More women than men have Alzheimer’s disease (AD). Retrospective studies suggested that hormone replacement therapy (HRT) might counteract this disparity by reducing the risk of developing dementia. However, a recent, large, prospective study revealed the puzzling result that HRT increased dementia risk. A review of the literature was conducted to generate hypotheses that might explain why more women than men have AD, and how HRT may increase dementia risk. Longer life span of women than men may be the largest factor in the preponderance of women with AD. Longer duration of disease, less vascular dementia, and less testosterone in women than men may also contribute somewhat. HRT might increase dementia risk by several mechanisms: greater risk of strokes, leading to dementia; use of medroxyprogesterone acetate and estrone, which might have somewhat different possible effects on neuronal and cerebrovascular function than may progesterone and estradiol; decrease of free testosterone which might protect against AD; a dose or delivery method perhaps producing drug levels that might lie outside a hypothetical beneficial range; and down-regulation of estrogen receptors on cholinergic neurons, possibly reducing cholinergic activity. Further study is required to discern by which of several possible mechanisms HRT increases dementia risk.

WHY DO MORE WOMEN THAN MEN HAVE ALZHEIMER’S DISEASE?

A review of many studies found that dementia prevalence is 0.3%–1.0% from age 60–64 years, and increases to 42%–68% over age 95, while incidence is 0.08%–0.4% per year for ages 60–64, and 5%–14% per year for ages over 95 (1). As a major cause of dementia, Alzheimer’s disease (AD) incidence also increases dramatically with age, from 0.35% per year at age 65–69 to 7.3% per year at age 85–89 in one study (2). The number of women living with AD is greater than the number of men with AD, whether in developed or developing countries. A cross-sectional study of people older than 40 years living in Mumbai, India found that 0.20% of the 11,875 men and 0.30% of the 12,613 women had AD (see Table 1) (3). A cross-sectional study of Beijing, China, residents found that 1.2% of the 1620 men over 65 and 2.3% of the 2108 women over 65 had AD (4). Of 3214 individuals representative of the population of Toledo, Spain, aged 65 years and older, 3.2% of men and 5.8% of women had AD (5). In a study of Boston, United States, residents older than 65 years, 24% of the 205 men and 32% of the 262 women had AD (6). Although these studies reported widely differing prevalences, perhaps due to the different populations and ages surveyed and different diagnostic criteria used, all the studies found that more women than men had AD.

What might cause this sex difference? Part of the difference may be explained by simply observing the data of the above examples. There are more women than men in these cross-sectional studies of elderly persons, reflecting the fact that, in cities or in developed countries, women live longer than men and thus comprise most of the elderly population. Thus, because AD risk rises dramatically with age, more women than men would be expected to have AD in these studies simply because of the sex difference in longevity. In some rural, developing areas, the sex difference in longevity is reversed (men live longer than women), and the AD-sex ratio is also reversed (more men than women with AD), supporting the above factor (7).

In addition to this longevity effect, might other factors contribute to the fact that more women than men have AD in developed regions? Epidemiological studies have controlled for the sex-longevity effect, yet still showed a sex difference in AD prevalence. The Canadian Study of Health and Aging estimated that, in all of Canada, about 43,000 men and 118,000 women had AD, for a female/male ratio of 2.7, which was reduced to 1.5 after age standardization (8). A combined analysis of 20 studies found a female/male ratio of approximately 6 for severe AD in each 5-year age bracket (9). The European Community Concerted Action on the Epidemiology and Prevention of Dementia Group (EURODEM) study (10) reported that, after age-adjustment, the relative risk for AD for women compared with men was 1.54. Therefore, other factors may also contribute to the excess of women with AD.

One possibility is that men get more vascular dementia (VaD), which would reduce the likelihood of being diagnosed with pure AD by masking early AD symptoms, thus artifactually lowering male AD prevalence (11).
higher rate of cardiovascular disease in men than women may be associated with the higher rate of VaD in men (12). A group of European studies found a nonsignificant trend toward greater VaD incidence in 80- to 84-year-old men than women: 5.2% per year (95% confidence interval [CI]: 2.6–10) vs 3.6% (95% CI: 1.9–6.9) (10). Among incident dementia identified during a prospective study in the United States, 14% of cases among men were VaD, while 8.8% of cases among women were VaD (13). Among demented patients in a Canadian study, 66% of VaD patients were men, but only 36% of AD patients were men (14). Although a diagnosis of mixed AD and VaD is often an option in studies, postmortem confirmation is needed to distinguish among mixed dementia, AD, and VaD with certainty, and the above possibility may contribute slightly to the AD sex difference.

