

Investigation of common risk factors between polycystic ovary syndrome and Alzheimer's disease

Nahid Sarahian

Shahid Beheshti University of Medical Sciences School of Medicine

Hosna Sarvazad

Kermanshah University of Medical Sciences

Elham Sajadi

Shiraz University

Nasrin Rahnejat

Kermanshah University of Medical Sciences

Narges Eskandari-Roozbahani (✉ neskandari32@gmail.com)

Kermanshah University of Medical Sciences <https://orcid.org/0000-0003-2509-9177>

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Abstract

The most common endocrine disorder among women is Polycystic ovary syndrome (PCOS), characterized by hyperandrogenism, chronic ovulation, and/or ultrasound evidence of small ovarian cysts. Obesity and insulin resistance are also the main factors influencing the clinical manifestations of this syndrome. High intakes of fat have been linked to more significant cognitive decline in old age, and due to the growing elderly population, maintaining long-term optimal cognitive function is very important.

Alzheimer's disease (AD) is the most typical progressive neurodegenerative disorder of the brain, and recent studies suggest a relationship between endocrinal dysregulation and neuronal loss during AD pathology.

In this narrative review, the international databases, including Google Scholar, Scopus, PubMed, and Web of Science databases, were searched for retrieving the relevant studies.

According to the factors involved in Alzheimer's and PCOS, it seems that both disorders may share some common risk factors. In this study, the relevant studies' summaries were categorized to discuss the possible pathways that may explain the association between Alzheimer's and PCOS signs/symptoms and complications. Future preclinical studies are needed to investigate the exact underlining mechanisms related to PCOS and Alzheimer's association.

Plain English Summary

Polycystic ovary syndrome is a disorder of the female reproductive system that can be caused by hormonal disorders; the disease is detected on ultrasound of the ovaries with small ovarian cysts. Obesity and insulin resistance are among the factors that can affect the clinical symptoms of this disease. Obesity due to high-fat consumption can affect cognitive functions with age. Among the diseases associated with disorders in the brain cells, Alzheimer's is bold; a link between hormonal disorders and Alzheimer's has recently been reported. We conducted a review of reports and articles published in connection with polycystic ovary syndrome and neurodegenerative disorder in reputable scientific databases. Studies have shown that the factors involved in polycystic ovary syndrome and Alzheimer's disease may indicate that both diseases have common risk factors. It may be linked to the symptoms and/or complications of Alzheimer's disease and polycystic ovary syndrome. Future preclinical studies are needed to closely examine the mechanisms associated with polycystic ovary syndrome and the association between Alzheimer's.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous group of disorders with metabolic and endocrine disorders that affect 4–12% of women of reproductive age. PCOS often shows a wide range of metabolic changes such as insulin resistance (IR), blood lipids, obesity, inflammation, increased oxidative stress, and hormonal changes (1). The exact cause of PCOS is not known, but genetic and environmental

factors appear to be involved. Recent studies have shown that hyperandrogenism (HA) and IR are the main causes and primary features of PCOS. Furthermore, these factors can interact in the occurrence and progression of PCOS (2).

IR directly or indirectly enhances androgen synthesis and secretion; hyperandrogenism stimulates the breakdown of visceral adipose tissue, leading to an increase in free fatty acids, which intensifies IR levels. Eventually, this can create a vicious cycle between hyperandrogenemia and IR in PCOS and lead to development and progression (3). Insulin also affects central nervous system (CNS) function by playing a role in regulating energy homeostasis, central action on peripheral glucose metabolism, learning, memory, cognition, and survival of brain neurons in adults (4). Therefore, any disturbance in insulin metabolism in the CNS may have adverse effects on brain function and cognitive activity (5).

Alzheimer's disease (AD) is an irreversible and progressive disorder with neuronal destruction characterized by behavioral changes and cognitive function loss in the elderly. AD accounts for 60 to 80% of dementia cases (6). Approximately 46 million people have dementia globally, and this number is projected to increase to 131.5 million by 2050 (7). Common symptoms include short-term memory loss, cognitive impairment, and inability to perform tasks in daily life (8).

