associated with an increased risk of metabolic disturbances, including T2D, in women.

Though no studies have directly examined sex differences in inflammation in the context of AD, a few studies have evaluated this relationship in terms of cognitive performance. Some research suggests that this relationship is stronger in women. For example, high inflammation was associated with poor cognitive performance in women but not men (Canon and Crimmins, 2011; Trollor et al., 2011). Similarly, another study found a correlation between high inflammation and mild cognitive impairment only in women (Trollor et al., 2010). In contrast, men may be vulnerable to other neural consequences of neuroinflammation. In support of this idea, the association between inflammatory cytokines and decreased brain volume is reportedly stronger in men (Jefferson et al., 2007). In an AD transgenic mouse model, the immune system is more impaired in male versus female mice (Giménez-Llort et al., 2008). Overall, findings point to increased inflammation in response

to obesity in females, as well as a greater association between inflammation and cognitive decline in women. These sex differences may be mediated in part by sex steroid hormones, as estrogens and androgens are known to modulate inflammation (Spence and Voskuhl, 2012; Tsilidis et al., 2013).

The anti-inflammatory role of estrogens has been well established in the literature (Arevalo et al., 2010; Ritzel et al., 2013), but this effect may be especially important in the context of obesity. For example, estradiol has been demonstrated to have anti-inflammatory effects in adipose tissue, neurons, and in the cardiovascular system, that may protect these tissues from the pro-inflammatory effects of high fat diet and obesity (Brown and Clegg, 2010). In support of this idea, ovariectomized female mice and males show higher weight gain on high fat diet, whereas mice treated with estrogen do not develop adipocyte hypertrophy nor adipose tissue inflammation, and are protected against liver steatosis and insulin resistance (Stubbins et al., 2011). Moreover, estrogen exerts its anti-inflammatory actions via ERα, as demonstrated by the fact that mice lacking ERα have increased adipose tissue inflammation even before obesity (Davis et al., 2013). Interestingly, mice lacking ERα specifically in adipocytes also have increased inflammation, and this is especially true in male mice (Davis et al., 2013). Pregnant mice on high fat diet show decreases in visceral adipose hypertrophy, inflammation, and less glucose intolerance during late gestation, a time that correlates with increases in visceral adipose tissue ERα signaling (Pedroni et al., 2014). The role of estrogens in inflammation is further supported by the fact that both ERα and ERβ are found on monocytes and macrophages, and estrogens act on these receptors to block pro-inflammatory responses (Vegeto et al., 2003). Additionally, estrogens modulate inflammation in the context of AD, such that ovariectomized mice have increased microglial reactivity around Aβ plaques, but this is reversed by estradiol treatment (Vegeto et al., 2008).

Like estrogens, androgens also have anti-inflammatory effects that may be important in the context of obesity and AD. Numerous studies have found that testosterone levels in men are inversely associated with C-reactive protein (CRP) (Kupelian et al., 2010; Tsilidis et al., 2013; Zhang et al., 2012). Even in young men, clinically low testosterone levels are associated with increased expression of TNFα and other inflammatory factors (Bobjer et al., 2013). Older men with androgen deficiency have higher levels of inflammatory cytokines (Maggio et al., 2006), which are reduced by testosterone treatment (Malkin et al., 2004). Moreover, low testosterone levels were shown to correlate with increased mortality, independent of metabolic syndrome, diabetes, or cardiovascular disease, but dependent on levels of the inflammatory enzymes, IL-6 and CRP (Laughlin et al., 2008), pointing to the interplay between androgens and inflammation. Experimental evidence suggests that androgens can reduce indices of inflammation (Norata et al., 2006; Schwinge et al., 2015). There is some evidence that testosterone treatment in aging men can lower inflammatory markers such as CRP (Giltay et al., 2008; Kalinchenko et al., 2010), though efficacy remains to be firmly established.

