**Sex differences and Modifiable Dementia Risk Factors Synergistically Influence Memory
over the Adult Lifespan**

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Abstract

INTRODUCTION: More women than men develop Alzheimer's disease, yet women show less age-related episodic memory decline, a contradiction that may be accounted for by modifiable risk factors for dementia.

METHODS: Associations between sex, modifiable dementia risk factors, and cognition were measured in a cross-sectional online sample ($n = 21,840$, ages 18-89).

RESULTS: Across four tests of associative memory and executive functions, only a Face-Name Association task revealed sex differences in age-related decline. Men had worse associative memory than women (the equivalent of four years of aging). Each additional risk factor had the equivalent of three and a half years of aging. Men had greater age-related decline in associative memory than women among those with no to one risk factors, but multiple risk factors eliminated the female advantage.

DISCUSSION: Because the relationship between dementia risk factors and age-related memory decline differs for men and women, sex-specific dementia prevention approaches are warranted.

Keywords: modifiable risk factors, sex differences, dementia, Alzheimer's disease, cognition, episodic memory, associative recognition, executive function, lifespan, age, online data collection, Cogniciti Brain Health Assessment

Research In Context

1. Systematic review: Online databases were searched for papers on sex differences, (cumulative) modifiable risk factors for dementia, or their interaction, on cognition/memory or age-related/lifespan cognitive decline. Papers were reviewed to gain insights into independent and synergistic effects of sex and modifiable risk factors on cognition and cognitive decline.
2. Interpretation: Our findings indicate an interaction between previously demonstrated sex differences and modifiable risk factor cumulative effects on cognition, indicating that a higher vulnerability in women than men to the adverse cognitive impact of accumulating risk factors.
3. Future directions: The findings can be used towards sex-related precision targeting of modifiable risk factors. This research highlights the need to integrate previously independent fields of sex differences and modifiable risk factors to understand prodromal Alzheimer's disease progression and promote healthy brain aging. Future work is needed on (1) objectively measured modifiable risk factors, (2) longitudinal effects of sex, modifiable risk factors, and age, and (3) mechanisms for the interaction between sex and modifiable risk factors.

Background

Recent calls highlight the need to study sex differences in dementia risk, based on findings that women are more likely than men to develop Alzheimer's disease (1, 2, 3), although these differences vary across populations (4, 5). The higher prevalence of Alzheimer's disease in women is contradicted by findings of better memory for events (episodic memory) in women compared to men (6, 7) and less age-related memory decline (6, 7, 8, 9, 10, 11), despite greater episodic memory impairment than normal being a potential precursor to Alzheimer's disease and a defining feature of Alzheimer's disease (12, 13). By contrast, no consistent sex differences occur in cognitive decline of other abilities impacted by Alzheimer's disease (14, 15).

The memory advantage in women suggests that sex alone does not account for the higher risk of dementia in women. Therefore, a critical question towards understanding sex-based differences in dementia aetiology is the extent to which other risk factors interact with sex to explain the difference in memory decline, and subsequently in dementia. Accumulating evidence has established that several modifiable lifestyle behaviours are associated with greater cognitive decline and likelihood of dementia in later life (16, 17, 18), and collectively account for 40% of dementias worldwide (19). Many of these modifiable risk factors vary by sex, leading to growing interest in how modifiable risk factors may explain sex differences in cognitive decline.

Some individual modifiable risk factors differentially influence cognitive decline and risk of dementia in men and women. In women, hypertension (6) and low education (20) are associated with greater episodic memory decline, and hypertension increases the likelihood of mild cognitive impairment (MCI; 21) and dementia (22, 23, 24). Diabetes is associated with greater cognitive impairment in women (25), and smoking is associated with greater episodic memory decline in men (6, 26, 27), but both factors have no sex-specific effects on general

cognitive decline or dementia likelihood (24, 28). Depression is associated with greater cognitive decline and dementia in women on some studies (29, 30), and on men in others (6, 21).

Moreover, newer research increasingly recommends studying combined rather than individual risk factor effects, based on findings that each additional modifiable risk factor lowers cognitive performance (31, 32, 33), and episodic memory (34), regardless of the type of risk factor (a dose-response effect). A cumulative approach also accounts for overlapping effects among individual factors (18, 19).