Intracellular inclusions of tau protein in the form of neurofibrillary tangles and extracellular plaque formation by accumulations of the amyloid beta-peptide (A β) derived from the β -amyloid precursor protein (APP) are two primary pathological lesions in the brains of Alzheimer's patients (9). Neurosteroids and sex steroids have been suggested as one reason for reducing the pathology of AD. Alzheimer's is more common in women than men, and estrogen depletion is generally associated with an increased risk of AD (10). The age-related decrease in brain levels of testosterone in men and E2 in women during menopause has been associated with a greater risk of developing AD (10).

Loss of neurons and synapses leads to atrophy of the cortex and subcortical areas (11). neurodegeneration in AD is associated with unregulated lipid and carbohydrate metabolism, cytokine-mediated inflammation, increased oxidative and cellular stress, ongoing cell death, and vascular destruction (12). These factors are also present in type 2 diabetes, metabolic syndrome, and non-alcoholic fatty liver disease and support the notion that insulin-resistant diseases are all related and could have the same origins, and maybe managed by similar if not identical therapeutic strategies.

There is no effective treatment to prevent or slow the progression of AD. Evidence suggests that in addition to hormonal disorders and obesity, vitamin deficiencies and sleep disorders are also risk factors for this disease (13).

Because Alzheimer's patients have risk factors similar to those of PCOS, such as insulin resistance, vitamin D deficiency, sexual hormonal changes, inflammation, and sleep disorders, it may be hypothesized that PCOS may increase the risk of Alzheimer's disease. This narrative review aimed to summarize the possible pathways that may explain the association between Alzheimer's and PCOS.

Methods

A comprehensive search of Google Scholar, Scopus, PubMed, and Web of Science (until February 01, 2021) was conducted during this review. Search parameters, MeSH indexing terms, included polycystic ovary syndrome, PCOS, vitamin D, obesity, sex hormones, androgens, estrogens, progesterone, insulin resistance, sleep apnea, memory, Alzheimer disease, and dementia. All human and animal articles were reviewed; non-English studies and conference abstracts were excluded. A total of 2876 articles from four databases were identified, and 110 studies that had inclusion criteria were subjected to careful review (figure 1).

Hypothalamic-pituitary-gonadal axis and estrogen

Hypothalamic-pituitary-gonadal (HPG) plays an essential role in regulating various activities, and impaired HPG axis can cause polycystic ovary syndrome; sex hormone levels are regulated by the HPG (14, 15). Deregulation in the HPG axis leads to menopause in women and andropause in men (16).

HPG axis hormone receptors (including steroid hormones, human chorionic gonadotropin, LH, and GnRH) are concentrated in the limbic system, especially hippocampal pyramidal neurons, and are involved in regulating the growth, structure, and function of the adult brain. These sections are very sensitive to AD pathology (17-19).

Estrogen receptors (ERs) by activating brain-derived neurotrophic factor (BDNF) have an essential effect on AD, and a significant reduction in postmenopausal estrogen may increase the risk of Alzheimer's (20, 21). Decreased sex gland hormones and increased gonadotropins such as LH are involved in cognitive dysfunction in aging and the pathogenesis of age-related disorders such as AD; This is especially important for women who are twice as likely to develop postmenopausal AD (22). The estrogen receptor network is one of the significant regulatory systems in the brain; under its influence, the brain responds to the ovarian-neural estrogen axis at appropriate intervals to regulate its energy metabolism (23). The Hippocampus, Prefrontal cortex, amygdala, and posterior cingulate cortex of the brain regions with substantial estrogen receptors are essential for learning and memory (24).

Because estrogen's protective effect on the brain is known, estrogen loss during menopause can partly lead to impaired brain metabolism and mitochondrial dysfunction in AD (25). In this regard, several studies have shown a strong association between decreased estrogen levels during menopause and AD development (9, 26). Studies using estradiol as the physiological form of estrogen have also shown that estrogen stabilizes or improves cognition in women with AD (27). Estrogen modulates neurogenesis by modulating learning and memory in the hippocampus in various species, from rodents to primates (28).

Due to the significant role of hormones in memory and cognition, in addition to clinical and epidemiological studies of estrogen and androgens in AD, it is necessary to study other hormones involved in the HPG axis.