Another hypothesis is that women have a higher incidence of AD than do men. In a group of European studies, the incidence of AD for ages 80–84 was 1.6% per year (95% CI: 1.1–2.3) for men and 2.9% (95% CI: 2.3–3.5) for women (10). In a Swedish study, incidence for ages 75–79 was 1.2% per year for men and 2.0% for women, and for ages over 90, incidence was 1.5% for men and 8.7% for women (15). A study in Baltimore, Maryland found a nonsignificant trend toward higher incidence for women than men over age 55: 1.1% per year (95% CI: 0.9–1.4) for men and 1.4% per year (95% CI: 1.1–1.9) for women (16). However, other studies did not find a sex difference in AD incidence rates. A study in Pittsburgh, Pennsylvania, found an incidence among persons older than 80 years of 6.8% per year for men and 7.1% per year for women, and among persons aged 70–74 years, of 1.5% per year for men and 1.2% per year for women (13). A study of Catholic nuns, priests, and brothers in the United States showed an incidence for ages 80–84 of 5.6% per year for men and 3.6% per year for women; however, such a specialized group of individuals might show rates different than those of the general population (17). A study of Boston, Massachusetts, residents older than 65 years found that 57 of the 362 women and 38 of the 280 men developed AD over an average of 4.3 years, with no significant sex difference in incidence (6). A Canadian study found no sex difference in incidence of AD, with an age- and education-adjusted odds ratio (OR) for AD risk in women versus men of 0.93 (95% CI: 0.67–1.31) (18). A very long study of Framingham, Massachusetts, residents also found no significant sex difference in incidence of AD (2). Why the discrepancies among these studies? Insufficient age adjustment might artifically increase incidence for women. Some studies compared 5-year age groups rather than modeled the risk, but AD risk of disease is not uniform within an age group, and more women than men are at the older, higher-risk end of each group because women generally live longer than men (6). Of the above studies, five seemed to account for this age effect properly, by calculating incidence as a function of age in 1-year increments (6,10,16–18), but three did not report correcting for this age effect (2,13,15). The higher incidence in women reported by one of the latter studies might thus be exaggerated (15).

The number of people with a disease is proportional not only to the incidence, but also to the duration of disease. This implies, a bit counterintuitively, that a lower disease prevalence could be due to higher disease mortality (19). Among nursing home patients with AD, the mortality rate among men (54%) was substantially greater than in women (33%), although this finding might reflect selection in the nursing home population due to men letting their wives go to a nursing home more easily and earlier than women their husbands (20). A review of many studies found several showing that men with AD die faster than women with AD (21). For example, a longitudinal study found that in surviving dementia patients, men decreased from 19% of the patients at the beginning of the study to 7% after 7 years (22). Consistent with this is a summary of 20 studies of elderly white populations worldwide, which found that 12.8% of men and 17.4% of women aged 85–89 had AD of at least mild severity, but found a much greater difference in prevalence of severe cases, 0.4% of men and 2.8% of women, suggesting possibly that men die sooner after their AD becomes severe (9). Therefore, women with AD may live longer than men with AD, increasing the female/male ratio among AD patients. But a longitudinal study in Baltimore, Maryland, found only a slight, nonsignificantly lower life
span in men with AD than in women with AD (23). A study in Boston, Massachusetts, also found only a small, non-significant additional risk of death for men with AD compared with women with AD (OR: 1.07; 95% CI: 0.43–2.7) (6). Therefore, it cannot yet be confirmed that women with AD live longer than men with AD, although most studies suggest it.