Emerging consensus also recommends a life-course perspective for modifiable risk factors, based on evidence that modifiable risk factors accumulate over life to influence likelihood of dementia later in life (18, 19). Similarly, the negative dose-response association between combined modifiable risk factors and cognition increases over the adult lifespan (32). A life-course perspective is especially relevant to the interaction between sex and modifiable risk factors, as sex differences in risk factor prevalence vary with age (e.g., diabetes and hypertension are more common in men in mid-adulthood, but equal or more common in women after menopause or in older adulthood; 27, 35, 36), as does the interaction between sex and individual risk factors on cognition (3, 7, 27).

In the current study, we examine the interaction of sex and modifiable risk factors on cognitive performance over the adult lifespan. Studies have confirmed effects of both sex and modifiable risk factors on cognition over the lifespan; what remains to be considered is the synergistic impact of these factors. We examine the interactive effects using an existing web-based dataset (37), collected using an online cognitive assessment designed for sensitivity to aging and age-associated cognitive disorders (38). The assessment was developed to be suitable for older adults, and was psychometrically validated showing acceptable internal consistency,

test-retest reliability, and alternate version reliability (38). It also showed good construct validity compared to traditional neuropsychological tests of the same constructs, and sensitivity at the higher end of function, making it suitable to assess a relatively healthy sample (39).

Our aims were to (a) characterize sex differences in the number and type of modifiable risk factors at different age periods; and (b) test if sex, the number of modifiable risk factors, and age interact to influence cognitive abilities impacted in Alzheimer's disease (specifically, interference control, set shifting, working memory, and associative memory). We predicted that sex and modifiable risk factors would interact to influence cognitive performance over age, specifically on associative memory.

Methods

Participants

We used data collected from 2016-2019 (93,363 attempts) in an existing web-based sample (37). Attempts were excluded if they were repetitions by the same person or had technical issues during data recording, and participants were excluded if they had missing or seemingly inaccurate demographic information or reported health conditions that significantly affect cognition (e.g., brain tumour, cancer, $n = 55,544$ removed). Data were cleaned with between-subjects iterative trimming per age, sex, and cognitive task ($n = 15,979$ removed), using a recursive moving criterion for the standard deviation based on the sample size (40). Extensive data cleaning is needed for online data, especially when not directly collected for a study, to account for low quality or inaccurate recordings (41). The final sample was $n = 21,840$ (age range = 18–89, $M = 64$ years, $SD = 12$; 6,620 men, mean age = 64, $SD = 13$; 15,220 women, mean age = 65, $SD = 12$).

Online Assessment

Participants completed a free web-based assessment in their homes (Cogniciti's Brain Health Assessment, www.cogniciti.com). The assessment consists of a background questionnaire (self-reported age, sex, level of education, and specific health conditions) and four cognitive tasks administered in the following order: (a) a Spatial Working Memory task, measured as the number of clicks to recall locations of six shape pairs over two trials; (b) a Face-Name associative memory task, measured as correctly recognized face and name pairs; (c) a number-word Stroop task of processing speed and interference control, measured as the response time when counting words for incongruent stimuli (e.g., "three three"); and (d) a Letter-Number Alternation task, an online version of the Trails B set shifting task, measured as the total completion time to click alternating numbers and letters in ascending order (for details on task development and validation, see 38).

Associative recognition memory was calculated from accuracy data on the Face-Name Association task. Process dissociation logic (42) was used to parse memory for individual items (item recognition memory) from memory for items and their associations (associative recognition memory), by comparing hits for intact face-name pairs to recombined pairs (for details on this procedure, see 43).

Modifiable Risk Factors

Eight self-reported modifiable risk factors were measured: low education, hearing loss, traumatic brain injury (TBI), alcohol or substance abuse, hypertension, smoking, diabetes, and depression. Based on previous research (19), low education was classified as less than completion of high school, and smoking was classified as being a smoker currently or in the past one to four years.

Composite risk scores were calculated as the total number of risk factors a person reported (0–8) and a risk amount adjusted for variance shared among risk factors (range 0–1). Adjusted risk amount was calculated by multiplying the relative effect of each risk factor (the population attributable fraction for each risk factor from the life-course model; 19), divided by the total population attributable fraction.

Statistical Analyses

Analyses were conducted with the R language and environment for statistical computing. Statistical test results were interpreted alongside effect sizes, because large sample sizes can produce low *p*-values regardless of their theoretical or practical importance.

