Neurochemistry International 127 (2019) 38–55

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

# Sex differences in risk factors for vascular contributions to cognitive impairment & dementia

O.J. Gannon, L.S. Robison, A.J. Custozzo, K.L. Zuloaga*

*Department of Neuroscience and Experimental Therapeutics, Albany Medical College, 47 New Scotland Ave, Albany, NY, 12208, USA*

ARTICLE INFO

*Keywords:*
Vascular dementia
Sex
Metabolic disease
Stroke
Menopause
Hormone replacement therapy

ABSTRACT

Vascular contributions to cognitive impairment and dementia (VCID) is the second most common cause of dementia. While males overall appear to be at a slightly higher risk for VCID throughout most of the lifespan (up to age 85), some risk factors for VCID more adversely affect women. These include female-specific risk factors associated with pregnancy related disorders (e.g. preeclampsia), menopause, and poorly timed hormone replacement. Further, presence of certain co-morbid risk factors, such as diabetes, obesity and hypertension, also may more adversely affect women than men. In contrast, some risk factors more greatly affect men, such as hyperlipidemia, myocardial infarction, and heart disease. Further, stroke, one of the leading risk factors for VCID, has a higher incidence in men than in women throughout much of the lifespan, though this trend is reversed at advanced ages. This review will highlight the need to take biological sex and common co-morbidities for VCID into account in both preclinical and clinical research. Given that there are currently no treatments available for VCID, it is critical that we understand how to mitigate risk factors for this devastating disease in both sexes.

## 1. Introduction

Vascular contributions to cognitive impairment and dementia (VCID) is a heterogeneous group of disorders defined by cognitive decline resulting from cerebrovascular pathology. VCID is the second most common cause of dementia, accounting for approximately 10% of dementia cases when it occurs as a single etiology dementia. Further, ~50% of those with Alzheimer's disease (AD) have co-morbid VCID pathology ("mixed dementia") (Alzheimer's Association, 2016). The cost of care for those with mixed AD/VCID pathology is estimated at 118 billion dollars per year in the US alone (Alzheimer's Association, 2016). Unfortunately, there is no cure for VCID, and current pharmacological treatments are only mildly effective for alleviating symptoms in the short-term rather than addressing underlying pathology. Therefore, identifying and targeting risk factors for VCID may now be the most effective means for combating this debilitating and deadly group of diseases. While aging is the largest risk factor for VCID, sex, cardiovascular disease, metabolic disease, and other sex-specific risk factors could work independently or in tandem with age to increase dementia risk. While this review will not give justice to the vast amount of research on VCID, it will give an overview of sex differences related to some of the most important risk factors for VCID. In addition to covering cardiovascular and metabolic factors that affect both sexes, we also focus on sex-specific risk factors including pregnancy, preeclampsia, menopause, and hormone replacement therapy (see Fig. 1 for a summary). Given that there are currently no treatments available for VCID, it is critical that we understand how to mitigate risk factors for this devastating disease in both sexes.

### 1.1. Overview of Vascular Contributions to Cognitive Impairment and Dementia (VCID)

The severity of VCID runs along a spectrum and can range from milder forms of cognitive deficits to severe vascular dementia (VaD) capable of impairing activities of daily living. Symptoms of VCID vary depending on insult, but can include mental slowness and deficits in executive function and memory, as well as a variety of behavioral, psychological, and neurological disturbances. The pathogenesis of VCID

*Abbreviations:* AD, Alzheimer's disease; AngII, angiotensin II; BBB, blood brain barrier; CBF, cerebral blood flow; CEE, conjugated equine estrogens; DHT, dihydrotestosterone; E2, 17-β estradiol; HRT, hormone replacement therapy; ICH, intracerebral hemorrhage; MCAO, middle cerebral artery occlusion; NFκB, nuclear factor kappa B; OC, oral contraceptive; OVX, ovariectomy; PE, preeclampsia; T, testosterone; VaD, vascular dementia; VCID, vascular contributions to cognitive impairment and dementia; VCAM-1, vascular cell adhesion molecule 1; VSM, vascular smooth muscle cells

* Corresponding author. Albany Medical College, 47 New Scotland Ave, MC-136, Albany, NY, 12208, USA.
*E-mail addresses:* gannono@amc.edu (O.J. Gannon), robisol@amc.edu (L.S. Robison), custoza@amc.edu (A.J. Custozzo), zuloagk@amc.edu (K.L. Zuloaga).

https://doi.org/10.1016/j.neuint.2018.11.014
Received 27 September 2018; Received in revised form 16 November 2018; Accepted 16 November 2018
Available online 22 November 2018

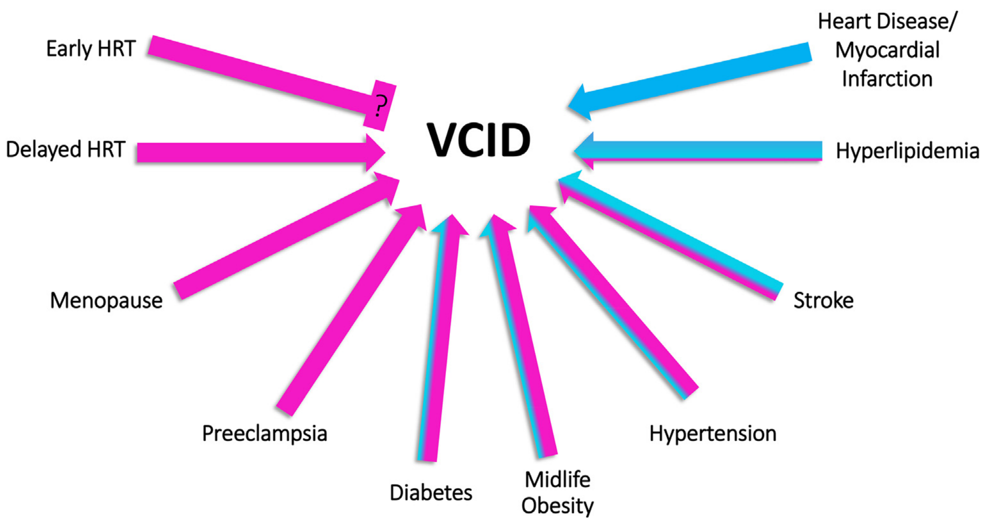


**Fig. 1.** Schematic of sex differences in risk factors for VCID. Risk factors that increase risk in females only are shown in pink arrows, and male risk factors are shown in blue arrows. Risk factors that increase risk in both sexes are shown in pink/blue with the proportion of each color indicating which sex is at greater risk. The inhibitory symbol is used instead of an arrow head to indicate factors which may decrease risk.

begins with vascular injuries such as damage to cerebral small blood vessels, carotid artery occlusion/stenosis, or stroke, with small vessel disease being the most common cause. Other vascular risk factors, such as cardiovascular disease, hypertension, and diabetes, can also contribute to VCID. Each of these insults leads to cerebral hypoperfusion and cognitive deficits (Iadecola, 2013). In addition to cognitive testing, VCID diagnosis is often also dependent on neuroimaging findings and therefore may go undiagnosed in the absence of stroke (Knopman et al., 2003). VCID is often visualized on MRI and may include: infarcts (or microinfarcts), small vessel disease (e.g. arteriolosclerosis or cerebral amyloid angiopathy), hemorrhages (or microbleeds), and white matter intensities (WMHs; areas of demyelination due to hypoperfusion) (Gorelick et al., 2011).

## 2. Sex differences in overall VCID risk

While overall dementia prevalence is higher in women (de Silva et al., 2003; Yamada et al., 1999), this sex difference appears to be largely driven by AD-related dementia (Andersen et al., 1999). VaD may be more common in men, although data is mixed. A few studies show trends for higher risk in men which do not reach statistical significance (Copeland et al., 1999; Fujishima and Kiyohara, 2002; Imfeld et al., 2013b), while others have observed no sex difference (Andersen et al., 1999). Yet, data from the Rotterdam Study, showed that VaD incidence was significantly higher among men in the 75–90yr age groups (Ruitenberg et al., 2001). Additionally, the ILSA study also found a significantly higher risk (RR = 2.23) of VaD in men vs. women (Di Carlo et al., 2002). A possible explanation for these varied results could be the age of the cohorts examined in the studies. A meta-analysis on various European studies found that sex differences in prevalence of VaD reversed their trend with advancing age. Before age 79, VaD was more prevalent among men, but after age 85 it was more prevalent among women (Lobo et al., 2000). This is in agreement with the Rotterdam Study which also found this reversal of the sex difference in those 90 + years of age (Ruitenberg et al., 2001). However, caution should be used when interpreting data in very old populations, due to the survival bias of women. Taken together, these sex differences in overall VCID risk led us to question how individual risk factors for VCID vary between the sexes.

## 3. Sex differences in cardiovascular risk factors

### 3.1. Stroke

Stroke is a debilitating and deadly neurological event affecting nearly 800,000 people each year in the U.S. alone (Benjamin et al., 2017). Stroke is divided into two categories: ischemic (~85% of cases) and hemorrhagic (~15% of cases) (Bamford et al., 1990). While stroke kills about 140,000 Americans per year making it the 5th leading cause of death in the U.S. (Yang et al., 2017), there is a vast number of individuals that survive stroke and must live with its disabling consequences, including post-stroke dementia, which occurs in up to one-third of stroke victims (Leys et al., 2005). Further, the relationship between stroke and VaD risk is reciprocal, whereby stroke increases risk of VaD and vice versa (Fujishima and Kiyohara, 2002; Imfeld et al., 2013a; Ivan et al., 2004; Yamada et al., 1999, 2009).

Sex differences exist in the overall incidence, outcomes, and mortality associated with stroke and appear to be dependent on age and hormone status (Appelros et al., 2009; Girijala et al., 2017; Liu and McCullough, 2012; Roy-O'Reilly and McCullough, 2018). While brain infarction and intracerebral hemorrhage (ICH) are more common in men, incidence rates of subarachnoid hemorrhage are higher in women (Appelros et al., 2009). Although men are more likely to suffer from stroke when compared to pre-menopausal women, the incidence of stroke among women begins catching up to that of men after menopause (Ahangar et al., 2018; Appelros et al., 2009; Petrea et al., 2009). While stroke incidence is reported to be higher in men than in women aged 45–84, this trend is reversed in the oldest age group (aged 85–94) (Petrea et al., 2009).

It is possible that aging/menopause inflates risk of stroke indirectly by increasing the incidence and severity of common risk factors in women, as will be discussed. This accrual of insults may also explain the long period of time between 17-β estradiol (E2) loss during menopause and the reversed sex trend that is not observed until more than three decades later.

Sex differences in efficacy of preventive medicine could also contribute. For example, aspirin was found to reduce risk of stroke in women but not men (1989; Ridker et al., 2005). Additionally, in patients treated with warfarin (an anti-coagulant medication) for atrial fibrillation, the risk of stroke was twice as high in women compared to men despite both sexes being anticoagulated to a similar degree (Poli et al., 2009).

Data on sex differences in VCID risk following stroke is mixed. Some studies found that there were no sex differences in incidence of VCID following ischemic stroke (Sachdev et al., 2006), ICH stroke (Tveiten et al., 2014), or any type of stroke (Wang et al., 2014). However, multiple studies have found that women suffer worse functional outcomes and cognitive decline after stroke than men do (Dhamoon et al., 2015; Rasquin et al., 2002). Results could be influenced by the age of the subjects, as several of these studies reported that female participants were, on average, older than males. In a study in which age was accounted for, no sex differences were found (Renoux et al., 2017). Further in another study limited to ischemic stroke survivors aged 55 through 85, men were more likely to suffer memory impairment after stroke (Pohjasvaara et al., 1997). Other studies examining sex differences in likelihood of post-stroke dementia have been mixed, with some showing higher rates in men (Corraini et al., 2017) and others in women (Andersson et al., 2012; Inzitari et al., 1998).

Sex differences in outcomes following stroke, including post-stroke dementia, could be attributable to the fact that women tend to experience greater stroke severity compared to men (Niewada et al., 2005). Sexual dimorphism in stroke could also be partially driven by efficacy of stroke treatments. For example, minocycline, a potential stroke medication, was found to only have beneficial effects in men (Amiri-Nikpour et al., 2015), while treatment with tissue plasminogen activator (tPA) may be more beneficial in women (Kent et al., 2008).

Studies in both humans and animals suggest a key role of sex hormones in stroke. Effects of hormone replacement therapy (HRT) are complex but results have generally been promising if HRT is initiated soon after menopause (Carrasquilla et al., 2017; Miller and Harman, 2017; Zandi et al., 2002). while HRT administered later in life has been shown to be detrimental. Thus, timing of HRT relative to menopause appears to be very important, as will be discussed in detail in the "menopause" section.

Clinical studies regarding the relationship between androgen levels in men and stroke risk suggest that a proper balance of testosterone (T) is vital. Low T and dihydrotestosterone (DHT) levels in men is associated with increased risk of stroke, as well as worse outcomes (Yeap et al., 2009, 2014), which could be related to increased presence of risk factors (Kupelian et al., 2008). Decreased serum T levels are seen in male stroke victims, and are correlated with stroke severity, mortality, and infarct size even when controlling for other risk factors (Jeppesen et al., 1996). Additionally, men treated for prostate cancer with androgen deprivation therapy are at a heightened risk of ischemic stroke (Chen et al., 2017). Conversely, T replacement therapy in males age 65+ increases the risk of cardio- and cerebrovascular events (Basaria et al., 2010). It therefore appears that the effects of androgens in men are dose-dependent, with both too high and too low levels of androgens putting men at increased risk of stroke.

Animal studies have consistently shown that female rodents are protected against stroke compared to males, demonstrated by less severe pathology and improved functional outcomes in females (Alkayed et al., 1998; Faber et al., 2017; Hall et al., 1991; Liu et al., 2009b; Manwani et al., 2013; McCullough et al., 2005; Zhang et al., 2010; Zhang et al., 2009). Interestingly, there is no sex difference in infarct size following MCAO in aged mice (20–22 mo), while others have shown that the female advantage (smaller infarct size) is no longer apparent in 16 month old reproductively senescent rats (Alkayed et al., 2000). This could be due to declining levels of ovarian sex hormones in females with age. The relationship between ovarian sex hormone levels and stroke outcomes are supported by findings of altered outcomes over the estrous cycle, with smaller infarct size seen during proestrus (high E2) (Carswell et al., 2000). Additionally, others have found that ischemia/stroke-related outcomes are exacerbated by both aging and OVX in females (Alkayed et al., 1998; Liu et al., 2009b). E2's protective effects in experimental stroke models have been reported in young male and female animals (Alkayed et al., 1998; Hawk et al., 1998; Toung et al., 1998; Yang et al., 2002a).

Studies suggest that E2's effects may be dose-dependent, such that E2 administered at physiological levels attenuates damage from experimental stroke (Alkayed et al., 2000; Cai et al., 2014; Rusa et al., 1999), while supraphysiological doses may be detrimental, increasing infarct size, oxidative stress, inflammation, and excitotoxicity (Ma et al., 2013; Strom et al., 2009, 2011).

The effects of E2 may also be age-dependent, being protective in young but ineffective or even deleterious in older rats and mice (Cai et al., 2014; Leon et al., 2012; Selvamani and Sohrabji, 2010); however, some have found that E2 reduces stroke damage in senescent female rats (Alkayed et al., 2000). There is evidence to suggest that it may not be older age per se that makes E2 ineffective in older/postmenopausal animals and humans, but rather prolonged hypoestrogenicity (Suzuki et al., 2007a). These findings provide evidence in favor of the "Timing Hypothesis" for HRT, such that E2 treatment must start soon after menopause to be effective (Carrasquilla et al., 2017; Roy-O'Reilly and McCullough, 2018; Sahathevan et al., 2012; Sohrabji et al., 2013).

Interestingly, the opposite is seen in males such that stroke outcomes are improved with aging. Most studies agree that aging and castration in males has a positive impact on stroke outcomes (Cheng et al., 2009; Liu et al., 2009b; Shapira et al., 2002), the only notable exception being one study which found no significant difference (Manwani et al., 2015). Protection provided by castration in young males is reversed by administration of T and DHT (Cheng et al., 2007, 2009; Hawk et al., 1998; Yang et al., 2002b). Like E2, the effects of androgens on stroke appear to be both dose- and age-dependent. While low doses of both T and DHT decrease infarct size after cerebral ischemia (Cheng et al., 2009, 2010; Pan et al., 2005; Uchida et al., 2009), higher doses worsen outcomes (Uchida et al., 2009), in agreement with findings in men that both low and high T are detrimental.

Sex differences in stroke risk and outcomes could be mediated in part by differences in blood flow. Some studies have shown that female rodents maintain cerebral blood flow in addition to having smaller infarcts than males after MCAO (Alkayed et al., 1998; Zhang et al., 2009, 2010). Even in healthy individuals, women consistently show higher CBF compared to men across the lifespan (Rodriguez et al., 1988; Satterthwaite et al., 2014; Tontisirin et al., 2007), and there is evidence to suggest that CBF is controlled by female sex hormones in humans (Brackley et al., 1999; Diomedi et al., 2001; Ohkura et al., 1995). Maintenance of CBF is dependent on cerebrovascular tone and reactivity. Females exhibit greater vasodilation and cerebrovascular reactivity (Ahnstedt et al., 2013; Geary et al., 1998; Zuloaga et al., 2014a), which is highly influenced by sex hormones. E2 promotes vasodilation by upregulating the production and activity of vasodilatory factors like NO (Geary et al., 1998, (Geary et al., 2000a); McNeill et al., 1999; McNeill et al., 2002; Murata et al., 2013; Sobey et al., 2004; Stirone et al., 2005; Stirone et al., 2003), while androgens promote vasoconstriction, attenuating the production of vasodilators and increasing the production of vasoconstrictors (Geary et al., 2000b; Gonzales et al., 2004, 2005). Additionally, sex effects in stroke could be mediated by other cerebrovascular factors, such as coagulation and thrombolysis (reviewed in (Roy-O'Reilly and McCullough, 2014)), as well as atherosclerosis (reviewed in (Haast et al., 2012)).

There is ample other evidence to suggest that sex hormones mediate stroke risk and outcomes via their diverse actions on the cerebrovasculature (Duckles and Krause, 2011; Krause et al., 2006). E2 particularly has protective effects on endothelial cell function and survival (Guo et al., 2010; Kemper et al., 2013). Additionally, sex hormones play a key role in mediating inflammation in the cerebrovasculature. E2 appears to exert potent anti-inflammatory effects following experimental stroke (Park et al., 2006; Santizo et al., 2000), which may be mediated in part via suppression of NFkB (Galea et al., 2002), and is accompanied by inhibition of pro-inflammatory mediators (Razmara et al., 2005; Sunday et al., 2007). Androgens may also exert anti-inflammatory effects in the cerebrovasculature under ischemic conditions, though these effects are believed to occur via an estrogenic pathway (Zuloaga and Gonzales, 2011). E2, and DHT via an estrogenic pathway, also attenuate the expression of cell adhesion molecules (e.g. ICAM-1, VCAM-1) that mediate leukocyte recruitment to the cerebrovasculature (Galea et al., 2002; Zuloaga et al., 2012). Additionally, females exhibit lower levels of cerebrovascular oxidative stress than males, and these sex differences appear to be driven by the presence of gonadal hormones (Miller et al., 2007a). Lastly, studies suggest protective effects of female sex and ovarian hormones on blood brain barrier (BBB) permeability (Shin et al., 2016), demonstrating variability of BBB integrity over the estrus cycle (Saija et al., 1990), in intact versus ovariectomized females (Cipolla et al., 2009; Saija et al., 1990; Wilson et al., 2008), and in young versus reproductively senescent females (Bake and Sohrabji, 2004). E2 treatment protects against BBB damage, disruption, and permeability in response to ischemia(Liu et al., 2005), while protective effects of T replacement are also seen for BBB permeability in castrated males (Atallah et al., 2017). E2 may reduce BBB permeability by increasing tight junction protein expression (Burek et al., 2010; Kang et al., 2006), an effect also seen with T treatment (Atallah et al., 2017), and reduce the production of matrix metalloproteinases that degrade tight junctions (Li et al., 2011; Liu et al., 2005). The benefits of E2 on BBB integrity and function following stroke also serve to attenuate edema (Auriat et al., 2005; O'Donnell et al., 2006) and reduce leukocyte transmigration (Santizo and Pelligrino, 1999; Santizo et al., 2000).

In addition to their wide range of actions on the cerebrovasculature, sex hormones also exert a multitude of effects on other cells types that can influence the pathogenesis of stroke. For example, E2 increases adult neurogenesis, synaptic plasticity, and neurotrophic growth factor signaling, attenuates autophagy, and is protective against excitotoxicity, inflammation, oxidative stress, and apoptosis (Batnasan et al., 2015; Herzog et al., 2017; Li et al., 2017a; McCullough and Hurn, 2003; Suzuki et al., 2007b; Zhang et al., 2017; Zheng et al., 2013). T can have neuroprotective effects by being aromatized into E2, while other mechanisms are mediated by androgenic signaling (reviewed in (Giatti et al., 2018; Gonzales, 2013)). This includes, for example, supporting synapses (Leranth et al., 2003) and increasing survival of adult-born neurons (Hamson et al., 2013; Spritzer and Galea, 2007), as well as promoting antioxidant activity and cell survival (Ahlbom et al., 2001; Lee et al., 2008). Conversely, androgens appear to promote excitotoxicity and resulting cell death (Yang et al., 2002b) as well as promoting apoptotic and antagonizing cell survival pathways (reviewed in (Quillinan et al., 2014)).