Insulin resistance (IR)

IR is a **pathological** condition in which **cells** fail to respond typically to normal circulating insulin levels, so insulin cannot provide average glucose and lipid homeostasis (29). IR and hyperinsulinemia play a major role in the cause of PCOS, and 50% to 70% of these patients present with IR. (30). Studies have shown that PCOS is associated with impaired insulin activity in classical target tissues such as adipose tissue and skeletal muscle with insulin resistance (31). IR, a common feature of women with PCOS, is an essential regulator of androgen synthesis, and studies have shown that hyperandrogenism can contribute to IR (2, 32). IR resistance is a common pathogen of other prevalent diseases, such as PCOS, AD, Parkinson's diseases, and several cancers (33).

Insulin is a major trophic factor in brain development (34) and, insulin irregularity and IR are other features of endocrine changes in the pathology of AD that may play a role in disease progression (35). So Patients with impaired insulin metabolism may be at higher risk for developing AD (4). Women with PCOS are more prone to a wide range of complications from metabolic disorders, so the question is whether PCOS can make women more susceptible to AD?

Metabolic diseases impair brain health and cognitive function (36), and insulin signaling affects the hippocampus's molecular cascades of flexibility, learning, and memory (37). Insulin has a wide range of effects on the CNS and regulates critical processes such as energy homeostasis, endocrine reproduction, learning, memory, and neuronal survival in adults (4). Insulin regulates neural proliferation, apoptosis and synaptic transmission, and pleiotropic effects in neurons (38). There is a mechanical link between A β metabolism and insulin resistance. It has been shown that in advanced AD cases, the higher the A β level, the more insulin receptors are removed from the cell surface (35). Studies have shown that IR or deficiency impairs learning and memory, so that insulin administration improves working memory and cognition and increases A β 42 clearance in the brain (39).

Alzheimer's disease should be considered as a degenerative metabolic disease due to brain insulin resistance and deficiency. Impaired insulin signaling can involve many essential abnormalities in AD, including neuroinflammation (40). The fact that neuroinflammation exacerbates IR, neurotoxicity, and cell death due to oxidation, gliosis, and toxicity of A β 42 means that the association between IR and neuroinflammation is very close (40).

Inflammation and Obesity

PCOS women are at higher risk for impaired fat metabolism. Abdominal obesity in PCOS patients is related to IR, hyperandrogenism, regular ovulation, and inflammation (41, 42). On the other hand, central obesity exacerbates endocrine and metabolic disorders in PCOS (43). Obesity is associated with an increase in inflammatory factors, including interleukins and peptides associated with the calcitonin gene, and it can upregulate ovarian androgen production (44). Inflammation associated with PCOS is partly due to IR and obesity but is more commonly associated with hyperandrogenemia (44). Inflammatory genes, such as interleukin-1 beta (IL-1 β), IL-8, leukemia inhibitory factor (LIF), NOS2, and prostaglandin-endoperoxide synthase 2 (PTGS2), are over-expressed in granulosa cells (GCs) of PCOS patients,

indicating inflammation of the ovarian GC responses (45). TNF α , as a proinflammatory agent, may exacerbate the development of IR in PCOS women (2).

Neuro-inflammation is a primary and consistent feature in many neurodegenerative diseases, including AD (46). Overweight people and diabetics are at higher risk for cognitive impairment and dementia (47), and by comparing obese and thin patients of the same age, obese patients show a higher degree of hyperandrogenism. Some studies have also shown that free fatty acids promote the development of amyloid fibers and tau in vitro (48), and therefore obesity is associated with mild cognitive impairment and changes in the structure and function of the hippocampus (49, 50).

Increased expression of proinflammatory cytokines in the vicinity of A β 42 plaques indicates that neuroinflammation is an essential mediator of AD neuro-degradation (51). Free fatty acids contribute to Alzheimer's pathology by causing inflammation, enhancing A β deposition, and inhibiting clearance of A β (52).

Also, neuro-inflammation promotes neuronal injury and cholinergic dysfunction (53). In this regard, epidemiological studies have shown that people who take chronic anti-inflammatory drugs or antioxidants have a lower risk of developing cognitive impairment and AD (54). increased systemic inflammation is thought to cause changes in the microglia, resulting in inflammation in the CNS, and may increase the risk of cognitive aging and Alzheimer's disease (55).