Prevalence was measured as the percentage of each risk factor and the total risk factors per age period. For prevalence estimates, ages were grouped into young adults (ages 18–44, $n = 1,448$), middle-aged adults (ages 45–65, $n = 8,737$), and older adults (ages 66–89, $n = 11,655$), based on the life-course model for modifiable risk factors (19). Chi-square tests were used to test for sex differences in the frequency of each risk factor per sex and age period.

The interaction of sex and modifiable risk factors on cognition with age was measured using quadratic regression models regressing cognitive performance for each task on age (linear and polynomial terms), sex, and composite risk score (either total risk factors or adjusted risk amount) on cognitive performance. Polynomial models were used as our previous analysis of this dataset indicated curvature in the relationship between age and cognition over the adult lifespan (37). Continuous predictors (age and total risk) were mean-centered so that coefficient estimates could be meaningfully interpreted (20). All variables of interest were included in the final model, to estimate the unique effect of each variable after accounting for any correlations among variables. To account for uneven sample sizes across ages, sex, and risk factors, regression

analyses were weighted by an inverse of the sample size per age, sex, and risk amount. To ensure reliability of obtained results, risk amounts were also removed from regression analyses if there were fewer than 25 people for that amount per age decade, sex, and number of risk factors (i.e., over four risk factors for all ages, over two risk factors for ages 18-50, and over three risk factors for ages 80-89; $n = 94$).

Results

Prevalence of Risk Factors By Sex

The number of risk factors increased with age. Women had fewer risk factors than men for all age periods (Figure 1). In young adults, 54% of men and 61% of women had no risk factors. In middle-aged adults, 43% of men and 48% of women had no risk factors. In older adults, 22% of men and 28% of women had no risk factors.

Chi-square tests revealed significant differences in the distribution of individual risk factors between sexes for young adults, middle aged adults, and older adults (Figure 2), $\chi^2(7, N = 1,448) = 24.3, p = .001$; $\chi^2(7, N = 8,737) = 136.1, p < .0001$; $\chi^2(7, N = 11,665) = 198.9, p < .0001$, respectively, with medium effect sizes (44), $\phi_c = 0.33$, $\phi_c = 0.33$, and $\phi_c = 0.34$, respectively. Post-hoc Pearson residual analyses revealed significant differences were driven by different risk factors per age group, all p 's $< .05$. In young adults, smoking was more common in men. In middle-aged adults, hearing loss and substance abuse were more common in men. In older adults, diabetes, hearing loss, smoking, and substance abuse were more common in men, hypertension was more common in women. Depression was more common in women at all age periods.

Effect of Total Risk Factors and Sex on Age-Related Decline in Cognition

Effects of age and risk factors were present on all tasks (for more detail, see 32).

Likewise, sex differences in cognitive performance and age by sex differences in cognitive performance were found for all tasks, all p 's $< .0001$. However, effect sizes were minimal for all tasks except Face-Name Association, $R^2 = .01$ (a small effect size; 45).

Quadratic regression revealed that age (linear and polynomial terms), sex, total risk factors, and their interactions, explained a significant amount of the variance in the associative recognition rate on the Face-Name Association task, $F(8, 21697) = 775.9$, $p < .0001$, with a medium effect size, $R^2 = .22$ (Table 1). The complete model had main effects of age, sex, and total risk factors. Across participants, each year of age was associated with a drop in associative recognition rates ($b = -0.9$). Moreover, each additional risk factor was associated with a lowering in associative recognition rates equivalent to three and half years of aging (the main effect of total risk factors, $b = -3.3$, is over three and half times larger than the main effect of age, $b = -0.9$). Being male was also associated with lower associative recognition rates equivalent to four years of aging (the main effect of sex, $b = 3.6$, is over four times larger than the main effect of age, $b = -0.9$).

Main effects were qualified by significant two-way interactions of age and sex (worse performance in men as age increased), and of age and total risk factors (worse performance for each additional risk factor as age increased), although both of these were qualified by a three-way interaction between age, sex, and total risk factors. Post-hoc simple slopes analyses revealed a stronger negative effect of age on performance in men ($\beta = -0.9$, $SE = 0.02$) than women ($\beta = -0.8$, $SE = 0.02$), $p < .0001$, but these sex differences were moderated by the number of risk factors. Among those with no or one risk factor, men had a significantly stronger negative effect