While sex hormone effects appear to mediate many of the sex differences in stroke risk and outcomes, contribution of sex chromosome effects have also been demonstrated. Using the 4 core genotypes model, in which the sex-determining SRY gene is moved from the Y chromosome to an autosome (De Vries et al., 2002), it was found that gonadal sex, rather than sex chromosomal complement (XX or XY), determines ischemic stroke outcomes in gonadally intact young mice. Specifically, E2 was found to mediate the improved outcomes in females (Manwani et al., 2015). However, in aged mice, sex complement determines ischemic stroke outcomes. While there were no differences in sex hormone (E2 and T) levels between groups, XX males and XX females had larger infarct size compared to XY males and XY females following MCAO, in addition to increased inflammation (McCullough et al., 2016). The importance of sex hormones vs. sex complement on sexual dimorphism in stroke outcomes may therefore be age-dependent. Cellular mechanisms of stroke also appear to be mediated by sex chromosomes, with XY neurons relying more on the AIF-dependent pathway and XX neurons relying on a cytochrome *c* dependent cell death pathway (Du et al., 2004). In vivo stroke studies have confirmed that XX chromosome status, rather than sex hormones, is responsible for the increased caspase-mediated cell death in females (Liu et al., 2009a). Taken together, these findings suggest that not only sex hormones, but also sex complement, can play a significant role in stroke outcomes.

### 3.2. Hypertension

Hypertension (systolic pressure > 140 mmHg) increases risk of VCID (Fujishima and Kiyohara, 2002; Yamada et al., 1999) and other dementia types (Iadecola et al., 2016). Men have a higher incidence of hypertension than women throughout most of the lifespan, although this sex difference dissipates after menopause (Gillis and Sullivan, 2016). However, multiple studies have found that hypertension increases the risk of developing VaD and negatively affects cognitive function in women, but not in men (Gilsanz et al., 2017; Hebert et al., 2000). For example, higher systolic blood pressure correlates with lower scores on mini-mental state examinations in hypertensive women but not in men (Seux et al., 1998). Further, age is an important factor to consider. Gilsanz et al. found that there was a 65% increased risk of dementia in women, but not men, who suffer from hypertension at midlife. Meanwhile, hypertension in early adulthood had no significant effect in either sex (Gilsanz et al., 2017). However, increased VaD risk in men with mid-life hypertension was observed in the Honolulu-Asia Aging Study (Freitag et al., 2006), although this study did not include any women for comparison. Recently it was also discovered that late-life hypertension increases VCID and AD pathology, in both women and men (Arvanitakis et al., 2018), however sex differences were not assessed. Taken together these studies suggest that mid-late life hypertension is a major risk factor for dementia, particularly in women. Therapeutic effects of anti-hypertensive medications in clinical trials for dementia have been mixed. However, recent preliminary results from the SPRINT MIND Study, presented at the 2018 Alzheimer's Association International Conference, suggested that the degree of blood pressure control may be key, with intensive systolic blood pressure control (< 120 mmHg) reducing combined risk of cognitive impairment and dementia compared to traditional blood pressure control (AAIC, 2018). Sex differences in the efficacy of intensive blood pressure control have yet to be assessed.

Sex differences in cognitive function in response to hypertension have also been examined with mixed results. A detailed comparison in male and female spontaneously hypertensive rats showed that females had worse spatial memory than males, and that middle-aged hypertensive rats of both sexes had poorer spatial memory than control rats of the same sex (Grunblatt et al., 2015).

Considering hypertension's influence on dementia risk, it is important to understand sex differences regarding blood pressure control and how this might change with age. The renin angiotensin system (RAS) is integral to blood pressure regulation, with components that increase [e.g. Angiotensin II (AngII),] and decrease blood pressure [e.g. Ang-(1–7)]. Sex differences within the RAS system have been reported. For example, sensitivity to AngII-induced increases in blood pressure are lower in gonadally intact females than in males. However, OVX increases sensitivity to the AngII-induced increases in blood pressure, while E2 replacement reverses this effect. The effects have been shown to be due to E2 upregulation of anti-hypertensive RAS components (Xue et al., 2014). This sex difference may also be mediated by changes in neuronal nitric oxide synthase (NOS), since NOS inhibitors allow greater blood pressure increase in response to AngII in females, while they produce no effect in males (Xue et al., 2009b). Finally, the female advantage may also be mediated by a more anti-inflammatory environment (Gillis and Sullivan, 2016). The protective effects of E2 on the RAS system are in line with the loss of female advantage in hypertension incidence in the decade after menopause (Gillis and Sullivan, 2016).

E2 treatment has also been shown to influence blood pressure in humans and in animal models. E2 improves endothelium-dependent vasodilation in hypertensive women (Lima et al., 2005). Gonadally intact females are protected from aldosterone/NaCl-induced increases in blood pressure relative to males; however, gonadectomized females lost this protection relative to males, which could be reversed by E2. Males were also protected by E2, and female protection was diminished by an estrogen receptor antagonist (Xue et al., 2009a). Beneficial effects of E2 have also been demonstrated in other models of hypertension, with central administration of E2 reducing AngII induced increases in blood pressure and oxidative stress (Xue et al., 2008). While loss of E2 with menopause increases blood pressure following AngII, systemic E2 given during perimenopause can reverse this effect in mice (Pollow et al., 2015).

T affects blood pressure differently in men and women. High T levels have been associated with increased blood pressure in post-menopausal women (Ziemens et al., 2013), while the reverse trend is observed in men (Khaw and Barrett-Connor, 1988). These opposing effects could contribute to sex differences as hormone levels change with age.

### 3.3. Other cardiovascular diseases

Many cardiovascular diseases, such as atherosclerosis, heart disease, heart failure, and myocardial infarction, increase VCID risk (Mortel et al., 1993; Sundboll et al., 2018). There are sex differences in the way that myocardial infarctions affect dementia risk. Data from the Rotterdam Study show that men, but not women, with unrecognized myocardial infarctions (a heart attack that was not reported but diagnosed based on EKG results) had greater dementia risk compared to those without myocardial infarction, and this correlated with greater cerebral small vessel disease pathology (white matter lesions and ischemic damage) on MRI, indicating VCID (Ikram et al., 2008). Likewise, a Canadian study found that heart disease was a risk factor for the development of VaD in men but not in women (Hebert et al., 2000). Thus, for myocardial infarction, the limited data available suggests this may be a larger risk factor for VCID in men than women.

## 4. Sex differences in metabolic risk factors

### 4.1. Diabetes

Likely due to the shortened lifespan (~68 yrs in women, ~66yrs in men) in type 1 diabetic patients (Livingstone et al., 2015), the role of type 1 diabetes in VaD or VCID risk has yet to be determined, thus our review will focus on type 2 diabetes. However, it is important to note that as lifespan increases in type 1 diabetic patients, this area of research should be addressed, as animal studies do suggest that type 1 diabetes induces VCID-like pathology (Sharma and Singh, 2011).

Type 2 diabetes increases overall dementia risk and doubles the risk of VaD (Ahtiluoto et al., 2010; Peila et al., 2002). Over 30 million people in the United States have type 2 diabetes and that number is increasing (CDC, 2017). While men are more prone to develop type 2 diabetes than women of a similar body weight, women are more prone to obesity, which is the leading risk factor for diabetes (Kautzky-Willer et al., 2016). Thus, due to these conflicting effects of sex on metabolic function no sex differences in diabetes prevalence are observed in the US (CDC, 2017). Interestingly one study found that among VaD patients diabetes was more prevalent in women than men (64% vs. 36%) (Liu et al., 2018). This raises the question of how and if female sex hormones influence the effect of diabetes on VCID and related dementias. It was found that high serum E2 levels put postmenopausal women at an increased risk of all-cause dementia; however, low E2 levels were equally risky, suggesting a J-shaped curve. Additionally, diabetes put these women at an even greater risk of developing dementia (Carcaillon et al., 2014).

Prediabetes, defined as glucose intolerance or insulin resistance in the absence of hyperglycemia, has also been found to be a risk factor for vascular dementia, all-cause dementia, and AD (Ohara et al., 2011). Interestingly, we have found middle-aged female mice develop more severe glucose intolerance than males when fed a high fat diet (Salinero et al., 2018). Sex differences in prediabetes in humans need further evaluation.

Evidence supports a sex difference in the effects of type 2 diabetes on VCID specifically, with women being more adversely affected than men. The Cache County study found that type 2 diabetes confers a 3.3-fold increased risk of VaD in women but not in men (Hayden et al., 2006). Further, a recent meta-analysis that included over 2.3 million individuals, found that compared to men with diabetes, women with diabetes have a 19% greater risk of developing vascular dementia (Chatterjee et al., 2016). Finally, a study of ischemic stroke patients found that diabetes was a risk factor for both VaD and VCI after stroke, and that women had greater levels of post stroke dementia, though lower levels of education which could have confounded results (Arauz et al., 2014). Taken together, these studies clearly show that type 2 diabetes is a risk factor for VCID, and suggests that the risk is particularly strong in women compared to men.

Mechanisms by which diabetes may increase VCID risk include increased oxidative stress, cerebrovascular remodeling, endothelial dysfunction/impaired vasodilation, and altered coagulation (Ergul et al., 2012; Kautzky-Willer et al., 2016). These factors lead to deficits in blood flow that appear to be reversible. For example, we have found that in rodent models of both type 1 (Jouihan et al., 2013) and type 2 diabetic stroke (Zuloaga et al., 2014b) inhibiting the breakdown of vasodilatory/neuroprotective epoxeicosatrienoic acids is neuroprotective (Zuloaga et al., 2014b), and accompanied by reversal of blood flow deficits (Zuloaga et al., 2014b). Other treatments, such as insulin replacement in type 1 diabetic rats, can also reverse impairments in cerebral vessel vasodilation (Mayhan et al., 2001). Further, we have found that in a rodent model of metabolic syndrome (chronic high fat diet), which causes cognitive deficits and reduced blood flow, a simple change in diet can lead to improved metabolic, cognitive and vascular function (Johnson et al., 2016). We have shown that, similar to stroke, metabolic syndrome increases cognitive deficits in mouse models of VCID through blood flow deficits as well as through increased neuroinflammation and neuronal loss (Zuloaga et al., 2016). These studies suggest that the effects of diabetes on VCID may be preventable with lifestyle interventions or medication to improve metabolic function.

The role of sex hormones within these processes offers explanation for clinical observations of sex differences in diabetic cerebrovascular diseases. In a meta-analysis of 64 studies, comprising over 775,000 individuals, it was found that women with type 2 diabetes have a 27% greater risk of stroke compared to diabetic men (Peters et al., 2014). Bearing in mind that stroke is a principal risk factor for VCID, mechanistic studies on the interplay between stroke and diabetes in women is critically important. When researchers compared stroke outcomes between males and females in rodent models of diabetes, varied results have been demonstrated. One study using a genetic model of diabetes (db/db mice) did find that, compared to females, males had worse outcomes after stroke regarding both ischemic infarct volume and mortality (Vannucci et al., 2001). However, the majority of studies have found that diabetic females are worse off than their male counterparts. For instance, in a different genetic model of diabetes (KKAy mice), female mice had much larger infarct sizes. Despite this female disadvantage, E2 was still found to be neuroprotective in these mice. Specifically, the female mice had larger ischemic areas that were worsened by ovariectomy and ameliorated by E2 treatment (Sakata et al., 2011). A type 2 diabetes model (high fat diet + low dose STZ) found that non-diabetic female rats had better outcomes after stroke than males, but this protection was lost when comparing diabetic males and females (Li et al., 2017b). Sex differences in the effects of diabetes on coagulation factors could contribute to differences seen in stroke, with women with diabetes being in a more pro-thrombic state (Alzahrani et al., 2012; Neergaard-Petersen et al., 2014).

Other clinical sex differences in diabetes have been observed. For example, women with diabetes had greater levels of systemic inflammation, as indicated by elevated plasma levels of C-reactive protein (Mrgan et al., 2018) and a strong trend ($p = 0.06$) toward lower hippocampal volumes (Hempel et al., 2012) than men with diabetes. In a small study, HRT was demonstrated to increase insulin clearance in newly post-menopausal women (age 56 ± 4 years) (Van Pelt et al., 2003). In line with this, the HERS study found that HRT (avg age 66 yrs) reduced diabetes incidence by 35% (Kanaya et al., 2003). However, while HRT was protective against metabolic impairment in this older population, timing/age of HRT onset is likely important for the cognitive effects of HRT (as discussed in depth in the HRT section below) since HRT initiated in diabetic women over 65 is actually linked to more grey matter loss (Espeland et al., 2015).

Animal models have also supported the role of sex hormones in diabetes-related inflammation and oxidative stress. For example, a genetic rodent model of diabetes (KKAy mice), found that female mice had higher NADPH oxidase activity in their brains (indicative of greater oxidative stress), worse cognitive performance, and worse glucose tolerance than diabetic males. When the females underwent OVX, E2 treatment attenuated NADPH oxidase activity and improved glucose tolerance (Sakata et al., 2010). There is still much unknown about the mechanisms that distinguish diabetes in men and women and how these differences could affect VCID.

### 4.2. Obesity

The number of people categorized as obese is increasing, and that trend is forecast to continue its upward climb (2016). Currently, nearly 40% of American adults are considered obese, with rates of obesity increasing with age. This is concerning, as studies have consistently found a link between obesity, particularly at middle age, and dementia risk in later life (Fitzpatrick et al., 2009; Whitmer et al., 2005, 2008). Obesity is a condition that could contribute to dementia risk directly or indirectly by influencing other risk factors. For example, human studies have revealed that abdominal adiposity is associated with stroke risk (Bodenant et al., 2011) and visceral fat with cerebral small vessel disease (Kim et al., 2017). Additionally, lifestyle factors such as poor nutrition and lack of physical activity could contribute to both obesity and dementia risk (reviewed in (Ahlskog et al., 2011; Morris and Tangney, 2014)). Some have attempted to parse out the relationship between obesity and subtypes of dementia. Body mass index (BMI), calculated using height and weight, is the tool most commonly used to assess whether an individual is overweight (BMI of 25–30) or obese (BMI of > 30). In a larger cohort study of over 10,000 individuals, individuals obese at midlife (40–45 years of age) had a 5x higher risk of VaD, versus 3x higher risk of AD compared to normal weight individuals. Individuals who were overweight had a 2x higher risk of both VaD and AD (Whitmer et al., 2007). These findings were independent of cardiovascular disease, stroke, and diabetes comorbidities. Additionally, obesity is associated with VCID pathology, with one study demonstrating increased risk and severity of white matter lesions with higher BMI in elderly women (Gustafson et al., 2004). Other studies suggest that the relationship between BMI and VaD may not be linear, but rather have more of an inverted-U shape, with both low and high BMI being associated with increased risk. For example, in a nested case-control study, low BMI (< 20.5; OR = 4.28), and being overweight/obese (> 25.5; OR = 4.62) were associated with increased VaD risk (Chiang et al., 2007).

One small study suggests that the relationship between BMI and VaD risk may be sex-dependent, affecting women more than men. While having a very low BMI between the ages of 20 and 40 increased the risk of VaD in both sexes, having a high BMI between the ages of 20 and 40 increased the risk of developing VaD in women only (Chen et al., 2010). Additionally, the relationship between BMI and dementia risk appears to be age-dependent, such that lower BMI in late life is associated with increased dementia risk (Fitzpatrick et al., 2009). It is possible that higher BMI in midlife is associated with increased vascular risk factors, while declining BMI in later life could be indicative of neurodegenerative processes and overall declining health (Arnoldussen et al., 2014; Kivimaki et al., 2018), as accelerated weight loss and lower BMI has been shown to precede dementia diagnosis in clinical populations (Johnson et al., 2006; Singh-Manoux et al., 2018). Obesity-induced inflammation and oxidative stress could negatively impact the brain and contribute to VaD. One study found that obesity in aging increases systemic inflammation, BBB disruption, neuroinflammation, oxidative stress, and cerebrovascular autoregulatory impairment (Tucsek et al., 2014).

While BMI is a commonly used measure of adiposity, it has been criticized for failing to take sex or body composition into account. Additionally, it has been suggested that body fat distribution could provide an improved indicator of health rather than global obesity (Czernichow et al., 2011), as ~10–40% of obese individuals do not exhibit symptoms of metabolic syndrome (Hinnouho et al., 2013), and some studies fail to show a link between BMI and VaD in men and women (Hayden et al., 2006; Yamada et al., 2009). While studies support a link between central adiposity/visceral fat and overall dementia risk (Gustafson et al., 2009), studies explicitly examining this link with VaD are scarcer. One study found that higher waist-to-hip ratio (WHR), a commonly used indicator of central obesity was associated with white matter hyperintensities and reductions in hippocampal volume in an older Latino population (Jagust et al., 2005). Central obesity, and particularly visceral fat, may promote VCID pathology and cognitive decline, as it is linked to greater metabolic impairment and increased severity of vascular risk factors, as well as increased risk of cardiovascular diseases (Fox et al., 2007; Gruzdeva et al., 2018). Additionally, visceral obesity is associated with an increased production of proinflammatory adipokines and decreased production of anti-inflammatory adipokines (reviewed in (González-Muniesa et al., 2017)). Higher levels of resistin, another pro-inflammatory adipokine produced by visceral adipose tissue, are seen in individuals with VaD and MxD (Bednarska-Makaruk et al., 2017). Removing visceral fat from aged male mice reduces proinflammatory cytokines and improves BBB integrity (Shin et al., 2015). Additionally, the authors found that removing visceral fat from these mice offered stroke protection, including smaller infarct volumes, less inflammation, and reduced BBB permeability after ischemic brain injury (Shin et al., 2015).

Females may be protected against the pathologic effects of abdominal/visceral fat due to sex differences in body fat distribution. Although rates of obesity are higher in women than in men (Collaboration, 2016; Fryar et al., 2016), and women have greater body fat compared to males of similar BMI range (Nielsen et al., 2004), men tend to accumulate abdominal/visceral fat ("android fat" distribution), whereas females tend to accumulate subcutaneous fat and fat in the gluteal-femoral regions ("gynoid fat" distribution) (Goodpaster et al., 2005; Nielsen et al., 2004; Yim et al., 2008). This sex difference in abdominal/visceral fat accumulation appears to diminish in older age groups (Camhi et al., 2011; Goodman-Gruen and Barrett-Connor, 1996), with women gaining central/visceral fat following menopause, suggesting an effect mediated by ovarian sex hormones (Ley et al., 1992; Lovejoy et al., 2008; Svendsen et al., 1995). Additionally, OVX leads to weight gain, increased visceral fat, and hyperlipidemia in female rats, with weight gain attenuated by E2 treatment (Babaei et al., 2017). Adipose tissue expresses receptors for estrogen, progesterone, and androgens, with this expression varying by sex and type of fat (i.e. subcutaneous vs. visceral), and studies suggest that sex hormones influence both amount and distribution of body fat (reviewed in (Rosenbaum and Leibel, 1999)). While E2 and progesterone appear to promote fat accumulation, E2 promotes fat storage in peripheral (rather than central locations); therefore, the redistribution of fat to central locations following menopause in women is likely due to a decrease in ovarian E2 production (Lobo et al., 1993; Lovejoy et al., 2008). Other studies have documented the protection in female rodents against the health consequences of obesity. One study found that although female rats on a high fat diet gained more weight than males, they maintained better insulin sensitivity and exhibited increased serum expression of the anti-diabetic/anti-inflammatory cytokine adiponectin compared to males (Amengual-Cladera et al., 2012). Others have found that although young weight-matched female mice on a high fat diet have increased adiposity and adipocyte size compared to males, they remain more glucose tolerant, have increased expression of adiponectin, and have reduced inflammation and oxidative stress in adipose tissue (Nickelson et al., 2012). Evidence suggests that leptin may play a role, since females show increased levels of circulating leptin compared to males of similar BMI (even when corrected for fat mass) (Maffei et al., 1995; Rosenbaum et al., 1996), which could be explained by findings that fat isolated from females secretes greater amounts of leptin compared to fat from males (Licinio et al., 1998). This sex difference is likely mediated by sex hormones. T is negatively associated with circulating leptin levels, while T administration attenuates leptin expression in adipose tissue in vitro (Wabitsch et al., 1997). OVX attenuates leptin levels that are restored by E2 replacement, while E2 treatment increases leptin levels in both rodents and humans (Shimizu et al., 1997). Additionally, E2 treatment increases leptin production of female adipose tissue in vitro (Casabiell et al., 1998). E2-mediated increased production of leptin by adipose tissue in females may be one mechanism by which females are protected in VCID, as leptin has been shown to be neuroprotective, for example in stroke. Leptin treatment reduces infarct volumes, and neurologic deficits in rodent models of ischemic stroke (Deng et al., 2014).