In some, but not all studies, a low level of education has been associated with a greater risk of developing AD (24–28). The brain reserve or cognitive reserve hypothesis suggests that education increases synaptic connections so as to delay appearance of AD symptoms (26,29). The detection bias hypothesis suggests that education delays detection of AD to a later pathological stage due to insensitivity of diagnostic procedures (28). Whichever the explanation, the negative association of education with AD risk may affect the sex ratio of AD patients. Decades ago, when the current cohort of elderly people was educated, men tended to spend more years in school than did women. Thus, the lower average level of education among elderly women than men may contribute to the greater number of women than men with AD. Among AD patients, a low level of education has also been associated with a lower mortality rate (28,29). This would increase the duration of disease, further contributing to the excess of women living with AD.

Hormones may be a factor. Could the difference in hormones between men and women cause a greater AD risk in women than men? Studies examining women with or without AD for levels of estradiol, the female estrogen which is most abundant before menopause, showed no consistent association between level and AD (30). Perhaps the estradiol level before menopause affects processes which later lead to AD. Perhaps other hormones affect AD risk. Testosterone is much more abundant in men than women (31), and in several (though not all) studies testosterone levels were positively associated with cognitive function in both elderly men and elderly women, whereas endogenous estradiol levels were either not associated or negatively associated with cognition (32–37). Testosterone treatment improved memory in a mouse model of AD and some aspects of cognition in both elderly men and in women also receiving estrogen (38–40). Hormone suppression treatment in men raised plasma Aβ levels (41). Thus testosterone might protect men more than women from AD risk.

The impression given by the above data suggests that, overall, of the factors contributing to the preponderance of women among AD patients, the longer life span of women than men may be the largest. Longer duration of disease (lower mortality) in women than men, due partly to differences in education and incidence of other diseases, may contribute somewhat. More VaD in men than women, and perhaps higher testosterone levels, might also contribute. The difference in incidence between men and women might be an artifact.

**Why May Hormone Replacement Therapy Cause Dementia?**

Both retrospective and cohort studies found that hormone replacement therapy (HRT) was associated with greatly reduced AD risk. A cohort study in Baltimore, Maryland, found that users of estrogen replacement therapy had a relative risk for AD only 45% that of nonusers, after adjusting for education (42). A summary of studies reported that estrogen replacement therapy was associated with a decreased risk for dementia (43). Several studies found that estrogen users had reduced risk of AD (44), including a prospective cohort study of 8877 residents of Leisure World Laguna Hills, California, showing a reduced risk as a function of duration and dose (45), and a New York cohort study of 1124 women showing a relative risk of 5.8% for AD in estrogen users versus 16% in nonusers, after adjustment for education, ethnicity, and apolipoprotein E genotype (46). A meta-analysis of 14 studies found a net OR of 0.56 (95% CI: 0.46–0.68) for AD risk in HRT users versus nonusers (30). These studies were supported by animal and cell culture research reporting many neuroprotective functions of estrogen (44).

Because of the promising studies described above, along with studies suggesting protective effects of HRT against cancer and heart disease, large, prospective HRT trials were conducted. The Women's Health Initiative Memory Study (WHIMS) treated 2229 women older than 65 years daily for several years with 5/8 mg of estrogen plus 2.5 mg of medroxyprogesterone acetate (MPA), and treated 2303 matched women with placebo. Of the women on HRT, 20 developed AD, but only 12 of the women on placebo developed AD. For all types of dementia, the ratio was 40:21. Thus, this double-blind, randomized, controlled trial showed that HRT significantly increased risk of dementia, with a hazard ratio of 2.1 (95% CI: 1.2–3.5) (47). How might the contradictory results of the previous studies be explained? First, we may explore hypotheses to explain the increased risk found in WHIMS. Then, we can consider how these factors may have produced apparently opposite results in earlier studies.

One hypothesis is that HRT increases risk of strokes, and microinfarcts can contribute to VaD and AD. Although HRT lowers the level of homocysteine, which is associated with risk of both vascular disease and AD, the Women's Health Initiative Memory Study (WHIMS) showed that HRT increased risk of stroke, with a hazard ratio of 1.50 (95% CI: 1.08–2.08) (48,49). As the WHIMS study authors pointed out, silent brain infarcts increased risk of AD in several studies, doubling risk of dementia in one (47). Supporting this hypothesis is the observation in WHIMS that VaD developed in five HRT recipients but in only one placebo recipient (47).