of age on performance compared to women ($\beta = -0.6$, $SE = 0.03$ for men, and $\beta = -0.5$, $SE = 0.02$ for women, $p < .001$; and $\beta = -0.5$, $SE = 0.03$ for men, and $\beta = -0.9$, $SE = 0.03$ for women, $p < .001$; respectively). By contrast, among those with two, three, or four modifiable risk factors, the negative effect of age on performance did not differ between men and women ($\beta = -0.5$, $SE = 0.03$ for men, and $\beta = -0.5$, $SE = 0.03$ for women, $p > .05$; $\beta = -0.8$, $SE = 0.06$ for men, and $\beta = -1.0$, $SE = 0.06$ for women, $p > .05$; and $\beta = -1.0$, $SE = 0.1$ for men, and $\beta = -1.0$, $SE = 0.1$ for women, $p > .05$; respectively). Thus, the cumulative effect of multiple modifiable risk factors on age-related cognitive decline, compared to none or one, was significantly larger in women ($\Delta\beta = 0.5$, $SE = 0.11$) than men ($\Delta\beta = 0.4$, $SE = 0.11$), $p < .0001$. Similar results were found on the Face-Name Association task for the adjusted risk amount, indicating that the relationship persists after controlling for shared variance among risk factors (Supplemental Figure 1). Quadratic regression revealed that age (with linear and polynomial terms), sex, adjusted risk amount, and their interactions, explained a significant amount of the variance in the associative recognition rate on the Face-Name Association task, $F(8, 21755) = 660.6$, $p < .0001$, with a medium effect size, $R^2 = .20$ (Table 2).

Discussion

Using a cross-sectional online adult lifespan sample, we found greater decreases in associative recognition with age in men than women (equivalent to three and half years of aging), and in people with more modifiable risk factors (equivalent to four years of aging per risk factor). We also found a novel small synergistic association between modifiable risk factors and sex— Among those with no to one risk factor, men show larger age-related decline in associative memory than women, but among those with multiple risk factors, both men and women show the

same decline. Thus, while women have better memory than men across all ages and smaller age-related decline in associative memory, the female memory advantage is not found in individuals with multiple modifiable risk factors. This finding was also evident after controlling for communality among risk factors.

The elimination of the female memory advantage is particularly striking as larger episodic memory decline than average is a sign of Alzheimer's disease (12, 13), and women are more likely than men to have Alzheimer's disease (1, 2, 3). The higher rates of Alzheimer's disease in women were previously contradicted by the finding of less episodic memory decline in women than men (6, 7, 8, 9, 10, 11, 27). We speculate that accounting for modifiable risk factors clarifies this contradiction. There is a greater decrease in recognition rates across age from no to many risk factors in women than men. The observed sex and modifiable risk factors interaction may be at least partially explained by shifts in hormonal levels with age, such as estrogen loss in menopause, possibly interacting with modifiable risk factors (46, 47).

The interaction of sex with age was of a smaller magnitude than the interaction of modifiable risk factors with age, which is encouraging, as modifiable risk factors are changeable by definition, while sex is not. People with many risk factors show the same negative association between age and associative memory regardless of sex. Thus modifiable risk factors must be studied in men and women alike, as both sexes have an increased risk for developing Alzheimer's disease as age increases (48).

We found sex differences across age for associative recognition, but not for interference control, set shifting/processing speed, and spatial working memory. Our findings align with past observations of better episodic memory and less age-related decline in women than men, and a

lack of consistent sex differences on the other cognitive abilities measured (14, 15). Further work is needed to confirm our findings using several cognitive measures per ability.

Future work could provide insights into Alzheimer's disease prevention by examining if sex also has protective effects with measured modifiable risk factors. For example, while low education and excess alcohol consumption are risk factors for dementia (19), high education and moderate alcohol consumption are more common in older adult women who perform above normal cognitive performance for their age (9). It would also be interesting to explore if modifiable risk factors and sex further interact with non-modifiable risk factors for Alzheimer's disease that show sex differences, such as apolipoprotein E genotype, APOE, β -amyloid burden, A β , or regional tau pathology (48, 49, 50).

A representative population sample is needed to confirm the sex differences in prevalence of individual modifiable risk factors. However, our findings align with published work on depression and late-life hypertension being more common in women, and smoking and substance abuse being more common in men (2, 3, 22, 35). The different prevalence of factors in men versus women suggests that primary prevention messages could be tailored towards sex-specific common factors.