Although females may accumulate less of the dangerous visceral fat compared to males, there is evidence to suggest that the fat of females may have greater pathological properties compared to males following loss of ovarian hormone production. Menopause not only heralds increased amounts of visceral fat, but differences in adipocyte characteristics. For example, adipose samples from pre- and post-menopausal women revealed greater adipocyte hypertrophy and oxidative stress in the visceral fat of post-menopausal women compared to pre-menopausal women, with in vitro findings suggesting that this could be mediated by E2's antioxidant properties (Narumi et al., 2018). Animal studies suggest that there are sex differences in inflammatory profiles of adipose tissue. Middle-aged, reproductively senescent, female mice had higher levels of CD8 + T cells compared to both middle-aged males and younger females. Since the levels of regulatory T cells were also reduced in the middle-aged females, the ratio of pro-inflammatory to anti-inflammatory cells was tilted towards a pro-inflammatory state (Ahnstedt et al., 2018). We have also shown that while juvenile females are protected from the metabolic effects of a high fat diet compared to males, this sex difference is reversed in middle-aged mice and females gain more weight than males(Salinero et al., 2018). Another study documented that OVX in female mice led to adipocyte hypertrophy and increased levels of oxidative stress and inflammation within their adipose tissue compared to intact female mice, which was rescued by E2 treatment (Stubbins et al., 2012). Taken together, these findings provide support that increasing risk factors and VCID in women after menopause could be linked to increased amounts of visceral fat and pathogenicity of fat tissue in females following loss of ovarian hormone production.

### *4.3. Hyperlipidemia & APOE*

Hyperlipidemia is a condition associated with increased risk of cardiovascular disease. Influenced by both genetics and diet, some researchers have investigated sex differences in the impact of lipids on VCID risk. For women without vascular pathologies, having low triglyceride levels offers protection against all-cause dementia. In men, but not in women, low HDL-C levels and high triglyceride levels were associated with increased all-cause dementia risk (Ancelin et al., 2013). While low HDL levels may be more detrimental in men in regard to all-cause dementia, this sex difference appears to be reversed in the context of pure VCID. Low HDL is associated with increased risk of periventricular white matter lesions, deep white matter lesions, and silent brain infarctions in women but not men(Yin et al., 2018).

A key player in lipoprotein metabolism and lipid transport is apolipoprotein E (APOE). APOE gene polymorphisms are linked to VaD risk (Yin et al., 2012). For example, data from the Cache County Study found that APOE4 allele increases risk of VaD in a dose-dependent manner(Chuang et al., 2010). A recent study found that the 10-year risk of VaD was 2.87 fold higher in those who carry two copies of the APOE4 allele compared to the APOE3 allele(Rasmussen et al., 2018). While sex differences in the effect of APOE4 on VCID have not been reported, data suggests that APOE4 allele is a stronger risk factor for AD in women compared to men(Altmann et al., 2014). These studies suggest that sex could impact the response to cardiovascular risk factors leading to divergent VCID risks.

## 5. Sex-specific risk factors in women

### *5.1. Introduction*

Given the effect of sex hormones on the cerebral vasculature and the sex differences observed in overall VCID risk, sex-specific risk factors should also be taken into consideration. There is little data on the association between gestational diabetes, breastfeeding, hot flashes, endometriosis, PCOS, hormonal birth control use, and maternal age in the risk of developing VCID despite these events having significant effects of hormone levels. For example, while oral contraceptives have been associated with increased risk of stroke (Roach et al., 2015), breastfeeding has been associated with a decreased risk of cardiovascular disease (Peters et al., 2017), stroke (Jacobson et al., 2018), and AD (Fox et al., 2013), but effects on VCID specifically are unknown. However, several sex-specific risk factors have received some attention including combined oral contraceptive use and cigarette smoking, pregnancy, hypertensive pregnancy disorders, menopause, and HRT.

### *5.2. Combination of oral contraceptive use and cigarette smoking*

Oral contraceptive (OC) use is a commonly prescribed form of birth control which has historically been associated with increased risk of thrombotic events involving both the arterial and venous systems due to the overall hypercoagulable effect of estrogens (Dulicek et al., 2018). In addition to venous thromboembolisms, oral contraceptives are associated with increased risk of arterial thrombotic events like ischemic stroke and transient ischemic attacks which have the potential to compromise cognitive function and contribute to VCID (Dulicek et al., 2018). A meta-analysis reported the overall relative risk estimate for ischemic stroke to be 2.75 (95% CI, 2.24–3.38) among current OC users compared to non-OC users. The study also found that the risk of ischemic stroke remained elevated even among patients receiving the lower-dose formulations currently used in clinical practice (Gillum et al., 2000). Smoking is another significant risk factor for dementia, a 2015 meta-analysis found a consistent link between smoking and all-cause dementia thought to be mediated by increased exposure to oxidative stress and vascular injury (Zhong et al., 2015). Current CDC guidelines advise caution when prescribing OC to smokers and is contraindicated among women over the age of 35 who smoke over 14 cigarettes per day. Guideline recommendations reflect results of several studies suggesting that concurrent OC use and smoking adds additional risk which may have a synergistic effect in causing adverse cardiovascular health outcomes (Lidegaard, 1999). The WHO found that the relative risk for cerebral thromboembolic attack was highest among OC users and smokers, reported to be 7.2. Smoking alone was only associated with a 1.2 relative risk and OC use alone had an estimated relative risk of 2.1 (WHO, 1996). Similarly, a study in England reported that the relative risk of cerebral thromboembolic attack for non-smokers using OC to be 1.8 with an increase to 3.5 among women who smoked < 15 cigarettes per day and an even more drastic increase to 20.8 among women who use OC's and smoke > 15 cigarettes/day (Croft and Hannaford, 1989). Since the combination of OC use and cigarette smoking increases risk for ischemic stroke and dementia, it is likely that VCID risk is also increased, although this has yet to be examined.

### *5.3. Pregnancy*

Pregnancy greatly modifies hormone production. In fact, there is a variant of estrogen that is specific to pregnant women and their fetuses:

estetrol. Human data on the effect of pregnancy on VCID, specifically, is lacking; though one small study did find that pregnancy did not affect the incidence of white matter lesions (Postma et al., 2014). This may be due to the well described cerebrovascular adaptations that are known to occur during pregnancy to maintain normal blood flow and vascular function in the presence of increased cardiovascular demand (Cipolla, 2013). However, major findings were made public at AAIC 2018, in which Dr. Gilsanz and colleagues showed that women with 3 or more pregnancies were at 12% decreased risk for dementia. Further Dr. Fox and colleagues demonstrated that greater number of months a woman spent pregnant the lower her risk of AD (Alzheimer's_Association, 2018); however, previous studies have shown greater numbers of pregnancies in AD patients compared to controls(Colucci et al., 2006). Studies have also found positive associations between number of children and neuropathy (Beeri et al., 2009), as well as increased risk of AD only in those women who have greater than 5 pregnancies (Jang et al., 2018). Thus, the effect of pregnancy on dementia risk may be a U-shaped curve, with 3–4 pregnancies being protective, but more than 5 pregnancies being detrimental. Clinical data regarding effects of pregnancy specifically on VCID/VaD is sparse. Clearly, more work is needed.

Preclinical data suggests that pregnancy might protect against VCID and related dementias. Rodent models investigating the impact of pregnancy on VCID risk factors offer compelling results that could, if also true in humans, reveal how pregnancy affects health later in life. Recently, Dr. McCullough and colleagues demonstrated that multiparous female mice had better functional outcomes after ischemic stroke compared to nulliparous female mice, likely mediated by immunosuppression, as well as migration of fetal cells to the site of injury, in multiparous mice (Ritzel et al., 2017). Middle-aged rats that had pregnancies had lower blood pressure and better spatial memory than those that had not (Cabrera-Pedraza et al., 2017). This research supports a beneficial effect of parity on the mother. Further, in a study modeling VCID using spontaneously hypertensive rats, it was found that a single previous pregnancy preserved spatial memory (Cabrera-Pedraza et al., 2017). Despite these results suggesting a protective effect of pregnancy on functional outcome, pregnancy does increase the risk of both ischemic and hemorrhagic strokes, key VCID risk factors, particularly for those who experience vascular-related pregnancy complications such as preeclampsia/eclampsia (Tate and Bushnell, 2011), as discussed below. Additional complicating factors include maternal age (Morton et al., 2017) and inflammatory insults during pregnancy (Li et al., 2016). Thus, the effect of pregnancy on VCID risk may depend on the health of the mother during pregnancy, the number of pregnancies, and the mother's age.

### 5.4. Preeclampsia/eclampsia

Chronic hypertension increases the risk of developing hypertensive pregnancy disorders, like preeclampsia, which can be dangerous for both the mother and fetus. Preeclampsia (PE), which is diagnosed by high blood pressure and proteinuria, can further progress to eclampsia (seizures) or HELLP syndrome. Evidence suggests that preeclampsia causes changes in the brain (for review see (Ijomone et al., 2018)) and may aggravate VCID pathology. One study found that women who had eclampsia were 3.3-fold more likely to have white matter lesions than women with normotensive pregnancies. Further, these lesions were larger in the eclampsia group and lesion load positively correlated with seizure frequency (Aukes et al., 2009). In an African population with high rates of chronic hypertension, 48% of women with severe preeclampsia had WMLs one year after delivering their babies. Additional differences were observed in the rate of WML formation among the preeclamptic women who had chronic hypertension versus those that were not chronically hypertensive (Soma-Pillay et al., 2017). These two studies reveal the relationship between hypertensive pregnancy disorders and WML and prompt investigation into associated cognitive effects.

A survey of women found that mothers who had gestational hypertension (without proteinuria, which excludes PE) self-reported cognitive impairment more often than women with non-hypertensive pregnancies (Tuovinen et al., 2013). A meta-analysis on the effects of PE on cognitive function had mixed results: while PE was associated with self-reported cognitive impairment, some standardized cognitive tests found differences in memory and some did not (Elharram et al., 2018). Additionally, compared to women with non-hypertensive pregnancies, women who had hypertensive pregnancies performed worse on tests of processing speed and had smaller brain volumes; these effects were evident decades after giving birth (Mielke et al., 2016). Moreover, a history of hypertensive pregnancy has been associated with a 5-fold greater risk of stroke (Leffert et al., 2015). Considering that both stroke and hypertension are risk factors for VCID, preeclampsia/eclampsia is likely a sex-specific risk factor for VCID. Several studies have found no association between hypertensive pregnancy and dementia (Andolf et al., 2017; Nelander et al., 2016). However, one of these studies that failed to find a correlation between hypertensive pregnancy and VaD did find a large effect of hypertension + proteinuria on VaD risk (Andolf et al., 2017). Considering the documented rise in the prevalence of severe PE in the United States, the connection between it and VaD is important to explore (Ananth et al., 2013).

PE involves insufficient placental blood flow which initiates a cascade of damaging events for the mother and the fetus. It is thought that genetic factors, the immune response of the mother, and the mother's vascular system can all contribute to the abnormal development of placental vessels and disease (Logue et al., 2016). How PE influences the long-term health of the mother is still under investigation. A rat model of PE demonstrated impaired autoregulation (ability to maintain blood pressure over a range of blood pressures) after the placental blood flow was surgically reduced, accompanied by cerebral edema and increased BBB permeability (Warrington et al., 2014). Impaired cerebral autoregulation has been observed in human patients who had previously had PE (Janzarik et al., 2014), suggesting that changes to cerebral autoregulation could persist after pregnancy.

One important contributor to changes in blood flow in women with PE is the development of AngII type 1 receptor autoantibodies (AT1-AA). Some studies have attributed long-lasting endothelial dysfunction to persistent increases in sensitivity to AngII, at least in the peripheral circulation (Stanhewicz et al., 2017). AT1-AA are increased in women with PE and have been shown to make vascular smooth muscle more responsive to AngII in rodents (Zhang et al., 2015). AT-AA's have even been shown to induce a PE phenotype in pregnant mice (Zhou et al., 2008). This effect is mediated via increased endothelin-1, a potent vasoconstrictor (Zhou et al., 2011). While there are studies that support the role of AT1-AA in human PE and hypertension (Liu et al., 2015), studies have not investigated the potential link between AT1-AA and cognitive function after PE in women or in animal models. However, AT1-AA have been found to be increased in AD patients (Giil et al., 2015); yet, their role in VCID is unexplored.

Inflammation is a proposed mechanism through which PE develops (Logue et al., 2016). Systemic inflammation has been shown to trigger a PE-phenotype in rats (Cotechini et al., 2014). Women with PE and eclampsia have increased levels of inflammatory markers after (Hubel et al., 2008) pregnancy. One study found that post-menopausal women who had prior PE had higher levels of C-reactive protein, a marker of systemic inflammation, 30 years later (Hubel et al., 2008). Additionally, PE could contribute to vascular endothelial dysfunction and hypertension by raising endothelin-1 (Sharma et al., 2011). This study and others demonstrate the long-lasting consequences of PE that could contribute to risk of VCID.

### 5.5. Menopause

Most women spend 1/3 of their lives in a post-menopausal state.

Menopause is defined as the cessation of menstruation for at least a year. This process, usually occurring around 55 years of age, is accompanied by major hormonal changes that accelerate the development of metabolic and cardiovascular diseases that are known mid-life risk factors for later development of dementia (Heianza et al., 2013; Kannel et al., 1976; Sutton-Tyrrell et al., 1998). For example, the earlier a woman goes through menopause the higher her risk is for developing diabetes(Muka et al., 2017), thus increasing her future risk for VCID.

While pre-menopausal women have reduced risk/severity of hypertension (Fryar et al., 2017) and cardiovascular disease (Benjamin et al., 2018) compared to age-matched men, women have increasing/higher rates of obesity, type II diabetes, dyslipidemia, hypertension, and other cardiovascular risk factors following menopause (Azad et al., 2007; Cignarella et al., 2010; Wildman et al., 2008). Early natural menopause also increases risk of stroke (Baba et al., 2010; Lisabeth et al., 2009). Earlier age at menopause has also been found to predict faster cognitive decline (Bove et al., 2014; Ryan et al., 2014). Like natural menopause, dementia risk is also increased in women who have hysterectomies, but only if the surgery occurs before natural menopause(Imtiaz et al., 2014; Rocca et al., 2011), suggesting that the increased risk is mediated by early loss of ovarian hormones.

The onset of menopause initiates a changing hormonal environment, impacting health independent of age. With the loss of ovarian E2 production, comes a loss of protection against VCID risk factors, which will be discussed in the "hormone replacement" section below. Clinical data supports a greater effect of endocrine aging over chronological aging on brain pathology. Even after controlling for age, white and grey matter volumes and brain glucose metabolism are lower in post-menopausal women compared to pre-menopausal women (Mosconi et al., 2017). Rodent studies provide some insight into additional underlying mechanisms. One study using an ovariectomy menopause model, demonstrated metabolic changes such as loss of insulin sensitivity, independent of weight gain, as well as increased adipose tissue inflammation (Vieira Potter et al., 2012). Using a VCD model of menopause, is has also been shown that menopause increases insulin resistance and glucose intolerance, and that these effects can be prevented by E2 replacement (Romero-Aleshire et al., 2009). Other studies have also indicated increased levels of inflammation and altered immune cell activity within postmenopausal women, including greater leukocyte adherence to an endothelial monolayer (Abu-Taha et al., 2009). In addition to these changes, menopause can contribute to diminished endothelial function (Moreau et al., 2012). These menopause related changes, and others, may alter susceptibility to VCID and VCID risk factors. More research is needed to evaluate the overlap between age and menopause as VCID risk factors.

### 5.6. Hormone replacement therapy

HRT is prescribed to menopausal women to manage the side effects of menopause, including vasomotor symptoms (e.g. hot flashes). Numerous animal studies show E2 has a variety of protective effects on the brain through its anti-oxidant, anti-inflammatory, vasodilatory, and anti-apoptotic effects (Gulinello et al., 2006; Koellhoffer and McCullough, 2013; Saldanha et al., 2009)) (see Fig. 2 for a summary). A large meta-analysis showed that HRT also has beneficial cognitive effects in women (LeBlanc et al., 2001). Therefore, it was assumed that HRT would protect against dementia. Observational studies and retrospective analyses also overwhelmingly supported the hypothesis that HRT has protective effects to reduce cardiovascular disease and dementia risk (Paganini-Hill and Henderson, 1994; Stampfer et al., 1985; Tang et al., 1996; Wolf et al., 1991; Zandi et al., 2002). This work prompted the Women's Health Initiative (WHI), the largest randomized, double-blind, placebo controlled HRT trial at the time. The results of the WHI, published in 2002, sent shock waves through the field with its surprising negative results – HRT increased dementia risk 2-fold and stroke risk 1.4-fold (Rossouw et al., 2002; Shumaker et al., 2003). It also failed to preserve cognitive function (Rapp et al., 2003). HRT use plummeted and the research community scrambled to try and make sense of these findings. One limitation of the 2002 WHI study was that it was performed exclusively among healthy postmenopausal women with the average age of participants being 65. The average onset age of menopause is much earlier ranging from late 40s-early 50s. Re-analysis of the WHI results and many landmark preclinical studies highlighted the importance of this age gap and offered support for the "timing hypothesis" first described in 2000 by Mader and Sano. The "timing hypothesis" (Marder and Sano, 2000), was based on several smaller trials of HRT and AD risk, suggests that HRT is beneficial only if given soon after menopause. Re-analysis of the WHI found that HRT (conjugated equine estrogens) had cardioprotective effects and decreased all-cause death in women who received HRT soon after menopause began. Conversely, women who were > 70 years when they began HRT (> 10yrs post-menopause) had increased risk of cardiovascular disease and death during the intervention period, although this risk dissipated over time (LaCroix et al., 2011).

This "timing hypothesis" was replicated in rodent studies which showed that immediate E2 therapy after ovariectomy is protective against ischemic brain injury but delayed E2 was not (Suzuki et al., 2007a). Mechanisms underlying this "timing" effect were explored and it was found that one key effect may be the inflammatory response. It was found that immediate E2 reduced inflammation while delayed E2 did not (Suzuki et al., 2007a). Other studies also showed that the benefits of HRT on vascular inflammation (Miller et al., 2007b), oxidative stress (Lopez-Grueso et al., 2014),and stroke protection (Leon et al., 2012; Selvamani and Sohrabji, 2010) are dependent on the timing of administration in regards to menopausal status. In an animal model investigating stroke, authors found that E2 treatment did not cause increased estrogen receptor expression in older mice but did in younger mice (Cai et al., 2014), suggesting E2 was ineffective at providing neuroprotection in the aged animals due to reduced availability of receptors. In additional studies, authors compared the effects of E2 replacement when it was initiated at different times in relation to ovariectomy: immediately, after 3, 6, or 9 weeks. Immediate E2 replacement improved brain glucose uptake and reduced oxidative stress; however, benefits of E2 were lost when HRT was delayed. The authors believe that this could be due to changes in the estrogen receptor alpha to estrogen receptor beta ratio. This ratio increased with ovariectomy but was rescued with simultaneous E2 replacement. Their results support that long-term E2 deprivation can lead to changes that make the body less susceptible to the beneficial effects of E2 replacement (Lopez-Grueso et al., 2014). Reproductive history may also alter the efficacy of HRT. One study found that multiparous rats had increased hippocampal neurogenesis in response to E2 but rats who had never had pups did not have any benefits of the E2 treatment (Barha and Galea, 2011). Further studies are needed to determine if the new cells would contribute to cognitive function. Thus, in animal models the timing of HRT influences outcome, similar to clinical findings.