Another possibility is that estrogen might protect against AD, whereas MPA may have an opposite effect. A 2-year cohort study of postmenopausal women showed a trend toward improving cognition among estrogen-only users but a significant decline among estrogen-progestin users, even after controlling for age, education, and surgical menopause (50). One mechanism might be a contribution by MPA to cerebrovascular damage that increases risk of AD. MPA partially counteracted the dilative effect of estrogen on atherosclerotic arteries in monkeys (51). In vitro, MPA displayed a greater oxidant and cytotoxic effect on aortic endothelial cells than did other progestins (52). Studies examining effects of HRT on blood lipid and glucose profiles generally showed more detrimental profiles with combined
Estrogen-MPA use than with estrogen either alone or with micronized progesterone or dydrogesterone (53–55). Another mechanism might be a direct effect on neurons. Estrogen, progesterone, and 19-norprogestosterone, alone or in combination, protected primary hippocampal neurons against glutamate toxicity, but MPA blocked both the protective effect of estrogen and the associated increase in expression of the anti-apoptotic protein Bcl-2 (56). Some steroid hormones are produced in the brain and act on brain neurotransmitter receptors, and different progestins may each have different effects at each class of receptor. Agonists of the \( \sigma_1 \) receptor affect calcium levels and improve cholinergic-dependent memory processes (57). Progesterone was the most potent \( \sigma_1 \) antagonist among steroids tested (\( K_i = 300 \text{ nM} \)), blocking memory-improving effects of \( \sigma_1 \) agonists in mice injected with \( \text{A} \beta_{25-35} \), but the effect of medroxyprogesterone has not been reported (57–59). Acetylcholine-containing neurons are particularly devastated in AD (60–62). Steroids differentially inhibit \( \alpha_2 \beta_2 \), nicotinic acetylcholine receptors (nAChRs), with progesterone more potent than \( 17\beta \)-estradiol (50% inhibition concentration [IC\(_{50}\)] of 1.8 \text{ \mu M vs 25 \mu M}) (63–66). Compared to acute treatment, chronic treatment with steroids blocks nAChRs more strongly and irreversibly (63,67).

Perhaps preferential action of MPA on nAChRs affects the course of AD. However, counter to the hypothesis that estrogen may protect better than combined estrogen-MPA therapy, estrogen users in nursing homes had similar rates of cognitive decline and AD prevalence as did nonusers (68), and WHIMS found a trend toward increased dementia both with combination therapy and with estrogen alone (47,69).

The particular estrogens used in the HRT mix might be important. Estradiol, or E2, is the most abundant estrogen in premenopausal women, but its level falls dramatically after menopause to below that of estrone, or E1 (30,70). Estrogen receptors are more sensitive to E2 than to E1 (30). The conjugated equine estrogens (CEEs) used in WHIMS are mostly E1 sulfate, but most studies of E1 in nondemented women did not find the beneficial cognitive effects seen in most of the E2 studies (30,71). Studies showing neuroprotective effects of estrogen on cultured cells and in animals have generally been conducted using E2, not E1 (72–78). Animal studies of E1 and more human studies of E2 may shed light on this issue.

Another possibility is that testosterone might protect against AD, but estrogen treatment in women is known to increase sex hormone-binding globulin, resulting in a decrease in free testosterone (35,39). In elderly men, free testosterone levels correlate positively with some measures of cognition and negatively with risk of later developing AD (34,35,40,79,80). Sex hormone-binding globulin is increased in men and women with AD in some but not all studies (35–37,81,82). Testosterone reduces A\( \beta \) production in cultured cells, and testosterone level correlates negatively with plasma A\( \beta \) level in men (41,79,83).

Testosterone treatment may improve memory, with mean AD Assessment Scale-cognitive subscale (ADAS-cog) falling from a score of 25 to 16.3 (\( p = .02 \)) in a 1-year pilot study of men with AD and verbal memory improving in a half-year study of hypogonadal men, although a 10-week study of men with early cognitive decline found no cognitive change (84–86). In postmenopausal women, supplementing HRT with methyltestosterone preserved one measure of memory better than did HRT alone (40).