The prevalence of modifiable risk factors is independent of their influence on cognitive decline. Men had more risk factors than women (a large effect size), but the effect of multiple risk factors on age-related decline in associative memory was larger in women (a small effect size). Similarly, past work shows a factor could occur more frequently in men but have a larger impact in women (e.g., midlife hypertension; 23), or a factor could occur with equal frequency in men and women but have a stronger effect in women (e.g., APOE, A β ; 48, 49).

Using a self-administered online assessment enabled collection of a large sample of different ages, but a limitation was that modifiable risk factors were self-reported. The sample had few risk factors, although the obtained prevalence estimates align with previously published work of low risk factor prevalence in healthy adults (31). While modifiable risk factors and sex may have a larger impact on cognitive decline in people at greater risk for Alzheimer's disease, it is notable to demonstrate these effects even in a relatively healthy sample.

Sex is a key variable in explaining the heterogeneity of Alzheimer's disease, and developing a precision medicine approach (35). As sex is not modifiable, considering how it interacts with modifiable risk factors will help target early treatment of Alzheimer's disease. We used cross-sectional data, and future work can build on this foundation to assess longitudinal effects to determine causality and remove cohort effects. The observed novel synergistic association of sex differences and modifiable risk factors on age-related decline in associative memory underscores the importance of modifying lifestyle behaviours linked to dementia in both women and men.

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References

1. Alzheimer's Association. (2020). 2020 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, 16(3), 391-460. <https://doi.org/10.1002/alz.12068>

2. Andrew, M. K., & Tierney, M. C. (2018). The puzzle of sex, gender and Alzheimer's disease: Why are women more often affected than men? *Women's Health*, 14, 1745506518817995. <https://doi.org/10.1177/1745506518817995>
3. Podcasy, J. L., & Epperson, C. N. (2016). Considering sex and gender in Alzheimer disease and other dementias. *Dialogues in Clinical Neuroscience*, 18(4), 437-446. <http://doi.org/10.31887/DCNS.2016.18.4/cepperson>
4. Fiest, K. M., Roberts, J. I., Maxwell, C. J., Hogan, D. B., Smith, E. E., Frolkis, A., Cohen, A., Kirk, A., Pearson, D., Pringsheim, T., Venegas-Torres, A., & Jetté, N. (2016). The prevalence and incidence of dementia due to Alzheimer's disease: A systematic review and meta-analysis. *Canadian Journal of Neurological Sciences*, 43(S1), S51-S82. <https://doi.org/10.1017/cjn.2016.36>
5. Perera, G., Pedersen, L., Ansel, D., Alexander, M., Arrighi, H. M., Avillach, P., Foskett, N., Gini, R., Gordon, M. F., Gungabissoon, U., Mayer, M., Novak, G., Rijnbeek, P., Trifiro, G., van der Lei, J., Visser, P. J., & Stewart, R. (2018). Dementia prevalence and incidence in a federation of European Electronic Health Record databases: The European Medical Informatics Framework resource. *Alzheimer's & Dementia*, 14(2), 130-139. <https://doi.org/10.1016/j.jalz.2017.06.2270>
6. Anstey, K. J., Peters, R., Mortby, M. E., Kiely, K. M., Eramudugolla, R., Cherbuin, N., Huque, H., & Dixon, R. A. (2021). Association of sex differences in dementia risk factors with sex differences in memory decline in a population-based cohort spanning 20–76 years. *Scientific Reports*, 11(1), 1-10. <https://doi.org/10.1038/s41598-021-86397-7>
7. Bloomberg, M., Dugravot, A., Dumurgier, J., Kivimaki, M., Fayosse, A., Steptoe, A., Britton, A., Singh-Manoux, A., & Sabia, S. (2021). Sex differences and the role of