Testosterone and inflammation have also been demonstrated to interact in the context of obesity. Men with low testosterone are more likely to have metabolic syndrome and high levels of CRP (Laaksonen et al., 2003). In men with metabolic syndrome, lower levels of testosterone were associated with higher levels of IL-6 (Gautier et al., 2013). Similarly, men

with T2D also have lower testosterone and higher CRP levels (Bhatia et al., 2006). In animal models, inflammatory effects of obesity can be attenuated by testosterone treatment (Vignozzi et al., 2011). Research on the association of testosterone and inflammation in AD are limited, however, one study demonstrated that men with AD have lower testosterone and luteinizing hormone levels, the latter of which inversely correlate with levels of TNFα (Butchart et al., 2013). Our lab recently demonstrated that testosterone depletion exacerbates metabolic, pro-inflammatory, and peripheral nerve injury outcomes of DIO in male mice, effects that were reversed by testosterone treatment (Jayaraman et al., 2014). Moreover, we have found that DIO-induced increases in Aβ levels are associated with neuroinflammation, exacerbated by testosterone loss, and prevented by testosterone treatment (unpublished observations). Thus, the anti-inflammatory effects of testosterone are likely to be important in the relationship between obesity and AD.

C. Interactions between inflammation and apoE in obesity and AD

In addition to being independent factors in AD pathogenesis, apoE4 and inflammation also have important interactions with each other and with obesity (Figure 1). One established function of apoE is regulation of inflammation. In support of this role, glia from apoE knock-out mice exhibit increased pro-inflammatory responses after exposures to Aβ (LaDu et al., 2001) and LPS (Lynch et al., 2001). Importantly, apoE isoforms differ in their inflammatory effects. That is, apoE4 is associated with greater levels of pro-inflammatory cytokines, both in humans (Colton et al., 2004; Gale et al., 2014) and in mouse models (Colton et al., 2004; Lynch et al., 2003; Ophir et al., 2005; Vitek et al., 2009). Interestingly, apoE4 carriers have lower expression of apoE and, as young adults, increased levels of pro-inflammatory cytokines that decrease with age, though this study may be limited by a small sample size (Ringman et al., 2012). However, apoE can also take on a pro-inflammatory role when overproduced by activated microglia, and this pro-inflammatory response is stronger in the presence of apoE4 than apoE3 (Guo et al., 2004). Additionally, LPS stimulation in the presence of apoE4 is associated with increased endoplasmic reticulum stress and macrophage cell death (Cash et al., 2012), greater neuron damage (Maezawa et al., 2006a), and failure to regenerate dendrites (Maezawa et al., 2006b). Effects of apoE on inflammation may vary by cell type, as one study found that apoE3 astrocytes displayed increased astrogliosis after LPS, while apoE4 astrocytes had no response (Ophir et al., 2003). Thus, apoE appears to be an important regulator of inflammatory processes, with apoE4 generally having a more pro-inflammatory effect than apoE3.

The relationship between apoE and inflammation is also important in the context of AD (Keene et al., 2011). Among AD patients, those with the apoE4 allele had greater baseline and stimulated levels of IL-1β (Olgiati et al., 2010). ApoE co-localizes with microglia around Aβ plaques (Liu et al., 2013), and apoE4 mice have greater microgliosis and astrogliosis in response to Aβ than do apoE3 mice (Belinson and Michaelson, 2009). Additionally, mice with both human apoE4 and familial AD mutations have higher levels of pro-inflammatory cytokines and increased microglial reactivity surrounding Aβ plaques than do their apoE3 counterparts (Rodriguez et al., 2014). Further, apoE4 macrophages are less effective at clearing Aβ (Zhao et al., 2009). ApoE4, but not apoE2 or apoE3, activates a pro-inflammatory factor in pericytes that causes blood brain barrier breakdown (Bell et al.,

2012). Thus, apoE4's pro-inflammatory actions may contribute to the finding that apoE4 carriers have increased blood brain barrier breakdown (Halliday et al., 2013). Interestingly, non-steroidal anti-inflammatory drugs have been found to reduce risk for AD only in apoE4 carriers (Barger and Harmon, 1997; Schram et al., 2007), reinforcing the possibility of significant interactions between apoE4 and inflammation in AD.

The interplay between apoE and inflammation in the context of obesity has not been well studied. Unfortunately, available evidence is inconsistent. Several studies indicate that apoE knockout mice show reduced gains in fat mass and body weight in response to HFD (Arbones-Mainar et al., 2008; Bartelt et al., 2010; Pereira et al., 2012; Wang et al., 2012). Nonetheless, how apoE status affects obesity-associated inflammation is unclear, as one study reported that apoE knockout mice show a stronger pro-inflammatory response in adipose tissue than wildtype mice (Pereira et al., 2012), whereas another study found that apoE knockout mice on HFD have lower levels of inflammatory cytokines in adipose tissue and skeletal muscle (Wang et al., 2012). Interestingly, apoE4 mice fed a HFD are more susceptible to motor deficits after stroke, and this is accompanied by increased inflammation (Dhungana et al., 2013). Overall, the literature demonstrates an interaction between apoE and obesity, but more research is needed to clarify how this relationship affects inflammation.