Further clinical trials supported the "timing hypothesis" and brought new understanding that formulation, dose, and length of treatment may also be key. The KEEPS trial, which enrolled women soon after menopause (< 3 years) tested two formulations of HRT – conjugated equine estrogens (used in the WHI) and E2 (used in the majority of preclinical studies that showed protection). This trial found no harm or benefit for dementia risk (Gleason et al., 2015); however, the follow up was only 4yrs, possibly making the women too young to adequately assess dementia risk. Interestingly, when they assessed E2 levels in these women, they found the conjugated equine estrogens actually increased estrone levels (another form of estrogen) rather than E2 levels. Further, they found that the dose of E2 used in the study only raised plasma E2 levels to ∼50 pg/ml, which is low compared to what pre-menopausal women experience over the course of the month as their E2 levels fluctuate from ∼30 to 400 pg/ml depending on the phase of the menstrual cycle. A second trial, the ELITE-Cog trial, also

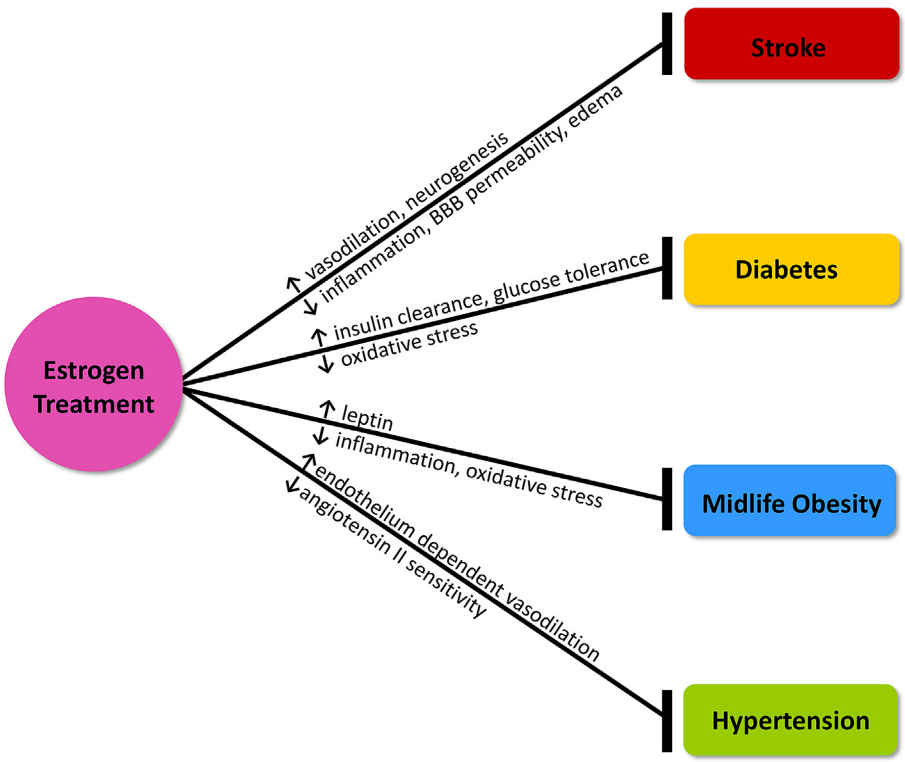


**Fig. 2.** Effects of estrogen on VCID risk factors. Estrogen has been shown to have a variety of protective effects on vascular and metabolic risk factors by enhancing vasodilation, neurogenesis, insulin and leptin sensitivity, and reducing inflammation and oxidative stress. However, when hormone replacement therapy is delayed (> 10 years post-menopause) some of these protective effects are lost (see Fig. 3).

tested the "timing hypothesis" by enrolling women who were < 5 years from menopause and > 10 years from menopause. This trial used only E2 and again found cardiovascular benefit in the younger group (Hodis et al., 2016) but no cognitive harm or benefit (Henderson et al., 2016). As with the previous trial, the follow-up time was short (2.5yrs) and thus was likely not long enough to adequately assess dementia. In support of the length of follow-up being important, long-term observational studies continue to show a benefit of HRT for dementia (Henderson et al., 2005; Imtiaz et al., 2017; Shao et al., 2012; Whitmer et al., 2011). For example, recent results of the 20-year observational OSTPRE study of over 8000 women showed that HRT cut AD risk in half but only for those who had taken HRT for 10 + years. When HRT was broken down into formulations, it was found that E2 specifically reduced AD risk by 70%. Importantly, in this study the average age of HRT onset was only 52 years of age, compared to 65 years of age in the WHI (Imtiaz et al., 2017). Finally, a recent pooled analysis from population-based cohort studies including nearly 90,000 postmenopausal women found that initiation of HRT less than 5 years after menopause is associated with decreased risk of overall stroke, and hemorrhagic stroke specifically. Contrastingly, later initiation of CEE therapy was associated with increased risk of stroke overall and hemorrhagic stroke specifically, while later initiation of combined estrogen and progesterone HRT is associated only with a higher risk of hemorrhagic stroke (Carrasquilla et al., 2017). For detailed reviews on the cognitive and cardiovascular effects of HRT please see reviews by Maki (2013) and Miller (Miller and Harman, 2017), respectively. Given the large benefits reported in observational studies, clinical trials with early initiation of HRT and long follow up times are needed, but will be extremely costly. Currently, due to lack of positive effects in clinical trials, HRT is not recommended for preservation of cognitive function or reduction of dementia risk.

Regarding VCID specifically, very little is known about the effect of HRT, but the results of the few published studies look promising. A recent study found that prolonged HRT (> 5yrs of treatment) decreased the risk of death due to VaD by 39%, an effect that was larger than the 15% reduction in risk of death from AD (Mikkola et al., 2017). While E2 has been shown to protect against cognitive impairment in a young male rats in a rodent model of VCID (Zhu et al., 2017), this has not been tested in females. However, one study did find that a phytoestrogen improved both vascular and cognitive function in high fat diet fed ovariectomized female rats (Verma and Sharma, 2015). Clearly, more research is needed to determine the effects of HRT on VCID.

## 6. Conclusion

While males overall appear to be at a slightly higher risk for VCID throughout most of the lifespan, some risk factors for VCID more adversely affect women. These include female specific risk factors associated with pregnancy related disorders (e.g. preeclampsia), menopause, and poorly timed HRT. However, several female-specific factors may also provide protection, including healthy pregnancies and potentially HRT given soon after menopause, although more evidence is needed before this can be recommended. Further, presence of comorbid risk factors, such as diabetes, obesity and hypertension, also may more adversely affect women than men. In contrast, some risk factors more greatly affect men, such as hyperlipidemia and myocardial infarction. Further, stroke, one of the leading risk factors for VCID, has a higher incidence in men than in women throughout much of the lifespan (Ahnstedt et al., 2016). A list of animal models that have been used to assess sex differences in these risk factors is shown in Table 1. Further, a summary of mechanisms by which each of these risk factors contributes to VCID pathology is shown in Fig. 3. Taken together, the sex differences in risk factors highlight the need to take common comorbidities for VCID (e.g. menopause, diabetes, hypertension) into account in both preclinical and clinical research. Importantly, researchers should consider these sex differences in risk factors and etiology when developing and testing novel therapeutics for VCID and related dementias.

## Declaration of interest

None.

**Table 1**
Examples of animal models that have been used to assess sex differences in VCID risk factors. For each risk factor an example of animal models and findings is presented. BBB, blood brain barrier; E2, estradiol; MCAO, middle cerebral artery occlusion; SHR, spontaneously hypertensive rat; STZ, Streptozotocin.

| VCID Risk Factor | Animal Model | Sex Difference/Effect | References for Sex Differences in VCID |
|---|---|---|---|
| Stroke | Middle cerebral artery occlusion (MCAO) | Infarct size > young ♂ vs. ♀ (loss of ♀ protection in aged rodents) | Alkayed et al., 1998 and 2000; Faber et al., 2017; Liu et al., 2009b; Manwani et al., 2013; McCullough et al., 2005; Zhang et al., 2009 and 2010 |
| Hypertension | Spontaneously hypertensive rats (SHR) | Memory impairment > ♀ vs. ♂ | Grunblatt et al., 2015 |
| | Aldosterone/NaCl | Blood pressure > ♂ vs. ♀ | Xue et al., 2009a |
| | Angiotensin II | E2 ↓ blood pressure | Pollow et al., 2015 (♀); Xue et al., 2008 (♂) |
| Metabolic Disease | High fat diet | Glucose intolerance > young ♂ vs. ♀ > middle-aged ♀ vs. ♂ | Salinero et al., 2018 |
| | High fat diet + low dose STZ + MCAO | Infarct size > ♀ vs. ♂ > ♀ vs. ♂ | Li et al, 2017a,b |
| | db/db mice + carotid ligation + hypoxia | Infarct size > ♂ vs. ♂ | Vannucci et al., 2001 |
| | KKAy mice + MCAO | Infarct size > ♀ vs. ♂ | Sakata et al., 2011 |
| Pregnancy | Multiparous SHR rats | Parity ↑ memory, ↓ blood pressure | Cabrera-Pedraza et al., 2017 |
| | Multiparous + MCAO | Parity ↑ functional outcome | Ritzel et al., 2017 |
| Preeclampsia | Placental ischemia | ↓ cerebral autoregulation, BBB function, ↑ edema | Warrington et al., 2014 |
| Menopause | Ovariectomy | ↑ insulin resistance, inflammation | Vieira Potter et al., 2012 |
| | Ovariectomy + MCAO | ↑ infarct size | Alkayed et al., 1998; Liu et al., 2009b; McCullough et al., 2005; Zhang et al., 2010; Zhang et al., 2009 |
| | 4-vinylcyclohexene diepoxide (VCD) | ↑ insulin resistance, glucose intolerance | Romero-Aleshire et al., 2009 |
| Hormone Replacement Therapy | Immediate vs. delayed E2 replacement | Immediate E2 = ↓ inflammation, ↓ oxidative stress, ↓ infarct size | Alkayed et al., 1998 and 2000; Liu et al., 2009b; Lopez-Grueso et al., 2014; Leon et al., 2012; McCullough et al., 2005; Miller et al., 2007b; Sakata et al., 2011; Selvamani and Sohrabji, 2010; Suzuki et al., 2007a; Zhang et al., 2010 |
| | | Delayed E2 protective effects are lost | Lopez-Grueso et al., 2014; Leon et al., 2012; Miller et al., 2007b; Selvamani and Sohrabji, 2010; Suzuki et al., 2007a |

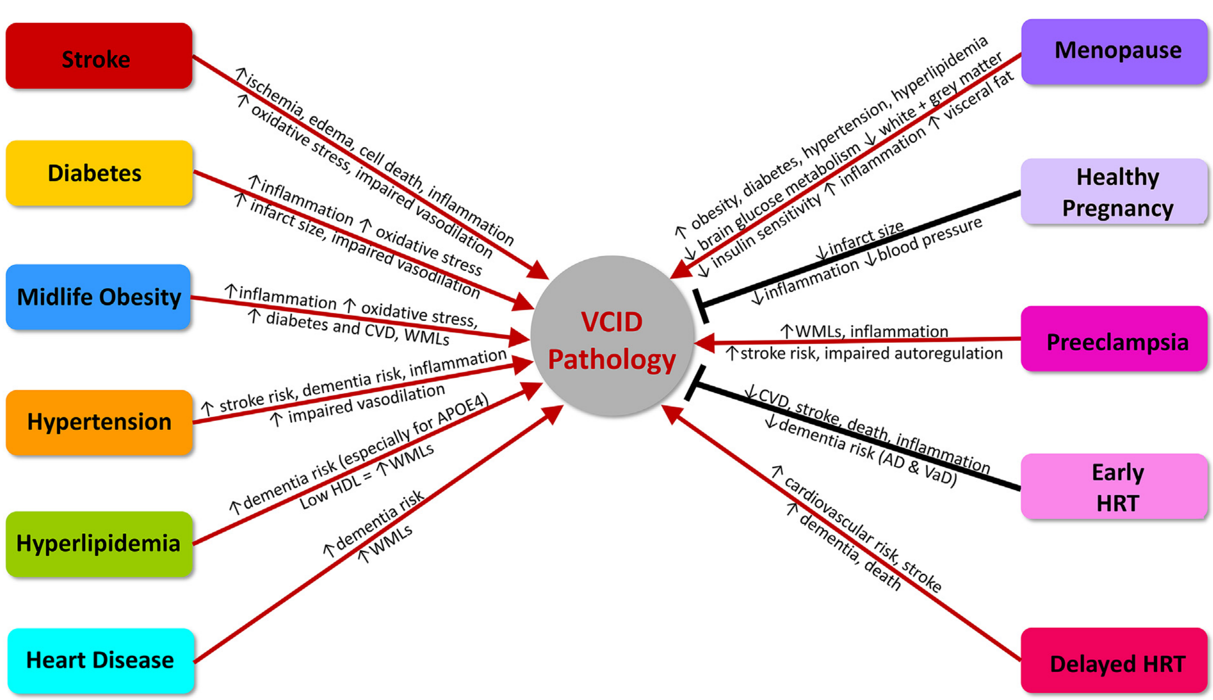


**Fig. 3.** Mechanisms by which VCID risk factors contribute to VCID pathology. Some of the most common mechanisms by which risk factors increase VCID pathology include inflammation, oxidative stress, increased risk of stroke, impaired vasodilation, and white matter lesions (WMLs).

## Funding

This work was supported by American Heart Association Scientist Development Grant 16SDG27190001 (KLZ) and Albany Medical College start up funds (KLZ).


## Author contributions

KLZ, OJG, and LSR created the outline of the manuscript. OJG, LSR, AJC, and KLZ performed the literature searches. OJG, LSR, AJC, and KLZ wrote the manuscript. OJG created the figures. KLZ and LSR checked each statement for scientific accuracy. KLZ, OJG, LSR, and AJC proof-read and approved the final manuscript.


## Acknowledgements

Thank you to Alyssa Galloway for her assistance in editing the manuscript.


## References


AAIC, 2018. Study Shows Intensive Blood Pressure Control Reduces Risk of Mild Cognitive Impairment (MCI) and the Combined Risk of MCI and Dementia. Press Release. https://www.alz.org/aaic/releases_2018/AAIC18-Wed-developing-topics.asp.

Abu-Taha, M., Rius, C., Hermenegildo, C., Noguera, I., Cerda-Nicolas, J.M., Issekutz, A.C., Jose, P.J., Cortijo, J., Morcillo, E.J., Sanz, M.J., 2009. Menopause and ovariectomy cause a low grade of systemic inflammation that may be prevented by chronic treatment with low doses of estrogen or losartan. J. Immunol. 183, 1393–1402.

Ahangar, A.A., Saadat, P., Heidari, B., Taheri, S.T., Alijanpour, S., 2018. Sex difference in types and distribution of risk factors in ischemic and hemorrhagic stroke. Int. J. Stroke 13, 83–86.

Ahlbom, E., Prins, G.S., Ceccatelli, S., 2001. Testosterone protects cerebellar granule cells from oxidative stress-induced cell death through a receptor mediated mechanism. Brain Res. 892, 255–262.

Ahlskog, J.E., Geda, Y.E., Graff-Radford, N.R., Petersen, R.C., 2011. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin. Proc. 86, 876–884.

Ahnstedt, H., Cao, L., Krause, D.N., Warfvinge, K., Saveland, H., Nilsson, O.G., Edvinsson, L., 2013. Male-female differences in upregulation of vasoconstrictor responses in human cerebral arteries. PLoS One 8, e62698.

Ahnstedt, H., McCullough, L.D., Cipolla, M.J., 2016. The importance of considering sex differences in translational stroke research. Transl Stroke Res 7, 261–273.

Ahnstedt, H., Roy-O'Reilly, M., Spychala, M.S., Mobley, A.S., Bravo-Alegria, J., Chauhan, A., Aronowski, J., Marrelli, S.P., McCullough, L.D., 2018. Sex differences in adipose tissue CD8(+) T cells and regulatory T cells in middle-aged mice. Front. Immunol. 9, 659.

Ahtiluoto, S., Polvikoski, T., Peltonen, M., Solomon, A., Tuomilehto, J., Winblad, B., Sulkava, R., Kivipelto, M., 2010. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. Neurology 75, 1195–1202.

Alkayed, N.J., Harukuni, I., Kimes, A.S., London, E.D., Traystman, R.J., Hurn, P.D., 1998. Gender-linked brain injury in experimental stroke. Stroke 29, 159–165 discussion 166.

Alkayed, N.J., Murphy, S.J., Traystman, R.J., Hurn, P.D., Miller, V.M., 2000. Neuroprotective effects of female gonadal steroids in reproductively senescent female rats. Stroke 31, 161–168.

Altmann, A., Tian, L., Henderson, V.W., Greicius, M.D., 2014. Sex modifies the APOE-related risk of developing Alzheimer disease. Ann. Neurol. 75, 563–573.

Alzahrani, S.H., Hess, K., Price, J.F., Strachan, M., Baxter, P.D., Cubbon, R., Phoenix, F., Gamlen, T., Ariens, R.A., Grant, P.J., Ajjan, R.A., 2012. Gender-specific alterations in fibrin structure function in type 2 diabetes: associations with cardiometabolic and vascular markers. J. Clin. Endocrinol. Metab. 97, E2282–E2287.

Alzheimer's_Association, 2016. 2016 Alzheimer's disease facts and figures. Alzheimer's Dementia 12, 459–509.

Alzheimer's_Association, 2018. Pregnancy and Reproductive History May Impact Dementia Risk Plus, the Move to Re-think the Impact of Hormone Therapy on Cognition. [Press Release]. Retrieved. https://www.alz.org/aaic/releases_2018/AAIC18-Mon-women-dementia-risk.asp.

Amengual-Cladera, E., Llado, I., Gianotti, M., Proenza, A.M., 2012. Sex differences in the effect of high-fat diet feeding on rat white adipose tissue mitochondrial function and insulin sensitivity. Metabolism 61, 1108–1117.

Amiri-Nikpour, M.R., Nazarbaghi, S., Hamdi-Holasou, M., Rezaei, Y., 2015. An open-label evaluator-blinded clinical study of minocycline neuroprotection in ischemic stroke: gender-dependent effect. Acta Neurol. Scand. 131, 45–50.

Ananth, C.V., Keyes, K.M., Wapner, R.J., 2013. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ 347, f6564.

Ancelin, M.-L., Ripoche, E., Dupuy, A.-M., Barberger-Gateau, P., Auriacombe, S., Rouaud, O., Berr, C., Carrière, I., Ritchie, K., 2013. Sex differences in the associations between lipid levels and incident dementia. J. Alzheim. Dis. 34, 519–528.

Andersen, K., Launer, L.J., Dewey, M.E., Letenneur, L., Ott, A., Copeland, J.R., Dartigues, J.F., Kragh-Sorensen, P., Baldereschi, M., Brayne, C., Lobo, A., Martinez-Lage, J.M., Stijnen, T., Hofman, A., 1999. Gender differences in the incidence of AD and vascular dementia: the EURODEM studies. EURODEM incidence research group. Neurology 53, 1992–1997.

Andersson, M., Guo, X., Borjesson-Hanson, A., Liebetrau, M., Ostling, S., Skoog, I., 2012. A population-based study on dementia and stroke in 97 year olds. Age Ageing 41, 529–533.

Andolf, E.G., Sydsjo, G.C., Bladh, M.K., Berg, G., Sharma, S., 2017. Hypertensive disorders in pregnancy and later dementia: a Swedish National Register Study. Acta Obstet. Gynecol. Scand. 96, 464–471.

Appelros, P., Stegmayr, B., Terént, A., 2009. Sex differences in stroke epidemiology: a systematic review. Stroke 40, 1082–1090.

Arauz, A., Rodriguez-Agudelo, Y., Sosa, A.L., Chavez, M., Paz, F., Gonzalez, M., Coral, J., Diaz-Olavarrieta, C., Roman, G.C., 2014. Vascular cognitive disorders and depression after first-ever stroke: the Fogarty-Mexico Stroke Cohort. Cerebrovasc. Dis. 38, 284–289.

Arnoldussen, I.A.C., Kiliaan, A.J., Gustafson, D.R., 2014. Obesity and dementia: adipokines interact with the brain. Eur. Neuropsychopharmacol 24, 1982–1999.

Arvanitakis, Z., Capuano, A.W., Lamar, M., Shah, R.C., Barnes, L.L., Bennett, D.A., Schneider, J.A., 2018. Late-life blood pressure association with cerebrovascular and Alzheimer disease pathology. Neurology 91, e517–e525.

Atallah, A., Mhaouty-Kodja, S., Grange-Messent, V., 2017. Chronic depletion of gonadal testosterone leads to blood-brain barrier dysfunction and inflammation in male mice. J. Cerebr. Blood Flow Metabol. 37, 3161–3175.

Aukes, A.M., de Groot, J.C., Aarnoudse, J.G., Zeeman, G.G., 2009. Brain lesions several years after eclampsia. Am. J. Obstet. Gynecol. 200–504 e501-505.

Auriat, A., Plahta, W.C., McGie, S.C., Yan, R., Colbourne, F., 2005. 17beta-Estradiol pretreatment reduces bleeding and brain injury after intracerebral hemorrhagic stroke in male rats. J. Cerebr. Blood Flow Metabol. 25, 247–256.

Azad, N.A., Al Bugami, M., Loy-English, I., 2007. Gender differences in dementia risk factors. Gender Medicine 4, 120–129.

Baba, Y., Ishikawa, S., Amagi, Y., Kayaba, K., Gotoh, T., Kajii, E., 2010. Premature menopause is associated with increased risk of cerebral infarction in Japanese women. Menopause 17, 506–510.

Babaei, P., Dastras, A., Tehrani, B.S., Pourali Roudbaneh, S., 2017. The effect of estrogen replacement therapy on visceral fat, serum glucose, lipid profiles and apelin level in ovariectomized rats. J Menopausal Med 23, 182–189.

Bake, S., Sohrabji, F., 2004. 17β-Estradiol differentially regulates blood-brain barrier permeability in young and aging female rats. Endocrinology 145, 5471–5475.

Bamford, J., Sandercock, P., Dennis, M., Burn, J., Warlow, C., 1990. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project–1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. J. Neurol. Neurosurg. Psychiatry 53, 16–22.

Barha, C.K., Galea, L.A., 2011. Motherhood alters the cellular response to estrogens in the hippocampus later in life. Neurobiol. Aging 32, 2091–2095.

Basaria, S., Coviello, A.D., Travison, T.G., Storer, T.W., Farwell, W.R., Jette, A.M., Eder, R., Tennstedt, S., Ulloor, J., Zhang, A., Choong, K., Lakshman, K.M., Mazer, N.A., Miciek, R., Krasnoff, J., Elmi, A., Knapp, P.E., Brooks, B., Appleman, E., Aggarwal, S., Bhasin, G., Hede-Brierley, L., Bhatia, A., Collins, L., LeBrasseur, N., Fiore, L.D., Bhasin, S., 2010. Adverse events associated with testosterone administration. N. Engl. J. Med. 363, 109–122.