- education in cognitive ageing: Analysis of two UK-based prospective cohort studies. *The Lancet Public Health*, 6(2), e106-e115. [https://doi.org/10.1016/S2468-2667\(20\)30258-9](https://doi.org/10.1016/S2468-2667(20)30258-9)
8. MacAulay, R. K., Halpin, A., Cohen, A. S., Calamia, M., Boeve, A., Zhang, L., Brouillette, R. M., Foil, H. C., Bruce-Keller, A., & Keller, J. N. (2020). Predictors of heterogeneity in cognitive function: APOE-e4, sex, education, depression, and vascular risk. *Archives of Clinical Neuropsychology*, 35(6), 660-670. <https://doi.org/10.1093/arclin/acia014>
9. Maccora, J., Peters, R., & Anstey, K. J. (2021). Gender differences in superior-memory SuperAgers and associated factors in an Australian cohort. *Journal of Applied Gerontology*, 40(4), 433-442. <https://doi.org/10.1177/0733464820902943>
10. McCarrey, A. C., An, Y., Kitner-Triolo, M. H., Ferrucci, L., & Resnick, S. M. (2016). Sex differences in cognitive trajectories in clinically normal older adults. *Psychology and Aging*, 31(2), 166–175. <https://doi.org/10.1037/pag0000070>
11. Olaya, B., Bobak, M., Haro, J. M., & Demakakos, P. (2017). Trajectories of verbal episodic memory in middle-aged and older adults: Evidence from the English Longitudinal Study of Ageing. *Journal of the American Geriatrics Society*, 65(6), 1274-1281. <https://doi.org/10.1111/jgs.14789>
12. Anderson, N. D. (2019). State of the science on mild cognitive impairment (MCI). *CNS Spectrums*, 24(1), 78–87. <https://doi.org/10.1017/S1092852918001347>
13. Gallagher, M., & Koh, M. T. (2011). Episodic memory on the path to Alzheimer's disease. *Current Opinion in Neurobiology*, 21(6), 929-934. <https://doi.org/10.1016/j.conb.2011.10.021>

14. Ferreira, L., Ferreira Santos-Galduróz, R., Ferri, C. P., & Fernandes Galduroz, J. C. (2014). Rate of cognitive decline in relation to sex after 60 years-of-age: A systematic review. *Geriatrics & Gerontology International*, 14(1), 23-31.
<https://doi.org/10.1111/ggi.12093>
15. Li, R., & Singh, M. (2014). Sex differences in cognitive impairment and Alzheimer's disease. *Frontiers in Neuroendocrinology*, 35(3), 385-403.
<https://doi.org/10.1016/j.yfrne.2014.01.002>
16. Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., & Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer's & Dementia*, 11(6), 718–726.
<https://doi.org/10.1016/j.jalz.2015.05.016>
17. Larsson, S. C., & Markus, H. S. (2018). Does treating vascular risk factors prevent dementia and Alzheimer's disease? A systematic review and meta-analysis. *Journal of Alzheimer's Disease*, 64(2), 657-668. <https://doi.org/10.3233/JAD-180288>
18. Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Larson, E. B., Ritchie, K., Rockwood, K., Sampson, E. L., Samus, Q., Schneider, L. S., Selbaek, G., Teri, L., & Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet*, 390(10113), 2673–2734.
[https://doi.org/10.1016/S0140-6736\(17\)31363-6](https://doi.org/10.1016/S0140-6736(17)31363-6)
19. Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L., Howard, R., Kales, H. C., Larson, E. B., Ritchie, K., Rockwood,

- K., Sampson, E. L., Samus, Q., Schneider, L. S., Selbaek, G., Teri, L., & Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, 396(10248), 413–446. [https://doi.org/10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6)
20. Reifegerste, J., Veríssimo, J., Rugg, M. D., Pullman, M. Y., Babcock, L., Gleib, D. A., Weinstein, M., Goldman, N., & Ullman, M. T. (2021). Early-life education may help bolster declarative memory in old age, especially for women. *Aging, Neuropsychology, and Cognition*, 28(2), 218-252. <https://doi.org/10.1080/13825585.2020.1736497>
21. Roberts, R. O., Cha, R. H., Mielke, M. M., Geda, Y. E., Boeve, B. F., Machulda, M. M., Knopman, D. S. & Petersen, R. C. (2015). Risk and protective factors for cognitive impairment in persons aged 85 years and older. *Neurology*, 84(18), 1854-1861. <https://doi.org/10.1212/WNL.0000000000001537>
22. Blanken, A. E., & Nation, D. A. (2020). Does gender influence the relationship between high blood pressure and dementia? Highlighting areas for further investigation. *Journal of Alzheimer's Disease*, 78 (1), 23-48. <https://doi.org/10.3233/JAD-200245>
23. 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(18), 1886-1893. <https://doi.org/10.1212/WNL.0000000000004602>
24. Gong, J., Harris, K., Hackett, M., Peters, S. A., Brodaty, H., Cooper, M., Hamet, P., Harrap, S., Mancina, G., MacMahon, S., Chalmers, J., & Woodward, M. (2021). Sex differences in risk factors for cognitive decline and dementia, including death as a