Interestingly, there appear to be sex differences in the interactions between apoE and inflammation. For example, among nonagenarians, those who carry the apoE4 allele have lower levels of the inflammatory marker CRP, an outcome that is more robust in women (Rontu et al., 2006). Experimental work in animal models has also found sex differences in this regard, with apoE4 being associated with a greater pro-inflammatory response in males but not in females (Colton et al., 2005), suggesting that apoE4 carrying males may have an exaggerated inflammatory response. In addition, female apoE4 mice are less responsive to the anti-inflammatory effects of 17-β-estradiol (Brown et al., 2008), and male apoE4 mice are less responsive to the anti-inflammatory effects of DHT (Brown et al., 2007). Thus, both male and female apoE4 carriers may be less responsive to the anti-inflammatory effects of sex steroid hormones (Brown et al., 2008; 2007).

6. Conclusions

As reviewed in this article, there are significant sex differences in obesity and AD, as well as in mechanisms that may be underlying these disease processes (see Table 1 for a summary of sex differences in the AD risk factors discussed in this article). For one, obesity, and specifically central adiposity at midlife are significant risk factors for AD later in life (Emmerzaal et al., 2015; Fitzpatrick et al., 2009; Meng et al., 2014; Profenno et al., 2010; Xu et al., 2011). This relationship may be especially important for women, as women are both more at risk for AD (Li and Singh, 2014), and experience an increase in central adiposity at menopause (Meyer et al., 2011; Sugiyama and Agellon, 2012). While there exists some evidence of sex differences in obesity-associated AD risk (Barron et al., 2013; Hwang et al., 2010; Wolf et al., 2012), results are inconclusive and more work is needed to determine the nature of this relationship. Two factors that may be mechanistically important in the relationship between obesity and AD are apoE4 and inflammation. First, apoE4 is a

risk factor for AD (Saunders et al., 1993; Strittmatter et al., 1993) and may contribute to obesity-related complications and metabolic syndrome (de-Andrade et al., 2000; Niu et al., 2009; Sima et al., 2007). Moreover, sex differences exist in the effects of apoE, with the apoE4-associated risk of AD being significantly higher in women (Altmann et al., 2014; Payami et al., 1994). Chronic inflammation is associated with both AD (Glass et al., 2010) and obesity (Engström et al., 2003; Yaffe et al., 2003) and several studies have demonstrated that the pro-inflammatory effects of obesity are stronger in women (Ahonen et al., 2012; Khera et al., 2009; Mascarenhas-Melo et al., 2013; Rudnicka et al., 2011). Finally, apoE and inflammation also interact with each other, such that apoE4 is associated with greater pro-inflammatory responses (Cash et al., 2012; Colton et al., 2004; Gale et al., 2014; Lynch et al., 2003). In summary, apoE4 and inflammation are important factors in the association between obesity and AD, and their differing actions in males and females may be significant in explaining sex differences in these conditions.

Though this article has focused mainly on apoE4 and inflammation as mechanisms underlying sex differences in obesity and AD, a number of other factors may also play important roles in this relationship. Vascular factors including blood brain barrier breakdown, are associated with both, obesity and AD. As previously discussed, a link between the blood brain barrier, inflammation and apoE4 was recently discovered. That is, apoE4 is associated with increased inflammation around pericytes that then leads to blood brain barrier breakdown (Halliday et al., 2013; Zlokovic, 2013). Though sex differences in blood brain barrier function are unknown, it has been established that men are at increased risk of a number of cardiovascular risk factors (Crea et al., 2015). Thus, it may be the case that, though obesity is a risk factor for AD in both men and women, there may be different pathways between the sexes through which obesity acts to influence AD risk. For example, several studies point to women having greater inflammation in response to obesity, whereas obese men have more cardiovascular risk factors. Yet, both inflammation and vascular risk factors are associated with AD, such that obesity may use different signaling pathways in men and women to drive AD pathogenesis. Moreover, apoE4 will also interact with these pathways and its interactions are likely to vary between the sexes.