Because sleep disorders have essential effects on inflammatory biology, inflammation may be a biologically acceptable pathway and a link between sleep disorders and the risk of Alzheimer's disease (56).

Obstructive sleep apnea (OSA)

Obstructive sleep apnea (OSA) is characterized by partial or total obstruction of the upper airways and recurrence during sleep that leads to intermittent hypoxemia, of which obesity is a pillar of its physical pathology (57). So that obese women with PCOS have a higher risk of obstructive sleep apnea than matched, healthy women (with normal reproduction) (58, 59).

Studies show that androgens affect sleep patterns and lead to OSA development (60, 61). As a result, women with PCOS have higher respiratory sleep levels, which may be associated with increased androgen levels associated with the syndrome (57). Due to hormonal disorders, it is well known that the prevalence of OSA is higher in women with PCOS compared with women without PCOS (62). A wide range of hormonal and metabolic abnormalities in PCOS is also associated with people's hormonal profile with OSA (63). The increasing prevalence of obstructive sleep apnea in PCOS patients is associated with an increase in androgens or a decrease in estrogens and an increase in visceral adiposity (64), so studies have shown higher levels of testosterone in PCOS patients are related to OSA (65). This is why sleep disorders in patients with PCOS are twice as common as in ordinary people (66). Hyperandrogenism, IR, and low estrogen and progesterone levels with PCOS have all been suggested to

cause OSA in PCOS patients (67). IR is associated with irregular sleep breathing (2). Progesterone increases respiratory pressure and the muscles' function that dilates the upper airway (68). This is why hormone therapy in postmenopausal women can be a protective factor against obstructive sleep apnea syndrome.

Evidence suggests that sleep disorders may lead to cognitive decline by increasing β -amyloid load, which increases the risk of dementia in AD (13). Respiratory disorders during sleep also increase the risk of dementia, and a higher incidence of all-cause dementia, AD, and vascular dementia are associated (69). In humans, the concentration of β -amyloid in CSF fluctuates and increases during the day and decreases at night, and sleep deprivation or insomnia can affect the pattern of secretion (70).

Animal studies showed that sleep increases clearance of soluble β -amyloid, and sleep-wake activity disorders interfere with eliminating potentially neurotoxic waste products, such as β -amyloid, which accumulate during the waking period (71, 72). Evidence suggests that depression is a risk factor for cognitive decline and dementia and that sleep disorders and insomnia can be risk factors for depression and recurrence of depression (73, 74). As a result, it can be said that there is usually a two-way relationship between sleep disorders and depression, also between sleep disorders and dementia.

Sleep is recognized as an essential modulator of several aspects of endocrine function, making it challenging to elucidate the relationship between these factors (62). However, there is no evidence that treatment for sleep disorders prevents cognitive decline or dementia.

Vitamin D

Over the past 25 years, vitamin D has been recognized as a serious candidate in the nervous system's development and functioning and a treatment option in several neurological pathologies (75).

Researchers have recently shown that vitamin D deficiency is a common complication of PCOS and that vitamin D levels are associated with reproductive ability, metabolic changes, and mental health in PCOS patients (76). In this regard, Krul-Poel et al. showed that women with PCOS and infertile have lower serum levels of 25 (OH) D than the fertile control group (77).

Vitamin D deficiency in PCOS may lead to IR (38), so vitamin D concentration is negatively correlated with IR parameters and body fat mass. Also, treatment with vitamin D improves the metabolism of IR and lipids, improving the metabolic disorders of PCOS patients (76).

Vitamin D increases the maturation of adipose cells, activates enzymes involved in lipid and carbohydrate metabolism, and increases adipose tissue (78). This suggests that the growth of oocytes in women with PCOS is closely related to vitamin D.

Vitamin D level is negatively correlated with serum androgen levels. Vitamin D administration lowers serum androgen and anti-Müllerian Hormone (AMH) levels and reduces endometrial thickness; this reduction in androgen levels in PCOS patients improves the menstrual cycle folliculogenesis (76).