As with any drug, the dose may be important. Studies have found a U-shaped (quadratic) relation between cognitive function and endogenous sex hormone levels (33,79). Therefore, HRT producing hormone levels outside a hypothetical ideal range might cause more harm than good. In microglia stimulated by lipopolysaccharide, low nanomolar concentrations of E2 suppressed superoxide production and phagocytosis, but 1 \text{ \mu M} applied at the same time as lipopolysaccharide had the opposite effect (87). Thus, low levels were anti-inflammatory whereas high levels were inflammatory. Because evidence suggests that inflammation exacerbates damage in AD brain, the dose of HRT drugs given and the manner of administering them (continuous patch vs discrete pill or injection) should be considered (88).

HRT might increase cognitive ability in the short term but decrease it in the long term. In rats, HRT increased choline acetyltransferase (the enzyme that synthesizes acetylcholine) activity and high affinity choline uptake in frontal cortex and hippocampus after 2 weeks (75). However, at longer times the levels returned to normal, and 13 months of continuous estrogen replacement actually reduced hippocampal high affinity choline uptake by 28% compared to untreated controls (75). The mechanism of the long-term effect may involve a decrease in estrogen receptor expression as a compensation for the raised estrogen level. Studies in rats have found reduced brain estrogen receptor levels after estrogen treatment (89–93). Some cholinergic neurons have estrogen receptors, thus estrogen receptor down-regulation might reduce cholinergic activity (75). Because cholinergic neurons are reduced in AD and cholinergic drugs help treat AD, and because the hippocampus is affected early in the course of AD (60–62,94–96), perhaps HRT might improve cognition in normal or demented individuals in short-term studies but worsen cognitive ability over a course of years. Beneficial cognitive effects of HRT on AD patients were seen at 2 months but not after longer treatment in a meta-analysis (71).

However, when looking at HRT in healthy women rather than in AD patients, some studies reported an AD-preventive effect that grew rather than disappeared with longer treatment (46,71,97,98). Perhaps this apparent contradiction might be due to the mechanisms of AD prevention and treatment being different, or due to the age at which HRT is started. With regard to the latter possibility, AD patients are generally much older than the age of menopause, and perhaps starting HRT many years after menopause eliminates possible protective effects of HRT. Women in WHIMS started HRT after age 65 (47). Perhaps this late start kept HRT from preventing AD. However, the mechanism for this putative age effect is not known.

A\( \beta \) peptide can be toxic to neurons, and this neurotoxicity is one possible mechanism of the neuronal damage in AD (99,100). Jun N-terminal kinase (JNK) helps transduce A\( \beta \) toxicity, as shown by neuroprotective effects of JNK inhibitors or mutations in the JNK pathway (101,102). Estrogen activates JNK in breast cancer cells and heart myocytes, suggesting that HRT might thereby increase the
neurotoxic effect of Aβ and accelerate AD (103,104). However, estrogen did not affect JNK activation in rat brain olfactory bulb or mesencephalic neuron cultures, reducing the likelihood that this is the mechanism by which HRT increases dementia risk (105,106).

The above hypotheses might have contributed to the result seen in WHIMS, but why did earlier studies produce apparently opposite results? First, some retrospective studies (107,108) also showed no benefit of HRT on cognition in AD. Some prospective, placebo-controlled, double-blind trials (109–112) also had not shown a beneficial effect of HRT on cognitive ability in AD patients, although it should be noted that these studies were attempts at dementia therapy rather than prevention as with WHIMS. Thus, although meta-analysis showed a protective effect of HRT on AD risk, this effect was not seen consistently in all studies (30). Meta-analysis also showed no positive effect of HRT in maintaining cognitive function in AD patients (71).

Among retrospective studies that did suggest a protective effect, bias in recalling HRT use might have been partly responsible. Studies ascertained previous HRT use by either asking individuals, asking their family or friends, or by checking medical or pharmacy records. Demented persons might not remember their previous drug use, and their under-reporting would result in a lower rate of reported HRT use in AD patients—an artifactually protective effect (30). Family and friends may also not recall or have been aware of HRT use; however, not being demented, they may have better recall than demented persons themselves. Medical records may be most accurate, although might still under-report use among persons who moved or changed doctors, or whose records are unavailable or incomplete. Indeed, a meta-analysis of studies using each of these methods shows such a trend, with studies that directly questioned individuals (46,97,113–116) showing the greatest apparent protective effect (OR = 0.43, 95% CI: 0.32–0.57), those that questioned family or friends (117–122) giving a lesser effect (OR = 0.66, 95% CI: 0.48–0.91), and those relying on records (98,108) showing the least effect (OR = 0.78, 95% CI: 0.51–1.19) (30). Another study using medical records showed a similar effect (OR = 0.77, 95% CI: 0.60–0.99) and directly demonstrated faulty recall of HRT use, with 91% of normal control but only 78% of demented individuals actually on HRT, as reported by medical records, reporting their HRT use (123). Thus, recall bias may have partially contributed to the discrepant results of the various HRT studies.