Batnasan, E., Wang, R., Wen, J., Ke, Y., Li, X., Bohio, A.A., Zeng, X., Huo, H., Han, L., Boldogh, I., Ba, X., 2015. 17-beta estradiol inhibits oxidative stress-induced accumulation of AIF into nucleolus and PARP1-dependent cell death via estrogen receptor alpha. Toxicol. Lett. 232, 1–9.

Bednarska-Makaruk, M., Graban, A., Wisniewska, A., Lojkowska, W., Bochynska, A., Gugala-Iwaniuk, M., Slawinska, K., Lugowska, A., Ryglewicz, D., Wehr, H., 2017. Association of adiponectin, leptin and resistin with inflammatory markers and obesity in dementia. Biogerontology 18, 561–580.

Beeri, M.S., Rapp, M., Schmeidler, J., Reichenberg, A., Purohit, D.P., Perl, D.P., Grossman, H.T., Prohovnik, I., Haroutunian, V., Silverman, J.M., 2009. Number of children is associated with neuropathology of Alzheimer's disease in women. Neurobiol. Aging 30, 1184–1191.

Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., Das, S.R., Deo, R., de Ferranti, S.D., Floyd, J., Fornage, M., Gillespie, C., Isasi, C.R., Jimenez, M.C., Jordan, L.C., Judd, S.E., Lackland, D., Lichtman, J.H., Lisabeth, L., Liu, S., Longenecker, C.T., Mackey, R.H., Matsushita, K., Mozaffarian, D., Mussolino, M.E., Nasir, K., Neumar, R.W., Palaniappan, L., Pandey, D.K., Thiagarajan, R.R., Reeves, M.J., Ritchey, M., Rodriguez, C.J., Roth, G.A., Rosamond, W.D., Sasson, C., Towfighi, A., Tsao, C.W., Turner, M.B., Virani, S.S., Voeks, J.H., Willey, J.Z., Wilkins, J.T., Wu, J.H., Alger, H.M., Wong, S.S., Muntner, P., 2017. Heart disease and stroke statistics-2017 update: a report from the american heart association. Circulation 135, e146–e603.

Benjamin, E.J., Virani, S.S., Callaway, C.W., Chamberlain, A.M., Chang, A.R., Cheng, S., Chiuve, S.E., Cushman, M., Delling, F.N., Deo, R., de Ferranti, S.D., Ferguson, J.F., Fornage, M., Gillespie, C., Isasi, C.R., Jimenez, M.C., Jordan, L.C., Judd, S.E., Lackland, D., Lichtman, J.H., Lisabeth, L., Liu, S., Longenecker, C.T., Lutsey, P.L., Mackey, J.S., Matchar, D.B., Matsushita, K., Mussolino, M.E., Nasir, K., O'Flaherty, M., Palaniappan, L.P., Pandey, A., Pandey, D.K., Reeves, M.J., Ritchey, M.D., Rodriguez, C.J., Roth, G.A., Rosamond, W.D., Sampson, U.K.A., Satou, G.M., Shah, S.H., Spartano, N.L., Tirschwell, D.L., Tsao, C.W., Voeks, J.H., Willey, J.Z., Wilkins, J.T., Wu, J.H., Alger, H.M., Wong, S.S., Muntner, P., 2018. Heart disease and stroke statistics-2018 update: a report from the American heart association. Circulation 137, e67–e492.

Bodenant, M., Kuulasmaa, K., Wagner, A., Kee, F., Palmieri, L., Ferrario, M.M., Montaye,

M., Amouyel, P., Dallongeville, J., 2011. Measures of abdominal adiposity and the risk of stroke: the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) study. Stroke 42, 2872–2877.
Bove, R., Secor, E., Chibnik, L.B., Barnes, L.L., Schneider, J.A., Bennett, D.A., De Jager, P.L., 2014. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology 82, 222–229.
Brackley, K.J., Ramsay, M.M., Broughton Pipkin, F., Rubin, P.C., 1999. The effect of the menstrual cycle on human cerebral blood flow: studies using Doppler ultrasound. Ultrasound Obstet. Gynecol. 14, 52–57.
Burek, M., Arias-Loza, P.A., Roewer, N., Forster, C.Y., 2010. Claudin-5 as a novel estrogen target in vascular endothelium. Arterioscler. Thromb. Vasc. Biol. 30, 298–304.
Cabrera-Pedraza, V.R., de Jesus Gomez-Villalobos, M., de la Cruz, F., Aguilar-Alonso, P., Zamudio, S., Flores, G., 2017 Jul 6. Pregnancy improves cognitive deficit and neuronal morphology atrophy in the prefrontal cortex and hippocampus of aging spontaneously hypertensive rats. Synapse. https://doi.org/10.1002/syn.21991. [Epub ahead of print].
Cai, M., Ma, Y.L., Qin, P., Li, Y., Zhang, L.X., Nie, H., Peng, Z., Dong, H., Dong, H.L., Hou, W.G., Xiong, L.Z., 2014. The loss of estrogen efficacy against cerebral ischemia in aged postmenopausal female mice. Neurosci. Lett. 558, 115–119.
Camhi, S.M., Bray, G.A., Bouchard, C., Greenway, F.L., Johnson, W.D., Newton, R.L., Ravussin, E., Ryan, D.H., Smith, S.R., Katzmarzyk, P.T., 2011. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity 19, 402–408.
Carcaillon, L., Brailly-Tabard, S., Ancelin, M.L., Rouaud, O., Dartigues, J.F., Guiochon-Mantel, A., Scarabin, P.Y., 2014. High plasma estradiol interacts with diabetes on risk of dementia in older postmenopausal women. Neurology 82, 504–511.
Carrasquilla, G.D., Frumento, P., Berglund, A., Borgfeldt, C., Bottai, M., Chiavenna, C., Eliasson, M., Engstrom, G., Hallmans, G., Jansson, J.H., Magnusson, P.K., Nilsson, P.M., Pedersen, N.L., Wolk, A., Leander, K., 2017. Postmenopausal hormone therapy and risk of stroke: a pooled analysis of data from population-based cohort studies. PLoS Med. 14 e1002445.
Carswell, H.V., Dominiczak, A.F., Macrae, I.M., 2000. Estrogen status affects sensitivity to focal cerebral ischemia in stroke-prone spontaneously hypertensive rats. Am. J. Physiol. Heart Circ. Physiol. 278, H290–H294.
Casabiell, X., Pineiro, V., Peino, R., Lage, M., Camina, J., Gallego, R., Vallejo, L.G., Dieguez, C., Casanueva, F.F., 1998. Gender differences in both spontaneous and stimulated leptin secretion by human omental adipose tissue in vitro: dexamethasone and estradiol stimulate leptin release in women, but not in men. J. Clin. Endocrinol. Metab. 83, 2149–2155.
CDC, 2017. National diabetes statistics report, 2017. In: Atlanta, G.C.f.D.C.a.P. (Ed.), US Department of Health and Human Services; 2017. Centers for Disease Control and Preventation 2018.
Chatterjee, S., Peters, S.A., Woodward, M., Mejia Arango, S., Batty, G.D., Beckett, N., Beiser, A., Borenstein, A.R., Crane, P.K., Haan, M., Hassing, L.B., Hayden, K.M., Kiyohara, Y., Larson, E.B., Li, C.Y., Ninomiya, T., Ohara, T., Peters, R., Russ, T.C., Seshadri, S., Strand, B.H., Walker, R., Xu, W., Huxley, R.R., 2016. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes Care 39, 300–307.
Chen, Y.C., Chen, T.F., Yip, P.K., Hu, C.Y., Chu, Y.M., Chen, J.H., 2010. Body mass index (BMI) at an early age and the risk of dementia. Arch. Gerontol. Geriatr. 50 (Suppl. 1), S48–S52.
Chen, D.Y., See, L.C., Liu, J.R., Chuang, C.K., Pang, S.T., Hsieh, I.C., Wen, M.S., Chen, T.H., Lin, Y.C., Liaw, C.C., Hsu, C.L., Chang, J.W., Kuo, C.F., Huang, W.K., 2017. Risk of cardiovascular ischemic events after surgical castration and gonadotropin-releasing hormone agonist therapy for prostate cancer: a nationwide cohort study. J. Clin. Oncol. 35, 3697–3705.
Cheng, J., Alkayed, N.J., Hurn, P.D., 2007. Deleterious effects of dihydrotestosterone on cerebral ischemic injury. J. Cerebr. Blood Flow Metabol. 27, 1553–1562.
Cheng, J., Hu, W., Toung, T.J., Zhang, Z., Parker, S.M., Roselli, C.E., Hurn, P.D., 2009. Age-dependent effects of testosterone in experimental stroke. J. Cerebr. Blood Flow Metabol. 29, 486–494.
Cheng, J., Uchida, M., Zhang, W., Grafe, M.R., Herson, P.S., Hurn, P.D., 2010. Role of salt-induced kinase 1 in androgen neuroprotection against cerebral ischemia. J. Cerebr. Blood Flow Metabol. 31, 339–350.
Chiang, C.J., Yip, P.K., Wu, S.C., Lu, C.S., Liou, C.W., Liu, H.C., Liu, C.K., Chu, C.H., Hwang, C.S., Sung, S.F., Hsu, Y.D., Chen, C.C., Liu, S.I., Yan, S.H., Fong, C.S., Chang, S.F., You, S.L., Chen, C.J., 2007. Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan. Am. J. Geriatr. Psychiatry 15, 762–771.
Chuang, Y.F., Hayden, K.M., Norton, M.C., Tschanz, J., Breitner, J.C., Welsh-Bohmer, K.A., Zandi, P.P., 2010. Association between APOE epsilon4 allele and vascular dementia: the Cache County study. Dement. Geriatr. Cognit. Disord. 29, 248–253.
Cignarella, A., Kratz, M., Bolego, C., 2010. Emerging role of estrogen in the control of cardiometabolic disease. Trends Pharmacol. Sci. 31, 183–189.
Cipolla, M.J., 2013. The adaptation of the cerebral circulation to pregnancy: mechanisms and consequences. J. Cerebr. Blood Flow Metabol. 33, 465–478.
Cipolla, M.J., Godfrey, J.A., Wiegman, M.J., 2009. The effect of ovariectomy and estrogen on penetrating brain arterioles and blood-brain barrier permeability. Microcirculation 16, 685–693.
Collaboration, N.R.F., 2016. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19· 2 million participants. Lancet 387, 1377–1396.
Colucci, M., Cammarata, S., Assini, A., Croce, R., Clerici, F., Novello, C., Mazzella, L., Dagnino, N., Mariani, C., Tanganelli, P., 2006. The number of pregnancies is a risk factor for Alzheimer's disease. Eur. J. Neurol. 13, 1374–1377.
Copeland, J.R., McCracken, C.F., Dewey, M.E., Wilson, K.C., Doran, M., Gilmore, C., Scott, A., Larkin, B.A., 1999. Undifferentiated dementia, Alzheimer's disease and vascular dementia: age- and gender-related incidence in Liverpool. The MRC-ALPHA Study. Br. J. Psychiatry 175, 433–438.
Corraini, P., Henderson, V.W., Ording, A.G., Pedersen, L., Horvath-Puho, E., Sorensen, H.T., 2017. Long-term risk of dementia among survivors of ischemic or hemorrhagic stroke. Stroke 48, 180–186.
Cotechini, T., Komisarenko, M., Sperou, A., Macdonald-Goodfellow, S., Adams, M.A., Graham, C.H., 2014. Inflammation in rat pregnancy inhibits spiral artery remodeling leading to fetal growth restriction and features of preeclampsia. J. Exp. Med. 211, 165–179.
Croft, P., Hannaford, P.C., 1989. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. BMJ 298, 165–168.
Czernichow, S., Kengne, A.-P., Huxley, R.R., Batty, G.D., de Galan, B., Grobbee, D., Pillai, A., Zoungas, S., Marre, M., Woodward, M., Neal, B., Chalmers, J., 2011. Comparison of waist-to-hip ratio and other obesity indices as predictors of cardiovascular disease risk in people with type 2 diabetes: a prospective cohort study from ADVANCE. Eur. J. Cardiovasc. Prev. Rehabil. : Off. J. Europ. Soc. Cardiol. 18, 312–319 Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology.
de Silva, H.A., Gunatilake, S.B., Smith, A.D., 2003. Prevalence of dementia in a semi-urban population in Sri Lanka: report from a regional survey. Int. J. Geriatr. Psychiatr. 18, 711–715.
De Vries, G.J., Rissman, E.F., Simerly, R.B., Yang, L.Y., Scordalakes, E.M., Auger, C.J., Swain, A., Lovell-Badge, R., Burgoyne, P.S., Arnold, A.P., 2002. A model system for study of sex chromosome effects on sexually dimorphic neural and behavioral traits. J. Neurosci. 22, 9005–9014.
Deng, Z.H., Liao, J., Zhang, J.Y., Liang, C., Song, C.H., Han, M., Wang, L.H., Xue, H., Zhang, K., Zabeau, L., Tavernier, J., Yan, G.T., 2014. Inhibition of the connexin 43 elevation may be involved in the neuroprotective activity of leptin against brain ischemic injury. Cell. Mol. Neurobiol. 34, 871–879.
Dhamoon, M.S., McClure, L.A., White, C.L., Lakshminarayan, K., Benavente, O.R., Elkind, M.S., 2015. Long-term disability after lacunar stroke: secondary prevention of small subcortical strokes. Neurology 84, 1002–1008.
Di Carlo, A., Baldereschi, M., Amaducci, L., Lepore, V., Bracco, L., Maggi, S., Bonaiuto, S., Perissinotto, E., Scarlato, G., Farchi, G., Inzitari, D., 2002. Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy. The ILSA Study. J. Am. Geriatr. Soc. 50, 41–48.
Diomedi, M., Cupini, L.M., Rizzato, B., Ferrante, F., Giacomini, P., Silvestrini, M., 2001. Influence of physiologic oscillation of estrogens on cerebral hemodynamics. J. Neurol. Sci. 185, 49–53.
Du, L., Bayir, H., Lai, Y., Zhang, X., Kochanek, P.M., Watkins, S.C., Graham, S.H., Clark, R.S., 2004. Innate gender-based proclivity in response to cytotoxicity and programmed cell death pathway. J. Biol. Chem. 279, 38563–38570.
Duckles, S.P., Krause, D.N., 2011. Mechanisms of cerebrovascular protection: estrogen, inflammation and mitochondria. Acta Physiol. 203, 149–154.
Dulicek, P., Ivanova, E., Kostal, M., Sadilek, P., Beranek, M., Zak, P., Hirmerova, J., 2018. Analysis of risk factors of stroke and venous thromboembolism in females with oral contraceptives use. Clin. Appl. Thromb. Hemost. 24, 797–802.
Elharram, M., Dayan, N., Kaur, A., Landry, T., Pilote, L., 2018. Long-term cognitive impairment after preeclampsia: a systematic review and meta-analysis. Obstet. Gynecol. 132, 355–364.
Ergul, A., Kelly-Cobbs, A., Abdalla, M., Fagan, S.C., 2012. Cerebrovascular complications of diabetes: focus on stroke. Endocr. Metab. Immune Disord. - Drug Targets 12, 148–158.
Espeland, M.A., Brinton, R.D., Manson, J.E., Yaffe, K., Hugenschmidt, C., Vaughan, L., Craft, S., Edwards, B.J., Casanova, R., Masaki, K., Resnick, S.M., 2015. Postmenopausal hormone therapy, type 2 diabetes mellitus, and brain volumes. Neurology 85, 1131–1138.
Faber, J.E., Moore, S.M., Lucitti, J.L., Aghajanian, A., Zhang, H., 2017. Sex differences in the cerebral collateral circulation. Transl Stroke Res 8, 273–283.
Final report on the aspirin component of the ongoing Physicians' Health Study. N. Engl. J. Med. 321, 129–135.
Fitzpatrick, A.L., Kuller, L.H., Lopez, O.L., Diehr, P., O'Meara, E.S., Longstreth Jr., W.T., Luchsinger, J.A., 2009. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch. Neurol. 66, 336–342.
Fox, C.S., Massaro, J.M., Hoffmann, U., Pou, K.M., Maurovich-Horvat, P., Liu, C.Y., Vasan, R.S., Murabito, J.M., Meigs, J.B., Cupples, L.A., D'Agostino, R.B., Sr, O'Donnell, C.J., 2007. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 116, 39–48.
Fox, M., Berzuini, C., Knapp, L.A., 2013. Maternal breastfeeding history and Alzheimer's disease risk. J Alzheimers Dis 37, 809–821.
Freitag, M.H., Peila, R., Masaki, K., Petrovitch, H., Ross, G.W., White, L.R., Launer, L.J., 2006. Midlife pulse pressure and incidence of dementia: the Honolulu-Asia Aging Study. Stroke 37, 33–37.
Fryar, C.D., Carroll, M.D., Ogden, C.L., 2016. Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults Aged 20 and over: United States, 1960-1962 through 2013-2014. Internet. https//www. cdc. gov/nchs/data/hestat/obesity_adult_13_14/obesity_adult_13_14.pdf, Accessed date: 2 March 2018.
Fryar, C.D., Ostchega, Y., Hales, C.M., Zhang, G., Kruszon-Moran, D., 2017. Hypertension Prevalence and Control Among Adults: United States, 2015-2016. pp. 1–8 NCHS Data Brief.
Fujishima, M., Kiyohara, Y., 2002. Incidence and risk factors of dementia in a defined elderly Japanese population: the Hisayama study. Ann. N. Y. Acad. Sci. 977, 1–8.
Galea, E., Santizo, R., Feinstein, D.L., Adamsom, P., Greenwood, J., Koenig, H.M.,

Pelligrino, D.A., 2002. Estrogen inhibits NF kappa B-dependent inflammation in brain endothelium without interfering with I kappa B degradation. Neuroreport 13, 1469–1472.

Geary, G.G., Krause, D.N., Duckles, S.P., 1998. Estrogen reduces myogenic tone through a nitric oxide-dependent mechanism in rat cerebral arteries. Am. J. Physiol. 275, H292–H300.

Geary, G.G., Krause, D.N., Duckles, S.P., 2000a. Estrogen reduces mouse cerebral artery tone through endothelial NOS- and cyclooxygenase-dependent mechanisms. Am. J. Physiol. Heart Circ. Physiol. 279, H511–H519.

Geary, G.G., Krause, D.N., Duckles, S.P., 2000b. Gonadal hormones affect diameter of male rat cerebral arteries through endothelium-dependent mechanisms. Am. J. Physiol. Heart Circ. Physiol. 279, H610–H618.

Giatti, S., Garcia-Segura, L.M., Barreto, G.E., Melcangi, R.C., 2018 Jul 4. Neuroactive steroids, neurosteroidogenesis and sex. Prog. Neurobiol. https://doi.org/10.1016/j.pneurobio.2018.06.007. pii: S0301-0082(18)30008-X. [Epub ahead of print].

Giil, L.M., Kristoffersen, E.K., Vedeler, C.A., Aarsland, D., Nordrehaug, J.E., Winblad, B., Cedazo-Minguez, A., Lund, A., Reksten, T.R., 2015. Autoantibodies toward the angiotensin 2 type 1 receptor: a novel autoantibody in alzheimer's disease. J Alzheimers Dis 47, 523–529.

Gillis, E.E., Sullivan, J.C., 2016. Sex differences in hypertension: recent advances. Hypertension 68, 1322–1327.

Gillum, L.A., Mamidipudi, S.K., Johnston, S.C., 2000. Ischemic stroke risk with oral contraceptives: a meta-analysis. J. Am. Med. Assoc. 284, 72–78.

Gilsanz, P., Mayeda, E.R., Glymour, M.M., Quesenberry, C.P., Mungas, D.M., DeCarli, C., Dean, A., Whitmer, R.A., 2017. Female sex, early-onset hypertension, and risk of dementia. Neurology 89, 1886–1893.

Girijala, R.L., Sohrabji, F., Bush, R.L., 2017. Sex differences in stroke: review of current knowledge and evidence. Vasc. Med. 22, 135–145.

Gleason, C.E., Dowling, N.M., Wharton, W., Manson, J.E., Miller, V.M., Atwood, C.S., Brinton, E.A., Cedars, M.I., Lobo, R.A., Merriam, G.R., Neal-Perry, G., Santoro, N.F., Taylor, H.S., Black, D.M., Budoff, M.J., Hodis, H.N., Naftolin, F., Harman, S.M., Asthana, S., 2015. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS–cognitive and affective study. PLoS Med. 12 e1001833.

Gonzales, R.J., 2013. Androgens and the cerebrovasculature: modulation of vascular function during normal and pathophysiological conditions. Pflueg. Arch. Eur. J. Physiol. 465, 627–642.

Gonzales, R.J., Krause, D.N., Duckles, S.P., 2004. Testosterone suppresses endothelium-dependent dilation of rat middle cerebral arteries. Am. J. Physiol. Heart Circ. Physiol. 286, H552–H560.

Gonzales, R.J., Ghaffari, A.A., Duckles, S.P., Krause, D.N., 2005. Testosterone treatment increases thromboxane function in rat cerebral arteries. Am. J. Physiol. Heart Circ. Physiol. 289, H578–H585.