Studies show that vitamin D deficiency is associated with the onset of the first symptoms of AD and can contribute to the onset of dementia. However, interventional studies did not improve cognitive function after administering vitamin D supplementation (75). Vitamin D plays an essential role in metabolic pathways, including calcium homeostasis, the insulin pathway, and the synthesis of sex hormones, all of which are affected by PCOS (79).

The main reason for taking vitamin D supplementation in PCOS women is its role in suppressing proinflammatory cytokines, glucose metabolism, increasing insulin receptor expression plus synthesis and secretion of that (80). Vitamin D deficiency is associated with many human diseases, especially age-related diseases, such as AD, cardiovascular disease, cancer, type II diabetes, multiple sclerosis, and various inflammatory disorders (81). The progression of dementia and non-communicable diseases such as AD is a major public health problem. One of the direct causes of neuronal loss and decreased recognition of A β accumulation is associated with increased inflammatory responses in the brain (82). Vitamin D deficiency is a growing problem and plays a significant role in the cytotoxicity of amyloid plaques, which affect a significant portion of the population in many countries (83). Vitamin D is involved in genomic and non-genomic effects on calcium homeostasis, neurotransmission, oxidative stress, A β and Tau accumulation, vascularization, and inflammation; all of these pathways can be impaired in AD (84). In addition to calcium homeostasis, vitamin D has numerous functions in the nervous system, including regulating the production of neurotrophic factors, neurotransmitter secretion, oxidative stress mechanisms, modulating the immune system, and currently known as an effective immune modulator (75). It also has the potential to regulate the inflammatory status in AD pathology (75).

LH/FSH ratio

The ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) (LH/FSH ratio) in women with PCOS is significantly higher than in normal women of the same age (85), and increasing this ratio is a powerful indicator of PCOS (86). In these patients, the increase in LH secretion may be due to a defective hypothalamic-pituitary-ovarian axis (87). LH is a gonadotropin secreted by the anterior pituitary gland that binds to luteinizing hormone receptors (LHR) and is found in the tissues of the gonad and non-gonad (88). In patients with PCOS, by increasing LH, the ovarian theca cells produce excess androgens, and low FSH contributes to impaired folliculogenesis and ovulation (2). Interestingly, IR and hyperinsulinemia, which are prominent PCOS features, stimulate LH secretion from the pituitary gland (thus increasing the LH / FSH ratio) and increase androgen production in ovarian follicular cells (89). LH in the ovaries and testes stimulates the production of gonadal hormones, including estrogens and androgens (90). An increase in LH increases androstenedione's production is converted to testosterone by 17 β reductase in thecal cells and released into the blood (91). Androstenedione can also be converted to estradiol by the FSH-dependent aromatase enzyme in ovarian granulosa cells (92).

Because in PCOS, LH levels are high compared to FSH, androstenedione accumulates in the ovaries. In the early stages, androstenedione causes the follicles to grow; however, the persistence of high levels promotes the growth of most follicles as they mature, so ovulation does not lead to the accumulation of

antral follicles, and the ovary becomes polycystic (41). Decreased FSH levels compared to LH in PCOS cause more conversion of androstenedione to testosterone, leading to hirsutism (42).

LH increases with age in both men and women. This hormone may be the main hormone in cognitive dysfunction and AD (93). In this regard, the evidence in epidemiological studies supports the increase of LH in exacerbating the age-related cognitive decline in men and women (93). There is an inverse relationship between LH and memory, and most studies show a correlation between serum LH concentration and amyloid-beta plasma accumulation and deposition (94). Elevated LH levels are involved in A β metabolism and accumulation and are associated with an increased risk of AD (17). Some studies suggest a link between LH and BDNF in the hippocampus, and these studies suggest that estrogen-increasing and LH-lowering treatments may both require BDNF signaling to improve spatial memory (95). While most studies have shown that LH increases BDNF levels in gonadal tissue, some studies have shown that LH decreases BDNF levels in the CNS (95). Genetic defects in the amyloid beta-AD pathway may increase GnRH and LH, which in turn may have a spiral effect on AD neurotoxicity.

There is not much research on the possible effects of FSH in this area, although one study found that there was a correlation between higher cognitive function in older women and increased FSH levels (47). However, as mentioned earlier, LH has the most significant effect on the hippocampus, and more research is needed.