Physician prescribing behavior might similarly bias results. Doctors may be less likely to prescribe HRT for women who are already demented out of fear of poor compliance or due to inability to obtain consent, and demented patients might be less likely to complain of symptoms or be concerned for their future health, and request HRT (30). Furthermore, physicians may tend to stop HRT in women who develop dementia, which might partly explain results of studies in which longer HRT use was related to lower risk of dementia (46,71,97,98). If prescribing and recall bias are major factors in dementia studies, one worries whether the retrospective studies showing impressive negative associations between AD and use of other drugs, such as anti-inflammatory drugs or statins, will also be contradicted by results of ongoing, controlled, clinical trials.

Another possible factor is differential mortality. The relation of smoking with AD might provide an analogy. Although many studies showed no association, several showed that patients with AD were about half as likely to have smoked cigarettes than were controls, and smokers were half as likely to have AD than were matched nonsmokers (124). However, a population-based cross-sectional and prospective study found no association between AD risk and smoking in the prospective phase, although the cross-sectional phase of the same study had found an apparent protective effect of smoking on AD risk of about the same magnitude as in the above studies (hazard ratio = 0.6, 95% CI: 0.4–1.1), suggesting recall bias and greater mortality among smokers with AD as causes of the discrepant results (125). As noted above in the section on why more women than men have AD, the ratio of women to men with severe AD is much greater than the ratio with mild AD (9). That may be due to the greater risk of other diseases in men than women at a given age, and due to the combination of other diseases with AD perhaps killing patients faster. In one study, nondemented persons who smoked had the same mortality risk as did nonsmokers (hazard ratio = 0.8, 95% CI: 0.5–1.2), but AD patients who smoked had a higher mortality risk than did nonsmokers (hazard ratio = 3.5, 95% CI: 1.4–8.8) (125); this effect would deplete a population of smokers by the time they reach the age of inclusion into case-control AD studies, thus potentially resulting in an artifically negative association of smoking with AD. It is interesting that a larger prospective study found that smoking was associated with a doubling of AD risk, reminiscent of the history of HRT studies (126). HRT has now been associated with greater risk of heart disease, breast cancer, and stroke by the WHI study (127). Although HRT was not associated with greater overall mortality than was placebo, if the combination of HRT with AD shortens survival of AD patients, cross-sectional studies would record a dearth of AD patients who had ever used HRT, which could be misinterpreted as a protective effect (19).

Conclusion

HRT is complex. Several dimensions of HRT might affect dementia risk: effects on other diseases, such as stroke; use of estrogen or other hormones, such as testosterone; inclusion or absence of a progestin; chemical form of progestin, such as MPA or progesterone; chemical form of estrogen, such as E1 or E2; dose of progestin; dose of estrogen; delivery, such as oral or patch; and duration. WHIMS has tested one of the many points in this multidimensional space and has shown a significantly increased risk of dementia. The WHIMS result may be extended to cover more than just one point if the possible explanations for contradictory results of earlier studies are accepted. However, the complexity of HRT leaves many combinations incompletely explored. Further study exploring the roles that hormones play in the development...
of dementia may shed light on its causes, and ultimately its treatment.

ACKNOWLEDGMENTS

I thank Professor Jean Woo for her recommendation for the writing of this review and for her helpful comments.

Address correspondence to Larry W. Baum, PhD, Department of Medicine and Therapeutics, Chinese University of Hong Kong, Shatin, Hong Kong. E-mail: lwbaum@cuhk.edu.hk

REFERENCES


SEX, HORMONES, AND AD


Received March 5, 2004
Accepted March 17, 2004
Decision Editor: John E. Morley, MB, BCh