González-Muniesa, P., Mártinez-González, M.-A., Hu, F.B., Després, J.-P., Matsuzawa, Y., Loos, R.J.F., Moreno, L.A., Bray, G.A., Martinez, J.A., 2017. Obesity. Nature Reviews Disease Primers 3, 17034.

Goodman-Gruen, D., Barrett-Connor, E., 1996. Sex differences in measures of body fat and body fat distribution in the elderly. Am. J. Epidemiol. 143, 898–906.

Goodpaster, B.H., Krishnaswami, S., Harris, T.B., Katsiaras, A., Kritchevsky, S.B., Simonsick, E.M., Nevitt, M., Holvoet, P., Newman, A.B., 2005. Obesity, regional body fat distribution, and the metabolic syndrome in older men and women. Arch. Intern. Med. 165, 777–783.

Gorelick, P.B., Scuteri, A., Black, S.E., Decarli, C., Greenberg, S.M., Iadecola, C., Launer, L.J., Laurent, S., Lopez, O.L., Nyenhuis, D., Petersen, R.C., Schneider, J.A., Tzourio, C., Arnett, D.K., Bennett, D.A., Chui, H.C., Higashida, R.T., Lindquist, R., Nilsson, P.M., Roman, G.C., Sellke, F.W., Seshadri, S., American Heart Association Stroke Council, C.o.E., Prevention, C.o.C.N.C.o.C.R, Intervention, Council on Cardiovascular, Anesthesia, S., 2011. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 42, 2672–2713.

Grunblatt, E., Bartl, J., Iuhos, D.I., Knezovic, A., Trkulja, V., Riederer, P., Walitza, S., Salkovic-Petrisic, M., 2015. Characterization of cognitive deficits in spontaneously hypertensive rats, accompanied by brain insulin receptor dysfunction. J Mol Psychiatry 3, 6.

Gruzdeva, O., Borodkina, D., Uchasova, E., Dyleva, Y., Barbarash, O., 2018. Localization of fat depots and cardiovascular risk. Lipids Health Dis. 17, 218.

Gulinello, M., Lebesgue, D., Jover-Mengual, T., Zukin, R.S., Etgen, A.M., 2006. Acute and chronic estradiol treatments reduce memory deficits induced by transient global ischemia in female rats. Horm. Behav. 49, 246–260.

Guo, J., Krause, D.N., Horne, J., Weiss, J.H., Li, X., Duckles, S.P., 2010. Estrogen-receptor-mediated protection of cerebral endothelial cell viability and mitochondrial function after ischemic insult in vitro. J. Cerebr. Blood Flow Metabol. 30, 545–554.

Gustafson, D.R., Steen, B., Skoog, I., 2004. Body mass index and white matter lesions in elderly women. An 18-year longitudinal study. Int. Psychogeriatr. 16, 327–336.

Gustafson, D.R., Bäckman, K., Waern, M., Östling, S., Guo, X., Zandi, P., Mielke, M.M., Bengtsson, C., Skoog, I., 2009. Adiposity indicators and dementia over 32 years in Sweden. Neurology 73, 1559–1566.

Haast, R.A.M., Gustafson, D.R., Kiliaan, A.J., 2012. Sex differences in stroke. J. Cerebr. Blood Flow Metabol. 32, 2100–2107.

Hall, E.D., Pazara, K.E., Linseman, K.L., 1991. Sex differences in postischemic neuronal necrosis in gerbils. J. Cerebr. Blood Flow Metabol. 11, 292–298.

Hamson, D.K., Wainwright, S.R., Taylor, J.R., Jones, B.A., Watson, N.V., Galea, L.A., 2013. Androgens increase survival of adult-born neurons in the dentate gyrus by an androgen receptor-dependent mechanism in male rats. Endocrinology 154, 3294–3304.

Hawk, T., Zhang, Y.Q., Rajakumar, G., Day, A.L., Simpkins, J.W., 1998. Testosterone increases and estradiol decreases middle cerebral artery occlusion lesion size in male rats. Brain Res. 796, 296–298.

Hayden, K.M., Zandi, P.P., Lyketsos, C.G., Khachaturian, A.S., Bastian, L.A., Charoonruk, G., Tschanz, J.T., Norton, M.C., Pieper, C.F., Munger, R.G., Breitner, J.C., Welsh-Bohmer, K.A., 2006. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimers Dis. Assoc. Disord. 20, 93–100.

Hebert, R., Lindsay, J., Verreault, R., Rockwood, K., Hill, G., Dubois, M.F., 2000. Vascular dementia : incidence and risk factors in the Canadian study of health and aging. Stroke 31, 1487–1493.

Heianza, Y., Arase, Y., Kodama, S., Hsieh, S.D., Tsuji, H., Saito, K., Shimano, H., Hara, S., Sone, H., 2013. Effect of postmenopausal status and age at menopause on type 2 diabetes and prediabetes in Japanese individuals: toranomon hospital health management center study 17 (TOPICS 17). Diabetes Care 36, 4007–4014.

Hempel, R., Onopa, R., Convit, A., 2012. Type 2 diabetes affects hippocampus volume differentially in men and women. Diabetes Metab Res Rev 28, 76–83.

Henderson, V.W., Benke, K.S., Green, R.C., Cupples, L.A., Farrer, L.A., 2005. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. J. Neurol. Neurosurg. Psychiatry 76, 103–105.

Henderson, V.W., St John, J.A., Hodis, H.N., McCleary, C.A., Stanczyk, F.Z., Shoupe, D., Kono, N., Dustin, L., Allayee, H., Mack, W.J., 2016. Cognitive effects of estradiol after menopause: a randomized trial of the timing hypothesis. Neurology 87, 699–708.

Herzog, R., Zendedel, A., Lammerding, L., Beyer, C., Slowik, A., 2017. Impact of 17beta-estradiol and progesterone on inflammatory and apoptotic microRNA expression after ischemia in a rat model. J. Steroid Biochem. Mol. Biol. 167, 126–134.

Hinnouho, G.M., Czernichow, S., Dugravot, A., Batty, G.D., Kivimaki, M., Singh-Manoux, A., 2013. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? Diabetes Care 36, 2294–2300.

Hodis, H.N., Mack, W.J., Henderson, V.W., Shoupe, D., Budoff, M.J., Hwang-Levine, J., Li, Y., Feng, M., Dustin, L., Kono, N., Stanczyk, F.Z., Selzer, R.H., Azen, S.P., 2016. Vascular effects of early versus late postmenopausal treatment with estradiol. N. Engl. J. Med. 374, 1221–1231.

Hubel, C.A., Powers, R.W., Snaedal, S., Gammill, H.S., Ness, R.B., Roberts, J.M., Arngrimsson, R., 2008. C-reactive protein is elevated 30 years after eclamptic pregnancy. Hypertension 51, 1499–1505.

Iadecola, C., 2013. The pathobiology of vascular dementia. Neuron 80. https://doi.org/10.1016/j.neuron.2013.1010.1008.

Iadecola, C., Yaffe, K., Biller, J., Bratzke, L.C., Faraci, F.M., Gorelick, P.B., Gulati, M., Kamel, H., Knopman, D.S., Launer, L.J., Saczynski, J.S., Seshadri, S., Zeki Al Hazzouri, A., 2016. Impact of hypertension on cognitive function: a scientific statement from the american heart association. Hypertension 68, e67–e94.

Ijomone, O.K., Shallie, P., Naicker, T., 2018. Changes in the structure and function of the brain years after Pre-eclampsia. Ageing Res. Rev. 47, 49–54.

Ikram, M.A., van Oijen, M., de Jong, F.J., Kors, J.A., Koudstaal, P.J., Hofman, A., Witteman, J.C., Breteler, M.M., 2008. Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. Stroke 39, 1421–1426.

Imfeld, P., Bodmer, M., Schuerch, M., Jick, S.S., Meier, C.R., 2013a. Risk of incident stroke in patients with Alzheimer disease or vascular dementia. Neurology 81, 910–919.

Imfeld, P., Brauchli Pernus, Y.B., Jick, S.S., Meier, C.R., 2013b. Epidemiology, co-morbidities, and medication use of patients with Alzheimer's disease or vascular dementia in the UK. J Alzheimers Dis 35, 565–573.

Imtiaz, B., Tuppurainen, M., Tiihonen, M., Kivipelto, M., Soininen, H., Hartikainen, S., Tolppanen, A.M., 2014. Oophorectomy, hysterectomy, and risk of Alzheimer's disease: a nationwide case-control study. J Alzheimers Dis 42, 575–581.

Imtiaz, B., Tuppurainen, M., Rikkonen, T., Kivipelto, M., Soininen, H., Kröger, H., Tolppanen, A.-M., 2017. Postmenopausal hormone therapy and Alzheimer disease: a prospective cohort study. Neurology 88, 1062–1068.

Inzitari, D., Di Carlo, A., Pracucci, G., Lamassa, M., Vanni, P., Romanelli, M., Spolveri, S., Adriani, P., Meucci, I., Landini, G., 1998. Incidence and determinants of poststroke dementia as defined by an informant interview method in a hospital-based stroke registry. Stroke 29, 2087–2093.

Ivan, C.S., Seshadri, S., Beiser, A., Au, R., Kase, C.S., Kelly-Hayes, M., Wolf, P.A., 2004. Dementia after stroke: the framingham study. Stroke 35, 1264–1268.

Jacobson, L., Hade, E.M., Collins, T.C., Margolis, K.L., Waring, M.E., Van Horn, L.V., Siver, B., Sattari, M., Bird, C.E., Kimminau, K., Wambach, K., Stefanick, M.L., 2018. Breastfeeding history and risk of stroke amoung parous postmenopausal women in the women's health initiative. Journal of the American Heart Association 7 e008739.

Jagust, W., Harvey, D., Mungas, D., Haan, M., 2005. Central obesity and the aging brain. Arch. Neurol. 62, 1545–1548.

Jang, H., Bae, J.B., Dardiotis, E., Scarmeas, N., Sachdev, P.S., Lipnicki, D.M., Han, J.W., Kim, T.H., Kwak, K.P., Kim, B.J., Kim, S.G., Kim, J.L., Moon, S.W., Park, J.H., Ryu, S.H., Youn, J.C., Lee, D.Y., Lee, D.W., Lee, S.B., Lee, J.J., Jhoo, J.H., Yannakoulia, M., Kosmidis, M.H., Hadjigeorgiou, G.M., Sakka, P., Kim, K.W., 2018. Differential effects of completed and incomplete pregnancies on the risk of Alzheimer disease. Neurology 91, e643–e651.

Janzarik, W.G., Ehlers, E., Ehmann, R., Gerds, T.A., Schork, J., Mayer, S., Gabriel, B., Weiller, C., Prompeler, H., Reinhard, M., 2014. Dynamic cerebral autoregulation in pregnancy and the risk of preeclampsia. Hypertension 63, 161–166.

Jeppesen, L.L., Jorgensen, H.S., Nakayama, H., Raaschou, H.O., Olsen, T.S., Winther, K., 1996. Decreased serum testosterone in men with acute ischemic stroke. Arterioscler. Thromb. Vasc. Biol. 16, 749–754.

Johnson, D.K., Wilkins, C.H., Morris, J.C., 2006. Accelerated weight loss may precede diagnosis in Alzheimer disease. Arch. Neurol. 63, 1312–1317.

Johnson, L.A., Zuloaga, K.L., Kugelman, T.L., Mader, K.S., Morre, J.T., Zuloaga, D.G., Weber, S., Marzulla, T., Mulford, A., Button, D., Lindner, J.R., Alkayed, N.J., Stevens, J.F., Raber, J., 2016. Amelioration of metabolic syndrome-associated cognitive

impairments in mice via a reduction in dietary fat content or infusion of non-diabetic plasma. EBioMedicine 3, 26–42.
Jouihan, S.A., Zuloaga, K.L., Zhang, W., Shangraw, R.E., Krasnow, S.M., Marks, D.L., Alkayed, N.J., 2013. Role of soluble epoxide hydrolase in exacerbation of stroke by streptozotocin-induced type 1 diabetes mellitus. J. Cerebr. Blood Flow Metabol. 33, 1650–1656.
Kanaya, A.M., Herrington, D., Vittinghoff, E., et al., 2003. Glycemic effects of postmenopausal hormone therapy: the heart and estrogen/progestin replacement study: a randomized, double-blind, placebo-controlled trial. Ann. Intern. Med. 138, 1–9.
Kang, H.S., Ahn, H.S., Kang, H.J., Gye, M.C., 2006. Effect of estrogen on the expression of occludin in ovariectomized mouse brain. Neurosci. Lett. 402, 30–34.
Kannel, W.B., Hjortland, M.C., Mc, N.P., Gordon, T., 1976. Menopause and risk of cardiovascular disease: the framingham study. Ann. Intern. Med. 85, 447–452.
Kautzky-Willer, A., Harreiter, J., Pacini, G., 2016. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocr. Rev. 37, 278–316.
Kemper, M.F., Zhao, Y., Duckles, S.P., Krause, D.N., 2013. Endogenous ovarian hormones affect mitochondrial efficiency in cerebral endothelium via distinct regulation of PGC-1 isoforms. J. Cerebr. Blood Flow Metabol. 33, 122–128.
Kent, D.M., Buchan, A.M., Hill, M.D., 2008. The gender effect in stroke thrombolysis: of CASES, controls, and treatment-effect modification. Neurology 71, 1080–1083.
Khaw, K.T., Barrett-Connor, E., 1988. Blood pressure and endogenous testosterone in men: an inverse relationship. J. Hypertens. 6, 329–332.
Kim, K.W., Seo, H., Kwak, M.S., Kim, D., 2017. Visceral obesity is associated with white matter hyperintensity and lacunar infarct. Int. J. Obes. 41, 683–688.
Kivimaki, M., Luukkonen, R., Batty, G.D., Ferrie, J.E., Pentti, J., Nyberg, S.T., Shipley, M.J., Alfredsson, L., Fransson, E.I., Goldberg, M., Knutsson, A., Koskenvuo, M., Kuosma, E., Nordin, M., Suominen, S.B., Theorell, T., Vuoksimaa, E., Westerholm, P., Westerlund, H., Zins, M., Kivipelto, M., Vahtera, J., Kaprio, J., Singh-Manoux, A., Jokela, M., 2018. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. Alzheimers Dement 14, 601–609.
Knopman, D.S., Parisi, J.E., Boeve, B.F., Cha, R.H., Apaydin, H., Salviati, A., Edland, S.D., Rocca, W.A., 2003. Vascular dementia in a population-based autopsy study. Arch. Neurol. 60, 569–575.
Koellhoffer, E.C., McCullough, L.D., 2013. The effects of estrogen in ischemic stroke. Transl Stroke Res 4, 390–401.
Krause, D.N., Duckles, S.P., Pelligrino, D.A., 2006. Influence of sex steroid hormones on cerebrovascular function. J. Appl. Physiol. 101, 1252–1261.
Kupelian, V., Hayes, F.J., Link, C.L., Rosen, R., McKinlay, J.B., 2008. Inverse association of testosterone and the metabolic syndrome in men is consistent across race and ethnic groups. J. Clin. Endocrinol. Metab. 93, 3403–3410.
LaCroix, A.Z., Chlebowski, R.T., Manson, J.E., et al., 2011. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. J. Am. Med. Assoc. 305, 1305–1314.
LeBlanc, E.S., Janowsky, J., Chan, B.K., Nelson, H.D., 2001. Hormone replacement therapy and cognition: systematic review and meta-analysis. J. Am. Med. Assoc. 285, 1489–1499.
Lee, S.H., Heo, J.S., Lee, M.Y., Han, H.J., 2008. Effect of dihydrotestosterone on hydrogen peroxide-induced apoptosis of mouse embryonic stem cells. J. Cell. Physiol. 216, 269–275.
Leffert, L.R., Clancy, C.R., Bateman, B.T., Bryant, A.S., Kuklina, E.V., 2015. Hypertensive disorders and pregnancy-related stroke: frequency, trends, risk factors, and outcomes. Obstet. Gynecol. 125, 124–131.
Leon, R.L., Li, X., Huber, J.D., Rosen, C.L., 2012. Worsened outcome from middle cerebral artery occlusion in aged rats receiving 17beta-estradiol. Endocrinology 153, 3386–3393.
Leranth, C., Petnehazy, O., MacLusky, N.J., 2003. Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. J. Neurosci. 23, 1588–1592.
Ley, C.J., Lees, B., Stevenson, J.C., 1992. Sex- and menopause-associated changes in body-fat distribution. Am. J. Clin. Nutr. 55, 950–954.
Leys, D., Hénon, H., Mackowiak-Cordoliani, M.-A., Pasquier, F., 2005. Poststroke dementia. Lancet Neurol. 4, 752–759.
Li, M., Zhang, Z., Sun, W., Koehler, R.C., Huang, J., 2011. 17β-estradiol attenuates breakdown of blood–brain barrier and hemorrhagic transformation induced by tissue plasminogen activator in cerebral ischemia. Neurobiol. Dis. 44, 277–283.
Li, X.Y., Wang, F., Chen, G.H., Li, X.W., Yang, Q.G., Cao, L., Yan, W.W., 2016. Inflammatory insult during pregnancy accelerates age-related behavioral and neurobiochemical changes in CD-1 mice. Age 38, 59.
Li, L., Chen, J., Sun, S., Zhao, J., Dong, X., Wang, J., 2017a. Effects of estradiol on autophagy and nrf-2/ARE signals after cerebral ischemia. Cell. Physiol. Biochem. 41, 2027–2036.
Li, W., Ward, R., Valenzuela, J.P., Dong, G., Fagan, S.C., Ergul, A., 2017 Mar 1b. Diabetes worsens functional outcomes in young female rats: comparison of stroke models, tissue plasminogen activator effects, and sexes. Transl Stroke Res. https://doi.org/10.1007/s12975-017-0525-7. [Epub ahead of print].
Licinio, J., Negrao, A.B., Mantzoros, C., Kaklamani, V., Wong, M.L., Bongiorno, P.B., Negro, P.P., Mulla, A., Veldhuis, J.D., Cearnal, L., Flier, J.S., Gold, P.W., 1998. Sex differences in circulating human leptin pulse amplitude: clinical implications. J. Clin. Endocrinol. Metab. 83, 4140–4147.
Lidegaard, O., 1999. Smoking and use of oral contraceptives: impact on thrombotic diseases. Am. J. Obstet. Gynecol. 180, S357–S363.
Lima, S.M., Aldrighi, J.M., Consolim-Colombo, F.M., Mansur Ade, P., Rubira, M.C., Krieger, E.M., Ramires, J.A., 2005. Acute administration of 17beta-estradiol improves endothelium-dependent vasodilation in postmenopausal women. Maturitas 50, 266–274.
Lisabeth, L.D., Beiser, A.S., Brown, D.L., Murabito, J.M., Kelly-Hayes, M., Wolf, P.A., 2009. Age at natural menopause and risk of ischemic stroke: the Framingham heart study. Stroke 40, 1044–1049.
Liu, F., McCullough, L.D., 2012. Interactions between age, sex, and hormones in experimental ischemic stroke. Neurochem. Int. 61, 1255–1265.
Liu, R., Wen, Y., Perez, E., Wang, X., Day, A.L., Simpkins, J.W., Yang, S.-H., 2005. 17β-Estradiol attenuates blood–brain barrier disruption induced by cerebral ischemia–reperfusion injury in female rats. Brain Res. 1060, 55–61.
Liu, F., Li, Z., Li, J., Siegel, C., Yuan, R., McCullough, L.D., 2009a. Sex differences in caspase activation after stroke. Stroke 40, 1842–1848.
Liu, F., Yuan, R., Benashski, S.E., McCullough, L.D., 2009b. Changes in experimental stroke outcome across the life span. J. Cerebr. Blood Flow Metabol. 29, 792–802.
Liu, C., Luo, R., Elliott, S.E., Wang, W., Parchim, N.F., Iriyama, T., Daugherty, P.S., Blackwell, S.C., Sibai, B.M., Kellems, R.E., Xia, Y., 2015. Elevated transglutaminase activity triggers angiotensin receptor activating autoantibody production and pathophysiology of preeclampsia. J Am Heart Assoc 4.
Liu, C.-L., Lin, M.-Y., Hwang, S.-J., Liu, C.-K., Lee, H.-L., Wu, M.-T., 2018. Factors associated with type 2 diabetes in patients with vascular dementia: a population-based cross-sectional study. BMC Endocr. Disord. 18, 45.
Livingstone, S.J., Levin, D., Looker, H.C., et al., 2015. Estimated life expectancy in a scottish cohort with type 1 diabetes, 2008-2010. J. Am. Med. Assoc. 313, 37–44.
Lobo, M., Remesar, X., Alemany, M., 1993. Effect of chronic intravenous injection of steroid hormones on body weight and composition of female rats. Biochem. Mol. Biol. Int. 29, 349–358.
Lobo, A., Launer, L.J., Fratiglioni, L., Andersen, K., Di Carlo, A., Breteler, M.M., Copeland, J.R., Dartigues, J.F., Jagger, C., Martinez-Lage, J., Soininen, H., Hofman, A., 2000. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 54, S4–S9.
Logue, O.C., George, E.M., Bidwell 3rd, G.L., 2016. Preeclampsia and the brain: neural control of cardiovascular changes during pregnancy and neurological outcomes of preeclampsia. Clin. Sci. (Lond.) 130, 1417–1434.
Lopez-Grueso, R., Gambini, J., Abdelaziz, K.M., Monleon, D., Diaz, A., El Alami, M., Bonet-Costa, V., Borras, C., Vina, J., 2014. Early, but not late onset estrogen replacement therapy prevents oxidative stress and metabolic alterations caused by ovariectomy. Antioxidants Redox Signal. 20, 236–246.
Lovejoy, J.C., Champagne, C.M., de Jonge, L., Xie, H., Smith, S.R., 2008. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int. J. Obes. 32, 949–958.
Ma, Y.L., Qin, P., Li, Y., Shen, L., Wang, S.Q., Dong, H.L., Hou, W.G., Xiong, L.Z., 2013. The effects of different doses of estradiol (E2) on cerebral ischemia in an in vitro model of oxygen and glucose deprivation and reperfusion and in a rat model of middle carotid artery occlusion. BMC Neurosci. 14, 118.
Maffei, M., Halaas, J., Ravussin, E., Pratley, R.E., Lee, G.H., Zhang, Y., Fei, H., Kim, S., Lallone, R., Ranganathan, S., et al., 1995. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat. Med. 1, 1155–1161.
Maki, P.M., 2013. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. Menopause 20, 695–709.
Manwani, B., Liu, F., Scranton, V., Hammond, M.D., Sansing, L.H., McCullough, L.D., 2013. Differential effects of aging and sex on stroke induced inflammation across the lifespan. Exp. Neurol. 249, 120–131.
Manwani, B., Bentivegna, K., Benashski, S.E., Venna, V.R., Xu, Y., Arnold, A.P., McCullough, L.D., 2015. Sex differences in ischemic stroke sensitivity are influenced by gonadal hormones, not by sex chromosome complement. J. Cerebr. Blood Flow Metabol. 35, 221–229.
Marder, K., Sano, M., 2000. Estrogen to treat Alzheimer's disease: too little, too late? So what's a woman to do? Neurology 54, 2035–2037.
Mayhan, W.G., Trauernicht, A.K., Irvine, S.D., 2001. Insulin reverses impaired acetylcholine-induced dilatation of the rat basilar artery during diabetes mellitus. Brain Res. 893, 195–201.
McCullough, L.D., Hurn, P.D., 2003. Estrogen and ischemic neuroprotection: an integrated view. Trends Endocrinol. Metabol. 14, 228–235.
McCullough, L.D., Zeng, Z., Blizzard, K.K., Debchoudhury, I., Hurn, P.D., 2005. Ischemic nitric oxide and poly (ADP-ribose) polymerase-1 in cerebral ischemia: male toxicity, female protection. J. Cerebr. Blood Flow Metabol. 25, 502–512.
McCullough, L.D., Mirza, M.A., Xu, Y., Bentivegna, K., Steffens, E.B., Ritzel, R., Liu, F., 2016. Stroke sensitivity in the aged: sex chromosome complement vs. gonadal hormones. Aging 8, 1432–1441.
McNeill, A.M., Kim, N., Duckles, S.P., Krause, D.N., Kontos, H.A., 1999. Chronic estrogen treatment increases levels of endothelial nitric oxide synthase protein in rat cerebral microvessels. Stroke 30, 2186–2190.
McNeill, A.M., Zhang, C., Stanczyk, F.Z., Duckles, S.P., Krause, D.N., 2002. Estrogen increases endothelial nitric oxide synthase via estrogen receptors in rat cerebral blood vessels: effect preserved after concurrent treatment with medroxyprogesterone acetate or progesterone. Stroke 33, 1685–1691.
Mielke, M.M., Milic, N.M., Weissgerber, T.L., White, W.M., Kantarci, K., Mosley, T.H., Windham, B.G., Simpson, B.N., Turner, S.T., Garovic, V.D., 2016. Impaired cognition and brain atrophy decades after hypertensive pregnancy disorders. 9. Circ Cardiovasc Qual Outcomes, pp. S70–S76.
Mikkola, T.S., Savolainen-Peltonen, H., Tuomikoski, P., Hoti, F., Vattulainen, P., Gissler, M., Ylikorkala, O., 2017. Lower death risk for vascular dementia than for alzheimer's disease with postmenopausal hormone therapy users. J. Clin. Endocrinol. Metab. 102, 870–877.
Miller, V.M., Harman, S.M., 2017. An update on hormone therapy in postmenopausal women: mini-review for the basic scientist. Am. J. Physiol. Heart Circ. Physiol. 313, H1013–h1021.