Hyperandrogenism

Androgens belong to the family of steroid hormones and hyperandrogenism is one of the main clinical manifestations of PCOS (96). Androgens include testosterone, androstenedione (A4), dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS) (97). Serum levels of various androgens in PCOS patients are constantly increasing compared to healthy individuals (98). Approximately 75% of PCOS patients having hyperandrogenism, and more than 80% having abnormally free testosterone levels (99). This may be due to oxidative stress and hyperinsulinemia, which stimulate theca-interstitial cell proliferation and androgen production (100, 101). Studies have shown that exposure of female fetuses to androgen overload in all models causes PCOS characteristics (102).

On the other hand, androgens may help reduce the process of AD, and decreased levels of gonadal hormones, especially estrogens and androgens, are commonly associated with the onset of AD (93). Some studies have shown that androgens' administration improves cognitive function (59); androgen administration reduces the expression of inflammatory factor IL-1 β , so reduces nerve death in the hippocampus (103).

Sex hormone-binding globulin (SHBG) is a sex steroid produced in the hepatic cells, and its low production may be involved in the pathogenesis of PCOS (104). SHBG has a slight tendency to bind estradiol and a high affinity for testosterone (105). The biological activity of androgens is also determined by free testosterone, and therefore SHBG levels are essential in assessing hyperandrogenism (104); in PCOS patients, one of the reasons for low serum SHBG levels is hyperandrogenemia (106).

SHBG binds to free androgens and lowers free androgen levels, reducing hyperandrogenism and IR (106). SHBG levels increase in AD patients and lower serum levels of bioactive sex steroids (18).

Discussion

PCOS is one of the most common endocrine disorders that HPG-axis play a central role in the pathophysiology of that (107). Hormones, especially gonadal hormones, widely affect the function and stability of the central nervous system (108). Also, cognitive function may depend on the level of sex steroids and gonadotropins, including HPG-based dysfunction (18).

AD is one of the most important neurodegenerative disorders with adverse effects on mental health, social ability, and high economic costs in human societies.

This study investigated some common factors such as IR, inflammation, sleep apnea, Vitamin D deficiency, LH/FSH ratio, and sex hormones that may play a role in the association between AD and PCOS.

Obesity and IR, which are also seen in PCOS patients, may increase the risk of cognitive decline and neurodegenerative diseases (36). On the other hand, due to the increased levels of androgens in PCOS patients, we expect cognitive activity to increase in these patients. However, oral contraceptive pills (OCPs) are drugs prescribed to women with PCOS as a first-line treatment to reduce androgen overexpression and regulate menstrual cycles (109). Because OCPs reduce androgens, they can have adverse effects on memory and cognition. Also, drugs such as *Metformin*, which reverses IR, are associated with increased SHBG levels in women with PCOS (110). As mentioned above, SHBG levels also increase in patients with AD. The use of these drugs may increase the symptoms of AD by increasing the level of SHBG. Although more research is needed, controlling SHBG levels may keep endogenous estrogens and androgens bioactive and improve cognition. Due to the variety of actions of estrogen, LH, and testosterone, combination hormone therapy may be more effective in preventing AD.

Studies in this area are not enough, and more animal research is needed to clarify the link between PCOS and AD.

Abbreviations

PCOS: polycystic ovary syndrome; AD: Alzheimer Disease; IR: insulin resistance; HA: hyperandrogenism; CNS: the central nervous system; A β : amyloid beta-peptide; APP: Amyloid precursor protein; HPG: Hypothalamic-pituitary-gonadal; ERs: Estrogen receptors; BDNF: brain-derived neurotrophic factor; GnRH: Gonadotropin-releasing hormone; IL-1 β : interleukin-1 beta; PTGS2: prostaglandin-endoperoxide synthase 2; LIF: leukemia inhibitory factor; TNF α : Tumor necrosis factor-alpha; OSA: Obstructive sleep apnea; AMH: anti-Müllerian Hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; LHR: luteinizing hormone receptors; DHT: dihydrotestosterone; DHEAs: dehydroepiandrosterone sulfate; OCPs: oral contraceptive pills; SHBG: Sex hormone-binding globulin

Declarations

Ethical considerations

Unethical issues (including plagiarism, informed consent, misconduct, data fabrication, and/or forgery, duplication and/or submission, redundancy, etc.) have been investigated by the authors.