Though a number of genetic and environmental risk factors for sporadic AD have been identified, none of these is conclusive in predicting who will develop the disease. Even amongst those who carry the apoE4 allele, there is only a 30% lifetime risk of AD (Genin 2011), so that a number of other factors must also influence risk. Research has generally focused on examining risk factors in isolation, however, AD is a multifactorial disease. Continuing AD research must consider not only the interactions between genetic and environmental factors, but also how these are differentially affected by sex.

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Highlights

- Sex and obesity independently and interactively affect Alzheimer's disease.
- Alzheimer's disease risk is increased by both apolipoprotein E and inflammation.
- Sex and obesity interactions may involve apolipoprotein E and inflammation.

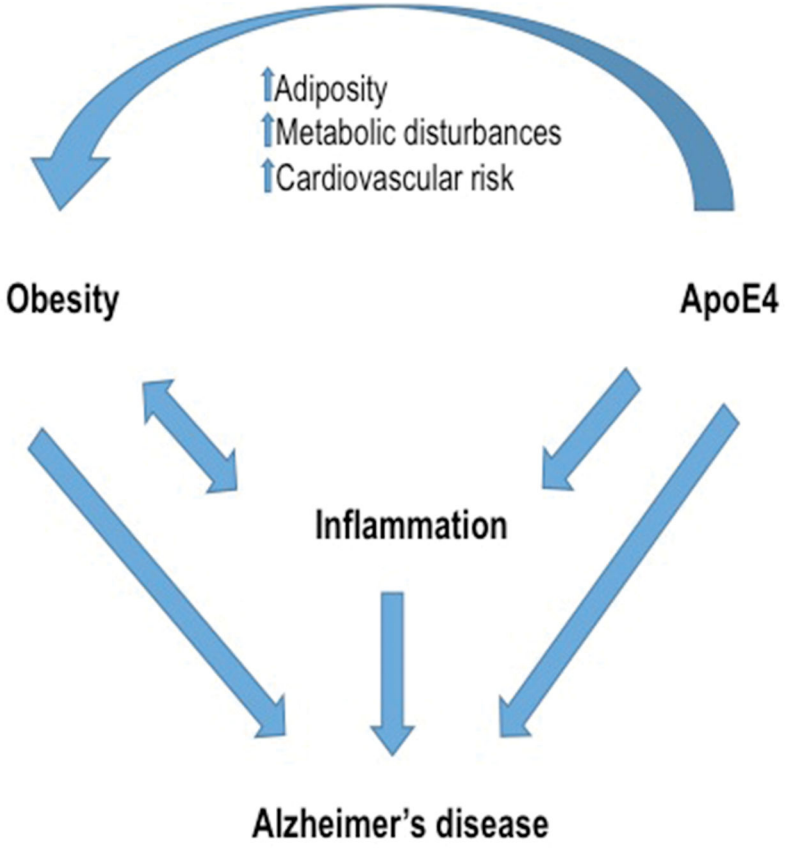

Figure 1. Interactions between obesity, apoE4 and inflammation in Alzheimer's disease

Alzheimer's disease (AD) risk and pathology are increased by a number of factors and pathways, many of which interact with each other. As diagrammed here and described in the text, apoE4 and obesity independently increase AD risk as well as inflammation, which also contributes to AD risk. Moreover, apoE4 carriers have been shown to be more at risk for a number of obesity-related complications, including increased adiposity, metabolic disturbances, and cardiovascular risk. Thus, apoE4 and obesity appear to both independently and cooperatively increase inflammation and AD risk.

Table 1

Sex differences in the Alzheimer's disease risk factors obesity, apolipoprotein E (apoE4), and inflammation.

AD risk factor	Sex differences	
	Males	**Females**
Obesity	Reduced by testosterone Causes greater visceral fat deposits Causes stronger metabolic and neurological effects in male rodents	Reduced by estrogens Causes greater subcutaneous fat deposits Food cues cause greater neural activation Increased risk of obesity after menopause
ApoE4	Alzheimer risk increased ~4X by two apoE4 alleles Lower testosterone in apoE4 carriers Testosterone has beneficial cognitive effects in apoE4 humans and rodents	Alzheimer risk increased ~4X by one apoE4 alleles and ~10X by two apoE4 alleles Greater increase in cognitive decline Estrogen may not be beneficial in apoE4-carrying women
Inflammation	Reduced by testosterone Inflammatory effects of obesity attenuated by testosterone	Reduced by estrogens Increased obesity associated with greater inflammation in women