Miller, A.A., Drummond, G.R., Mast, A.E., Schmidt, H.H., Sobey, C.G., 2007a. Effect of gender on NADPH-oxidase activity, expression, and function in the cerebral circulation: role of estrogen. Stroke 38, 2142–2149.

Miller, A.P., Xing, D., Feng, W., Fintel, M., Chen, Y.F., Oparil, S., 2007b. Aged rats lose vasoprotective and anti-inflammatory actions of estrogen in injured arteries. Menopause 14, 251–260.

Moreau, K.L., Hildreth, K.L., Meditz, A.L., Deane, K.D., Kohrt, W.M., 2012. Endothelial function is impaired across the stages of the menopause transition in healthy women. J. Clin. Endocrinol. Metab. 97, 4692–4700.

Morris, M.C., Tangney, C.C., 2014. Dietary fat composition and dementia risk. Neurobiol. Aging 35 (Suppl. 2), S59–S64.

Mortel, K.F., Wood, S., Pavol, M.A., Meyer, J.S., Rexer, J.L., 1993. Analysis of familial and individual risk factors among patients with ischemic vascular dementia and Alzheimer's disease. Angiology 44, 599–605.

Morton, J.S., Care, A.S., Kirschenman, R., Cooke, C.-L., Davidge, S.T., 2017. Advanced maternal age worsens postpartum vascular function. Front. Physiol. 8, 465.

Mosconi, L., Berti, V., Quinn, C., McHugh, P., Petrongolo, G., Varsavsky, I., Osorio, R.S., Pupi, A., Vallabhajosula, S., Isaacson, R.S., de Leon, M.J., Brinton, R.D., 2017. Sex differences in Alzheimer risk. Brain imaging of endocrine vs chronologic aging 89, 1382–1390.

Mrgan, M., Gram, J., Hecht Olsen, M., Dey, D., Linde Norgaard, B., Gram, J., Ronnow Sand, N.P., 2018. Sex differences in coronary plaque composition evaluated by coronary computed tomography angiography in newly diagnosed Type 2 diabetes: association with low-grade inflammation. Diabet. Med. 35, 1588–1595.

Muka, T., Asllanaj, E., Avazverdi, N., Jaspers, L., Stringa, N., Milic, J., Ligthart, S., Ikram, M.A., Laven, J.S.E., Kavousi, M., Dehghan, A., Franco, O.H., 2017. Age at natural menopause and risk of type 2 diabetes: a prospective cohort study. Diabetologia 60, 1951–1960.

Murata, T., Dietrich, H.H., Xiang, C., Dacey Jr., R.G., 2013. G protein-coupled estrogen receptor agonist improves cerebral microvascular function after hypoxia/reoxygenation injury in male and female rats. Stroke 44, 779–785.

Narumi, M., Takahashi, K., Yamatani, H., Seino, M., Yamanouchi, K., Ohta, T., Takahashi, T., Kurachi, H., Nagase, S., 2018. Oxidative stress in the visceral fat is elevated in postmenopausal women with gynecologic cancer. J Womens Health (Larchmt) 27, 99–106.

Neergaard-Petersen, S., Hvas, A.M., Kristensen, S.D., Grove, E.L., Larsen, S.B., Phoenix, F., Kurdee, Z., Grant, P.J., Ajjan, R.A., 2014. The influence of type 2 diabetes on fibrin clot properties in patients with coronary artery disease. Thromb. Haemostasis 112, 1142–1150.

Nelander, M., Cnattingius, S., Akerud, H., Wikstrom, J., Pedersen, N.L., Wikstrom, A.K., 2016. Pregnancy hypertensive disease and risk of dementia and cardiovascular disease in women aged 65 years or older: a cohort study. BMJ Open 6 e009880.

Nickelson, K.J., Stromsdorfer, K.L., Pickering, R.T., Liu, T.W., Ortinau, L.C., Keating, A.F., Perfield 2nd, J.W., 2012. A comparison of inflammatory and oxidative stress markers in adipose tissue from weight-matched obese male and female mice. Exp. Diabetes Res. 859395.

Nielsen, S., Guo, Z., Johnson, C.M., Hensrud, D.D., Jensen, M.D., 2004. Splanchnic lipolysis in human obesity. J. Clin. Invest. 113, 1582–1588.

Niewada, M., Kobayashi, A., Sandercock, P.A., Kaminski, B., Czlonkowska, A., 2005. Influence of gender on baseline features and clinical outcomes among 17,370 patients with confirmed ischaemic stroke in the international stroke trial. Neuroepidemiology 24, 123–128.

O'Donnell, M.E., Lam, T.I., Tran, L.Q., Foroutan, S., Anderson, S.E., 2006. Estradiol reduces activity of the blood–brain barrier Na–K–Cl cotransporter and decreases edema formation in permanent middle cerebral artery occlusion. J. Cerebr. Blood Flow Metabol. 26, 1234–1249.

Ohara, T., Doi, Y., Ninomiya, T., Hirakawa, Y., Hata, J., Iwaki, T., Kanba, S., Kiyohara, Y., 2011. Glucose tolerance status and risk of dementia in the community: the Hisayama study. Neurology 77, 1126–1134.

Ohkura, T., Teshima, Y., Isse, K., Matsuda, H., Inoue, T., Sakai, Y., Iwasaki, N., Yaoi, Y., 1995. Estrogen increases cerebral and cerebellar blood flows in postmenopausal women. Menopause 2, 13–18.

Paganini-Hill, A., Henderson, V.W., 1994. Estrogen deficiency and risk of Alzheimer's disease in women. Am. J. Epidemiol. 140, 256–261.

Pan, Y., Zhang, H., Acharya, A.B., Patrick, P.H., Oliver, D., Morley, J.E., 2005. Effect of testosterone on functional recovery in a castrate male rat stroke model. Brain Res. 1043, 195–204.

Park, E.M., Cho, S., Frys, K.A., Glickstein, S.B., Zhou, P., Anrather, J., Ross, M.E., Iadecola, C., 2006. Inducible nitric oxide synthase contributes to gender differences in ischemic brain injury. J. Cerebr. Blood Flow Metabol. 26, 392–401.

Peila, R., Rodriguez, B.L., Launer, L.J., 2002. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study. Diabetes 51, 1256–1262.

Peters, S.A., Huxley, R.R., Woodward, M., 2014. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet 383, 1973–1980.

Peters, S.A.E., Yang, L., Guo, Y., Chen, Y., Bian, Z., Du, J., Yang, J., Li, S., Li, L., Woodward, M., Chen, Z., 2017. Breastfeeding and the risk of maternal cardiovascular disease: a prospective study of 300 000 Chinese women. J Am Heart Assoc 6.

Petrea, R.E., Beiser, A.S., Seshadri, S., Kelly-Hayes, M., Kase, C.S., Wolf, P.A., 2009. Gender differences in stroke incidence and poststroke disability in the framingham heart study. Stroke 40, 1032–1037.

Pohjasvaara, T., Erkinjuntti, T., Vataja, R., Kaste, M., 1997. Dementia three months after stroke. Baseline frequency and effect of different definitions of dementia in the Helsinki Stroke Aging Memory Study (SAM) cohort. Stroke 28, 785–792.

Poli, D., Antonucci, E., Grifoni, E., Abbate, R., Gensini, G.F., Prisco, D., 2009. Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment. Thromb. Haemostasis 101, 938–942.

Pollow, D.P., Romero-Aleshire, M.J., Sanchez, J.N., Konhilas, J.P., Brooks, H.L., 2015. ANG II-induced hypertension in the VCD mouse model of menopause is prevented by estrogen replacement during perimenopause. Am. J. Physiol. Regul. Integr. Comp. Physiol. 309, R1546–R1552.

Postma, I.R., de Groot, J.C., Aukes, A.M., Aarnoudse, J.G., Zeeman, G.G., 2014. Cerebral white matter lesions and perceived cognitive dysfunction: the role of pregnancy. Am. J. Obstet. Gynecol. 211 (257), e251–e255.

Quillinan, N., Deng, G., Grewal, H., Herson, P.S., 2014. Androgens and stroke: good, bad or indifferent? Exp. Neurol. 0, 10–15.

Rapp, S.R., Espeland, M.A., Shumaker, S.A., et al., 2003. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. The women's health initiative memory study: a randomized controlled trial 289, 2663–2672.

Rasmussen, K.L., Tybjærg-Hansen, A., Nordestgaard, B.G., Frikke-Schmidt, R., 2018. Absolute 10-year risk of dementia by age, sex and < em > APOE < /em > genotype: a population-based cohort study. Can. Med. Assoc. J. 190, E1033–E1041.

Rasquin, S.M., Verhey, F.R., Lousberg, R., Winkens, I., Lodder, J., 2002. Vascular cognitive disorders: memory, mental speed and cognitive flexibility after stroke. J. Neurol. Sci. 203–204, 115–119.

Razmara, A., Krause, D.N., Duckles, S.P., 2005. Testosterone augments endotoxin-mediated cerebrovascular inflammation in male rats. Am. J. Physiol. Heart Circ. Physiol. 289, H1843–H1850.

Renoux, C., Coulombe, J., Li, L., Ganesh, A., Silver, L., Rothwell, P.M., 2017. Confounding by pre-morbid functional status in studies of apparent sex differences in severity and outcome of stroke. Stroke 48, 2731–2738.

Ridker, P.M., Cook, N.R., Lee, I.M., Gordon, D., Gaziano, J.M., Manson, J.E., Hennekens, C.H., Buring, J.E., 2005. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N. Engl. J. Med. 352, 1293–1304.

Ritzel, R.M., Patel, A.R., Spychala, M., Verma, R., Crapser, J., Koellhoffer, E.C., Schrecengost, A., Jellison, E.R., Zhu, L., Venna, V.R., McCullough, L.D., 2017. Multiparity improves outcomes after cerebral ischemia in female mice despite features of increased metabovascular risk. Proc. Natl. Acad. Sci. U. S. A. 114, E5673–e5682.

Roach, R.E., Helmerhorst, F.M., Lijfering, W.M., Stijnen, T., Algra, A., Dekkers, O.M., 2015. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev, pp. Cd011054.

Rocca, W.A., Grossardt, B.R., Shuster, L.T., 2011. Oophorectomy, menopause, estrogen treatment, and cognitive aging: clinical evidence for a window of opportunity. Brain Res. 1379, 188–198.

Rodriguez, G., Warkentin, S., Risberg, J., Rosadini, G., 1988. Sex differences in regional cerebral blood flow. J. Cerebr. Blood Flow Metabol. 8, 783–789.

Romero-Aleshire, M.J., Diamond-Stanic, M.K., Hasty, A.H., Hoyer, P.B., Brooks, H.L., 2009. Loss of ovarian function in the VCD mouse-model of menopause leads to insulin resistance and a rapid progression into the metabolic syndrome. Am. J. Physiol. Regul. Integr. Comp. Physiol. 297, R587–R592.

Rosenbaum, M., Leibel, R.L., 1999. Role of gonadal steroids in the sexual dimorphisms in body composition and circulating concentrations of Leptin1. J. Clin. Endocrinol. Metabol. 84, 1784–1789.

Rosenbaum, M., Nicolson, M., Hirsch, J., Heymsfield, S.B., Gallagher, D., Chu, F., Leibel, R.L., 1996. Effects of gender, body composition, and menopause on plasma concentrations of leptin. J. Clin. Endocrinol. Metabol. 81, 3424–3427.

Rossouw, J.E., Anderson, G.L., Prentice, R.L., LaCroix, A.Z., Kooperberg, C., Stefanick, M.L., Jackson, R.D., Beresford, S.A., Howard, B.V., Johnson, K.C., Kotchen, J.M., Ockene, J., 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. J. Am. Med. Assoc. 288, 321–333.

Roy-O'Reilly, M., McCullough, L.D., 2018. Age and sex are critical factors in ischemic stroke pathology. Endocrinology 159, 3120–3131.

Roy-O’Reilly, M., McCullough, L.D., 2014. Sex differences in stroke: the contribution of coagulation. Exp. Neurol. 259, 16–27.

Ruitenberg, A., Ott, A., van Swieten, J.C., Hofman, A., Breteler, M.M., 2001. Incidence of dementia: does gender make a difference? Neurobiol. Aging 22, 575–580.

Rusa, R., Alkayed, N.J., Crain, B.J., Traystman, R.J., Kimes, A.S., London, E.D., Klaus, J.A., Hurn, P.D., 1999. 17beta-estradiol reduces stroke injury in estrogen-deficient female animals. Stroke 30, 1665–1670.

Ryan, J., Scali, J., Carriere, I., Amieva, H., Rouaud, O., Berr, C., Ritchie, K., Ancelin, M.L., 2014. Impact of a premature menopause on cognitive function in later life. Bjog 121, 1729–1739.

Sachdev, P.S., Brodaty, H., Valenzuela, M.J., Lorentz, L., Looi, J.C., Berman, K., Ross, A., Wen, W., Zagami, A.S., 2006. Clinical determinants of dementia and mild cognitive impairment following ischaemic stroke: the Sydney Stroke Study. Dement. Geriatr. Cognit. Disord. 21, 275–283.

Sahathevan, R., Brodtmann, A., Donnan, G.A., 2012. Dementia, stroke, and vascular risk factors; a review. Int. J. Stroke 7, 61–73.

Saija, A., Princi, P., D'Amico, N., De Pasquale, R., Costa, G., 1990. Aging and sex influence the permeability of the blood-brain barrier in the rat. Life Sci. 47, 2261–2267.

Sakata, A., Mogi, M., Iwanami, J., Tsukuda, K., Min, L.J., Jing, F., Iwai, M., Ito, M., Horiuchi, M., 2010. Female exhibited severe cognitive impairment in type 2 diabetes mellitus mice. Life Sci. 86, 638–645.

Sakata, A., Mogi, M., Iwanami, J., Tsukuda, K., Min, L.J., Jing, F., Ohshima, K., Ito, M., Horiuchi, M., 2011. Female type 2 diabetes mellitus mice exhibit severe ischemic brain damage. J Am Soc Hypertens 5, 7–11.

Saldanha, C.J., Duncan, K.A., Walters, B.J., 2009. Neuroprotective actions of brain aromatase. Front. Neuroendocrinol. 30, 106–118.