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Figures

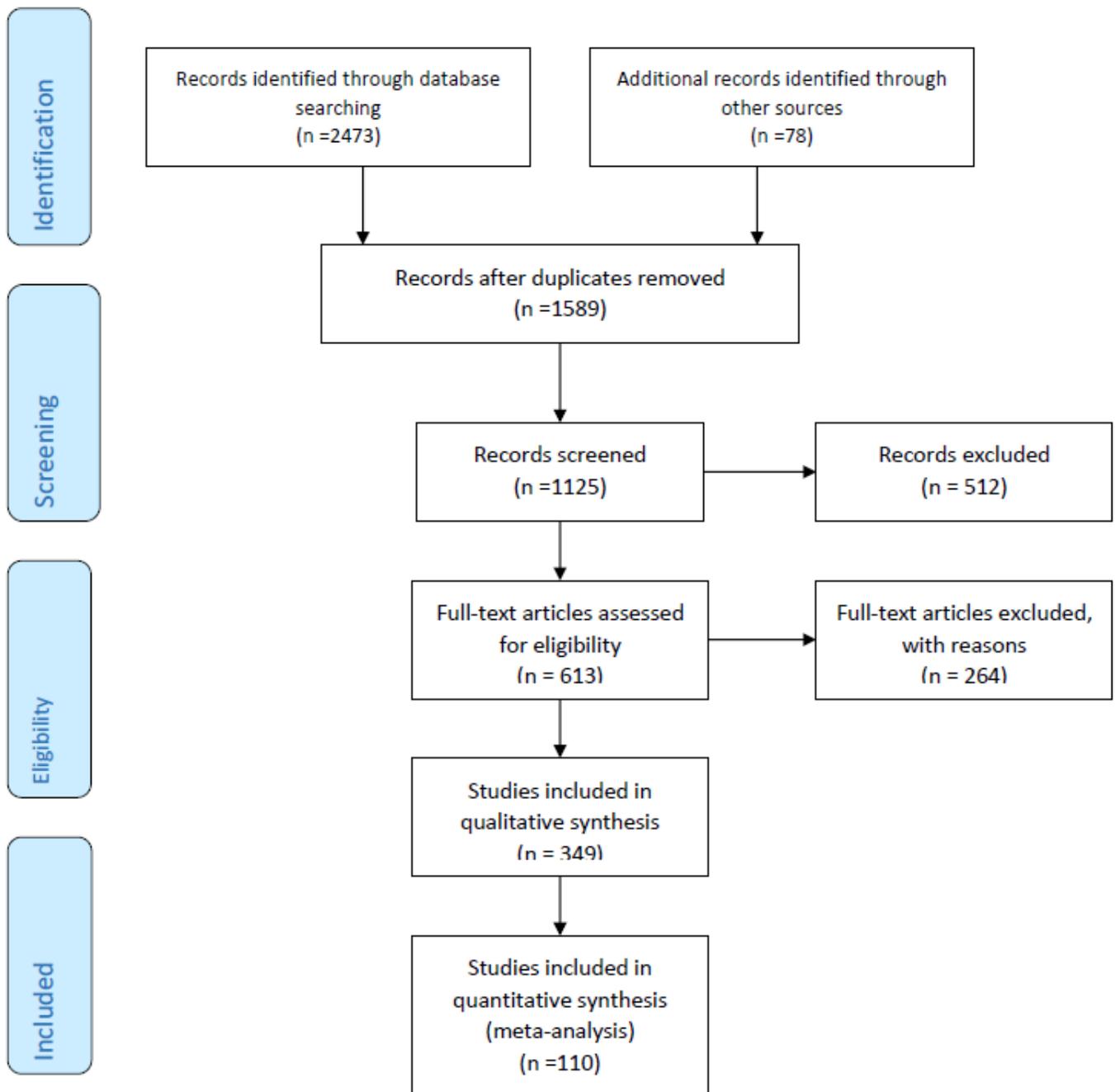


Figure 1

The flow diagram of study selection for the present literature review on the poly cystic ovary syndrome (PCOS), and Alzheimer's disease.