Salinero, A.E., Anderson, B.M., Zuloaga, K.L., 2018. Sex differences in the metabolic

effects of diet-induced obesity vary by age of onset. Int. J. Obes (Lond). 42, 1088–1091.
Santizo, R., Pelligrino, D.A., 1999. Estrogen reduces leukocyte adhesion in the cerebral circulation of female rats. J. Cerebr. Blood Flow Metabol. 19, 1061–1065.
Santizo, R.A., Anderson, S., Ye, S., Koenig, H.M., Pelligrino, D.A., 2000. Effects of estrogen on leukocyte adhesion after transient forebrain ischemia. Stroke 31, 2231–2235.
Satterthwaite, T.D., Shinohara, R.T., Wolf, D.H., Hopson, R.D., Elliott, M.A., Vandekar, S.N., Ruparel, K., Calkins, M.E., Roalf, D.R., Gennatas, E.D., Jackson, C., Erus, G., Prabhakaran, K., Davatzikos, C., Detre, J.A., Hakonarson, H., Gur, R.C., Gur, R.E., 2014. Impact of puberty on the evolution of cerebral perfusion during adolescence. Proc. Natl. Acad. Sci. U. S. A. 111, 8643–8648.
Selvamani, A., Sohrabji, F., 2010. Reproductive age modulates the impact of focal ischemia on the forebrain as well as the effects of estrogen treatment in female rats. Neurobiol. Aging 31, 1618–1628.
Seux, M.L., Thijs, L., Forette, F., Staessen, J.A., Birkenhager, W.H., Bulpitt, C.J., Girerd, X., Jaaskivi, M., Vanhanen, H., Kivinen, P., Yodfat, Y., Vanska, O., Antikainen, R., Laks, T., Webster, J.R., Hakamaki, T., Lehtomaki, E., Lilov, E., Grigorov, M., Janculova, K., Halonen, K., Kohonen-Jalonen, P., Kermowa, R., Nachev, C., Tuomilehto, J., 1998. Correlates of cognitive status of old patients with isolated systolic hypertension: the Syst-Eur Vascular Dementia Project. J. Hypertens. 16, 963–969.
Shao, H., Breitner, J.C.S., Whitmer, R.A., Wang, J., Hayden, K., Wengreen, H., Corcoran, C., Tschanz, J., Norton, M., Munger, R., Welsh-Bohmer, K., Zandi, P.P., 2012. Hormone therapy and alzheimer disease dementia: new findings from the Cache county study. Neurology 79, 1846–1852.
Shapira, S., Sapir, M., Wengier, A., Grauer, E., Kadar, T., 2002. Aging has a complex effect on a rat model of ischemic stroke. Brain Res. 925, 148–158.
Sharma, B., Singh, N., 2011. Attenuation of vascular dementia by sodium butyrate in streptozotocin diabetic rats. Psychopharmacology 215, 677–687.
Sharma, D., Singh, A., Trivedi, S.S., Bhattacharjee, J., 2011. Role of endothelin and inflammatory cytokines in pre-eclampsia - a pilot North Indian study. Am. J. Reprod. Immunol. 65, 428–432.
Shimizu, H., Shimomura, Y., Nakanishi, Y., Futawatari, T., Ohtani, K., Sato, N., Mori, M., 1997. Estrogen increases in vivo leptin production in rats and human subjects. J. Endocrinol. 154, 285–292.
Shin, J.A., Jeong, S.I., Kim, M., Yoon, J.C., Kim, H.S., Park, E.M., 2015. Visceral adipose tissue inflammation is associated with age-related brain changes and ischemic brain damage in aged mice. Brain Behav. Immun. 50, 221–231.
Shin, J.A., Yoon, J.C., Kim, M., Park, E.M., 2016. Activation of classical estrogen receptor subtypes reduces tight junction disruption of brain endothelial cells under ischemia/reperfusion injury. Free Radic. Biol. Med. 92, 78–89.
Shumaker, S.A., Legault, C., Rapp, S.R., Thal, L., Wallace, R.B., Ockene, J.K., Hendrix, S.L., Jones 3rd, B.N., Assaf, A.R., Jackson, R.D., Kotchen, J.M., Wassertheil-Smoller, S., Wactawski-Wende, J., 2003. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. J. Am. Med. Assoc. 289, 2651–2662.
Singh-Manoux, A., Dugravot, A., Shipley, M., Brunner, E.J., Elbaz, A., Sabia, S., Kivimaki, M., 2018. Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. Alzheimer's Dementia 14, 178–186.
Sobey, C.G., Weiler, J.M., Boujaoude, M., Woodman, O.L., 2004. Effect of short-term phytoestrogen treatment in male rats on nitric oxide-mediated responses of carotid and cerebral arteries: comparison with 17beta-estradiol. J. Pharmacol. Exp. Therapeut. 310, 135–140.
Sohrabji, F., Selvamani, A., Balden, R., 2013. Revisiting the timing hypothesis: biomarkers that define the therapeutic window of estrogen for stroke. Horm. Behav. 63, 222–230.
Soma-Pillay, P., Suleman, F.E., Makin, J.D., Pattinson, R.C., 2017. Cerebral white matter lesions after pre-eclampsia. Pregnancy Hypertens 8, 15–20.
Spritzer, M.D., Galea, L.A., 2007. Testosterone and dihydrotestosterone, but not estradiol, enhance survival of new hippocampal neurons in adult male rats. Dev Neurobiol 67, 1321–1333.
Stampfer, M.J., Willett, W.C., Colditz, G.A., Rosner, B., Speizer, F.E., Hennekens, C.H., 1985. A prospective study of postmenopausal estrogen therapy and coronary heart disease. N. Engl. J. Med. 313, 1044–1049.
Stanhewicz, A.E., Jandu, S., Santhanam, L., Alexander, L.M., 2017. Increased angiotensin II sensitivity contributes to microvascular dysfunction in women who have had preeclampsia. Hypertension 70, 382–389.
Stirone, C., Chu, Y., Sunday, L., Duckles, S.P., Krause, D.N., 2003. 17 Beta-estradiol increases endothelial nitric oxide synthase mRNA copy number in cerebral blood vessels: quantification by real-time polymerase chain reaction. Eur. J. Pharmacol. 478, 35–38.
Stirone, C., Boroujerdi, A., Duckles, S.P., Krause, D.N., 2005. Estrogen receptor activation of phosphoinositide-3 kinase, akt, and nitric oxide signaling in cerebral blood vessels: rapid and long-term effects. Mol. Pharmacol. 67, 105–113.
Strom, J.O., Theodorsson, A., Theodorsson, E., 2009. Dose-related neuroprotective versus neurodamaging effects of estrogens in rat cerebral ischemia: a systematic analysis. J. Cerebr. Blood Flow Metabol. 29, 1359–1372.
Strom, J.O., Theodorsson, A., Theodorsson, E., 2011. Mechanisms of estrogens' dose-dependent neuroprotective and neurodamaging effects in experimental models of cerebral ischemia. Int. J. Mol. Sci. 12, 1533–1562.
Stubbins, R.E., Najjar, K., Holcomb, V.B., Hong, J., Núñez, N.P., 2012. Estrogen alters adipocyte biology and protects female mice from adipocyte inflammation and insulin resistance. Diabetes Obes. Metabol. 14, 58–66.
Sunday, L., Osuna, C., Krause, D.N., Duckles, S.P., 2007. Age alters cerebrovascular inflammation and effects of estrogen. Am. J. Physiol. Heart Circ. Physiol. 292, H2333–H2340.
Sundboll, J., Horvath-Puho, E., Adelborg, K., Schmidt, M., Pedersen, L., Botker, H.E., Henderson, V.W., Toft Sorensen, H., 2018. Higher risk of vascular dementia in myocardial infarction survivors. Circulation 137, 567–577.
Sutton-Tyrrell, K., Lassila, H.C., Meilahn, E., Bunker, C., Matthews, K.A., Kuller, L.H., 1998. Carotid atherosclerosis in premenopausal and postmenopausal women and its association with risk factors measured after menopause. Stroke 29, 1116–1121.
Suzuki, S., Brown, C.M., Dela Cruz, C.D., Yang, E., Bridwell, D.A., Wise, P.M., 2007a. Timing of estrogen therapy after ovariectomy dictates the efficacy of its neuroprotective and antiinflammatory actions. Proc. Natl. Acad. Sci. U. S. A. 104, 6013–6018.
Suzuki, S., Gerhold, L.M., Bottner, M., Rau, S.W., Dela Cruz, C., Yang, E., Zhu, H., Yu, J., Cashion, A.B., Kindy, M.S., Merchenthaler, I., Gage, F.H., Wise, P.M., 2007b. Estradiol enhances neurogenesis following ischemic stroke through estrogen receptors alpha and beta. J. Comp. Neurol. 500, 1064–1075.
Svendsen, O.L., Hassager, C., Christiansen, C., 1995. Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy X-ray absorptiometry. Metabolism 44, 369–373.
Tang, M.X., Jacobs, D., Stern, Y., Marder, K., Schofield, P., Gurland, B., Andrews, H., Mayeux, R., 1996. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 348, 429–432.
Tate, J., Bushnell, C., 2011. Pregnancy and stroke risk in women. Women's Health 7, 363–374.
Tontisirin, N., Muangman, S.L., Suz, P., Pihoker, C., Fisk, D., Moore, A., Lam, A.M., Vavilala, M.S., 2007. Early childhood gender differences in anterior and posterior cerebral blood flow velocity and autoregulation. Pediatrics 119, e610–615.
Toung, T.J., Traystman, R.J., Hurn, P.D., 1998. Estrogen-mediated neuroprotection after experimental stroke in male rats. Stroke 29, 1666–1670.
Tucsek, Z., Toth, P., Sosnowska, D., Gautam, T., Mitschelen, M., Koller, A., Szalai, G., Sonntag, W.E., Ungvari, Z., Csiszar, A., 2014. Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. J Gerontol A Biol Sci Med Sci 69, 1212–1226.
Tuovinen, S., Eriksson, J.G., Kajantie, E., Lahti, J., Pesonen, A.K., Heinonen, K., Osmond, C., Barker, D.J., Raikkonen, K., 2013. Maternal hypertensive disorders in pregnancy and self-reported cognitive impairment of the offspring 70 years later: the Helsinki Birth Cohort Study. Am. J. Obstet. Gynecol. 208, 200–209.
Tveiten, A., Ljostad, U., Mygland, A., Naess, H., 2014. Functioning of long-term survivors of first-ever intracerebral hemorrhage. Acta Neurol. Scand. 129, 269–275.
Uchida, M., Palmateer, J.M., Herson, P.S., DeVries, A.C., Cheng, J., Hurn, P.D., 2009. Dose-dependent effects of androgens on outcome after focal cerebral ischemia in adult male mice. J. Cerebr. Blood Flow Metabol. 29, 1454–1462.
Van Pelt, R.E., Gozansky, W.S., Schwartz, R.S., Kohrt, W.M., 2003. Intravenous estrogens increase insulin clearance and action in postmenopausal women. Am. J. Physiol. Endocrinol. Metab. 285, E311–E317.
Vannucci, S.J., Willing, L.B., Goto, S., Alkayed, N.J., Brucklacher, R.M., Wood, T.L., Towfighi, J., Hurn, P.D., Simpson, I.A., 2001. Experimental stroke in the female diabetic, db/db, mouse. J. Cerebr. Blood Flow Metabol. 21, 52–60.
Verma, A., Sharma, S., 2015. Beneficial effect of protein tyrosine phosphatase inhibitor and phytoestrogen in dyslipidemia-induced vascular dementia in ovariectomized rats. J. Stroke Cerebrovasc. Dis. 24, 2434–2446.
Vieira Potter, V.J., Strissel, K.J., Xie, C., Chang, E., Bennett, G., Defuria, J., Obin, M.S., Greenberg, A.S., 2012. Adipose tissue inflammation and reduced insulin sensitivity in ovariectomized mice occurs in the absence of increased adiposity. Endocrinology 153, 4266–4277.
Wabitsch, M., Blum, W.F., Muche, R., Braun, M., Hube, F., Rascher, W., Heinze, E., Teller, W., Hauner, H., 1997. Contribution of androgens to the gender difference in leptin production in obese children and adolescents. J. Clin. Invest. 100, 808–813.
Wang, Q., Mejía-Guevara, I., Rist, P.M., Walter, S., Capistrant, B.D., Glymour, M.M., 2014. Changes in memory before and after stroke differ by age and sex, but not by race. Cerebrovasc. Dis. 37, 235–243.
Warrington, J.P., Fan, F., Murphy, S.R., Roman, R.J., Drummond, H.A., Granger, J.P., Ryan, M.J., 2014. Placental ischemia in pregnant rats impairs cerebral blood flow autoregulation and increases blood-brain barrier permeability. Phys. Rep. 2.
Whitmer, R.A., Gunderson, E.P., Barrett-Connor, E., Quesenberry, C.P., Yaffe, K., 2005. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ Br. Med. J. (Clin. Res. Ed.) 330 1360-1360.
Whitmer, R.A., Gunderson, E.P., Quesenberry Jr., C.P., Zhou, J., Yaffe, K., 2007. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr. Alzheimer Res. 4, 103–109.
Whitmer, R.A., Gustafson, D.R., Barrett-Connor, E., Haan, M.N., Gunderson, E.P., Yaffe, K., 2008. Central obesity and increased risk of dementia more than three decades later. Neurology 71, 1057–1064.
Whitmer, R.A., Quesenberry, C.P., Zhou, J., Yaffe, K., 2011. Timing of hormone therapy and dementia: the critical window theory revisited. Ann. Neurol. 69, 163–169.
WHO, 1996. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 348, 498–505.
Wildman, R.P., Colvin, A.B., Powell, L.H., Matthews, K.A., Everson-Rose, S.A., Hollenberg, S., Johnston, J.M., Sutton-Tyrrell, K., 2008. Associations of endogenous sex hormones with the vasculature in menopausal women: the study of women’s health across the nation (SWAN). Menopause (New York, N.Y.) 15, 414–421.
Wilson, A.C., Clemente, L., Liu, T., Bowen, R.L., Meethal, S.V., Atwood, C.S., 2008. Reproductive hormones regulate the selective permeability of the blood-brain barrier. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1782, 401–407.
Wolf, P.H., Madans, J.H., Finucane, F.F., Higgins, M., Kleinman, J.C., 1991. Reduction of

cardiovascular disease-related mortality among postmenopausal women who use hormones: evidence from a national cohort. Am. J. Obstet. Gynecol. 164, 489–494.
Xue, B., Zhao, Y., Johnson, A.K., Hay, M., 2008. Central estrogen inhibition of angiotensin II-induced hypertension in male mice and the role of reactive oxygen species. Am. J. Physiol. Heart Circ. Physiol. 295, H1025–H1032.
Xue, B., Badaue-Passos, D., Guo, F., Gomez-Sanchez, C.E., Hay, M., Johnson, A.K., 2009a. Sex differences and central protective effect of 17β-estradiol in the development of aldosterone/NaCl-induced hypertension. Am. J. Physiol. Heart Circ. Physiol. 296, H1577–H1585.
Xue, B., Singh, M., Guo, F., Hay, M., Johnson, A.K., 2009b. Protective actions of estrogen on angiotensin II-induced hypertension: role of central nitric oxide. Am. J. Physiol. Heart Circ. Physiol. 297, H1638–H1646.
Xue, B., Zhang, Z., Beltz, T.G., Guo, F., Hay, M., Johnson, A.K., 2014. Estrogen regulation of the brain renin-angiotensin system in protection against angiotensin II-induced sensitization of hypertension. Am. J. Physiol. Heart Circ. Physiol. 307, H191–H198.
Yamada, M., Sasaki, H., Mimori, Y., Kasagi, F., Sudoh, S., Ikeda, J., Hosoda, Y., Nakamura, S., Kodama, K., 1999. Prevalence and risks of dementia in the Japanese population: RERF's adult health study Hiroshima subjects. Radiation Effects Research Foundation. J. Am. Geriatr. Soc. 47, 189–195.
Yamada, M., Mimori, Y., Kasagi, F., Miyachi, T., Ohshita, T., Sasaki, H., 2009. Incidence and risks of dementia in Japanese women: radiation effects research foundation adult health study. J. Neurol. Sci. 283, 57–61.
Yang, S.-H., Perez, E., Cutright, J., Liu, R., He, Z., Day, A.L., Simpkins, J.W., 2002a. Testosterone increases neurotoxicity of glutamate in vitro and ischemia-reperfusion injury in an animal model. J. Appl. Physiol. 92, 195–201.
Yang, S.H., Perez, E., Cutright, J., Liu, R., He, Z., Day, A.L., Simpkins, J.W., 2002b. Testosterone increases neurotoxicity of glutamate in vitro and ischemia-reperfusion injury in an animal model. J. Appl. Physiol. 92, 195–201.
Yang, Q., Tong, X., Schieb, L., Vaughan, A., Gillespie, C., Wiltz, J.L., King, S.C., Odom, E., Merritt, R., Hong, Y., George, M.G., 2017. Vital signs: recent trends in stroke death rates — United States, 2000–2015. MMWR Morb. Mortal. Wkly. Rep. 66, 933–939.
Yeap, B.B., Hyde, Z., Almeida, O.P., Norman, P.E., Chubb, S.A., Jamrozik, K., Flicker, L., Hankey, G.J., 2009. Lower testosterone levels predict incident stroke and transient ischemic attack in older men. J. Clin. Endocrinol. Metab. 94, 2353–2359.
Yeap, B.B., Alfonso, H., Chubb, S.A., Hankey, G.J., Handelsman, D.J., Golledge, J., Almeida, O.P., Flicker, L., Norman, P.E., 2014. In older men, higher plasma testosterone or dihydrotestosterone is an independent predictor for reduced incidence of stroke but not myocardial infarction. J. Clin. Endocrinol. Metab. 99, 4565–4573.
Yim, J.-E., Heshka, S., Albu, J.B., Heymsfield, S., Gallagher, D., 2008. Femoral-gluteal subcutaneous and intermuscular adipose tissues have independent and opposing relationships with CVD risk. J. Appl. Physiol. 104, 700–707.
Yin, Y.W., Li, J.C., Wang, J.Z., Li, B.H., Pi, Y., Yang, Q.W., Fang, C.Q., Gao, C.Y., Zhang, L.L., 2012. Association between apolipoprotein E gene polymorphism and the risk of vascular dementia: a meta-analysis. Neurosci. Lett. 514, 6–11.
Yin, Z.G., Wang, Q.S., Yu, K., Wang, W.W., Lin, H., Yang, Z.H., 2018. Sex differences in associations between blood lipids and cerebral small vessel disease. Nutr. Metabol. Cardiovasc. Dis. 28, 28–34.
Zandi, P.P., Carlson, M.C., Plassman, B.L., Welsh-Bohmer, K.A., Mayer, L.S., Steffens, D.C., Breitner, J.C., 2002. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. J. Am. Med. Assoc. 288, 2123–2129.
Zhang, W., Iliff, J.J., Campbell, C.J., Wang, R.K., Hurn, P.D., Alkayed, N.J., 2009b. Role of soluble epoxide hydrolase in the sex-specific vascular response to cerebral ischemia. J. Cerebr. Blood Flow Metabol. 29, 1475–1481.
Zhang, B., Subramanian, S., Dziennis, S., Jia, J., Uchida, M., Akiyoshi, K., Migliati, E., Lewis, A.D., Vandenbark, A.A., Offner, H., Hurn, P.D., 2010. Estradiol and G1 reduce infarct size and improve immunosuppression after experimental stroke. J. Immunol. 184, 4087–4094.
Zhang, W., Zheng, Y., Liu, F., Wang, X., Jin, Z., Zhi, J., 2015. Mechanism of agonistic angiotensin II type I receptor autoantibody-amplified contractile response to Ang II in the isolated rat thoracic aorta. Acta Biochim. Biophys. Sin. 47, 851–856.
Zhang, Z.L., Qin, P., Liu, Y., Zhang, L.X., Guo, H., Deng, Y.L., Yizhao, L., Hou, Y.S., Wang, L.Y., Miao, Y., Ma, Y.L., Hou, W.G., 2017. Alleviation of ischaemia-reperfusion injury by endogenous estrogen involves maintaining Bcl-2 expression via the ERalpha signalling pathway. Brain Res. 1661, 15–23.
Zheng, J., Zhang, P., Li, X., Lei, S., Li, W., He, X., Zhang, J., Wang, N., Qi, C., Chen, X., Lu, H., Liu, Y., 2013. Post-stroke estradiol treatment enhances neurogenesis in the subventricular zone of rats after permanent focal cerebral ischemia. Neuroscience 231, 82–90.
Zhong, G., Wang, Y., Zhang, Y., Guo, J.J., Zhao, Y., 2015. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. PLoS One 10 e0118333.
Zhou, C.C., Zhang, Y., Irani, R.A., Zhang, H., Mi, T., Popek, E.J., Hicks, M.J., Ramin, S.M., Kellems, R.E., Xia, Y., 2008. Angiotensin receptor agonistic autoantibodies induce pre-eclampsia in pregnant mice. Nat. Med. 14, 855–862.
Zhou, C.C., Irani, R.A., Dai, Y., Blackwell, S.C., Hicks, M.J., Ramin, S.M., Kellems, R.E., Xia, Y., 2011. Autoantibody-mediated IL-6-dependent endothelin-1 elevation underlies pathogenesis in a mouse model of preeclampsia. J. Immunol. 186, 6024–6034.
Zhu, Y., Zhang, Q., Zhang, W., Li, N., Dai, Y., Tu, J., Yang, F., Brann, D.W., Wang, R., 2017. Protective effect of 17beta-estradiol upon hippocampal spine density and cognitive function in an animal model of vascular dementia. Sci. Rep. 7, 42660.
Ziemens, B., Wallaschofski, H., Volzke, H., Rettig, R., Dorr, M., Nauck, M., Keevil, B.G., Brabant, G., Haring, R., 2013. Positive association between testosterone, blood pressure, and hypertension in women: longitudinal findings from the Study of Health in Pomerania. J. Hypertens. 31, 1106–1113.
Zuloaga, K.L., Gonzales, R.J., 2011. Dihydrotestosterone attenuates hypoxia inducible factor-1alpha and cyclooxygenase-2 in cerebral arteries during hypoxia or hypoxia with glucose deprivation. Am. J. Physiol. Heart Circ. Physiol. 301, H1882–H1890.
Zuloaga, K.L., Swift, S.N., Gonzales, R.J., Wu, T.J., Handa, R.J., 2012. The androgen metabolite, 5alpha-androstane-3beta,17beta-diol, decreases cytokine-induced cyclooxygenase-2, vascular cell adhesion molecule-1 expression, and P-glycoprotein expression in male human brain microvascular endothelial cells. Endocrinology 153, 5949–5960.
Zuloaga, K.L., Davis, C.M., Zhang, W., Alkayed, N.J., 2014a. Role of aromatase in sex-specific cerebrovascular endothelial function in mice. Am. J. Physiol. Heart Circ. Physiol. 306, H929–H937.
Zuloaga, K.L., Krasnow, S.M., Zhu, X., Zhang, W., Jouihan, S.A., Shangraw, R.E., Alkayed, N.J., Marks, D.L., 2014b. Mechanism of protection by soluble epoxide hydrolase inhibition in type 2 diabetic stroke. PLoS One 9, e97529.
Zuloaga, K.L., Johnson, L.A., Roese, N.E., Marzulla, T., Zhang, W., Nie, X., Alkayed, F.N., Hong, C., Grafe, M.R., Pike, M.M., Raber, J., Alkayed, N.J., 2016. High fat diet-induced diabetes in mice exacerbates cognitive deficit due to chronic hypoperfusion. J. Cerebr. Blood Flow Metabol. 36, 1257–1270.