- competing risk, in individuals with diabetes: Results from the ADVANCE trial. *Diabetes, Obesity and Metabolism*, 23(8), 1775-1785. <https://doi.org/10.1111/dom.14391>
25. Chireh, B., & D'Arcy, C. (2020). A comparison of the prevalence of and modifiable risk factors for cognitive impairment among community-dwelling Canadian seniors over two decades, 1991–2009. *PLoS One*, 15(12), e0242911.
<https://doi.org/10.1371/journal.pone.0242911>
 26. Lipnicki, D. M., Sachdev, P. S., Crawford, J., Reppermund, S., Kochan, N. A., Trollor, J. N., Draper, B., Slavin, M. J., Kang, K., Lux, O., Mather, K. A., & Brodaty, H. (2013). Risk factors for late-life cognitive decline and variation with age and sex in the Sydney Memory and Ageing Study. *PLoS One*, 8(6), e65841.
<https://doi.org/10.1371/journal.pone.0065841>
 27. van Zutphen, E. M., Rijnhart, J. J. M., Rhebergen, D., Muller, M., Huisman, M., Beekman, A., Kok, A., & Appelman, Y. (2021). Do cardiovascular risk factors and cardiovascular disease explain sex differences in cognitive functioning in old age? *Journal of Alzheimer's Disease*, 80(4), 1643-1655. <https://doi.org/10.3233/JAD-201173>
 28. Arntzen, K. A., Schirmer, H., Wilsgaard, T. and Mathiesen, E. B. (2011) Impact of cardiovascular risk factors on cognitive function: The Tromso study. *European Journal of Neurology*, 18, 737-743 <https://doi.org/10.1111/j.1468-1331.2010.03263.x>
 29. Gong, J., Harris, K., Peters, S. A., & Woodward, M. (2021b). Sex differences in the association between major cardiovascular risk factors in midlife and dementia: A cohort study using data from the UK Biobank. *BMC Medicine*, 19(1), 1-11.
<https://doi.org/10.1186/s12916-021-01980>

30. Kim, S., Kim, M. J., Kim, S., Kang, H. S., Lim, S. W., Myung, W., Lee, Y., Hong, C. H., Choi, S. H., Na, D. L., Seo, S. W., Ku, B. D., Kim, S. Y., Jeong, J. H., Park, S. A., Carroll, B. J., & Kim, D. K. (2015). Gender differences in risk factors for transition from mild cognitive impairment to Alzheimer's disease: A CREDOS study. *Comprehensive Psychiatry*, 62, 114-122. <https://doi.org/10.1016/j.comppsy.2015.07.002>
31. Adams, M. L., & Grandpre, J. (2016). Dose-response gradients between a composite measure of six risk factors and cognitive decline and cardiovascular disease. *Preventive Medicine*, 91, 329–334. <https://doi.org/10.1016/j.ypmed.2016.09.004>
32. LaPlume, A. A., McKetton, L., Levine, B., Anderson, N. D., & Troyer, A. K. D. (In review). The adverse effect of modifiable dementia risk factors on cognition amplify across the adult lifespan.
33. Peters, R., Booth, A., Rockwood, K., Peters, J., D'Este, C., & Anstey, K. J. (2019). Combining modifiable risk factors and risk of dementia: A systematic review and meta-analysis. *British Medical Journal*, 9(1), e022846. <http://doi.org/10.1136/bmjopen-2018-022846>
34. Olaya, B., Moneta, M. V., Bobak, M., Haro, J. M., & Demakakos, P. (2019). Cardiovascular risk factors and memory decline in middle-aged and older adults: The English Longitudinal Study of Ageing. *BMC Geriatrics*, 19(1), 337. <https://doi.org/10.1186/s12877-019-1350-5>
35. Ferretti, M. T., Iulita, M. F., Cavedo, E., Chiesa, P. A., Dimech, A. S., Chadha, A. S., Baracchi, F., Girouard, H., Misoch, S., Giacoboni, E., Depypere, H., & Hampel, H. (2018). Sex differences in Alzheimer disease—the gateway to precision medicine. *Nature Reviews Neurology*, 14(8), 457-469. <https://doi.org/10.1038/s41582-018-0032-9>

36. Kim, M. Y., Kim, K., Hong, C. H., Lee, S. Y., & Jung, Y. S. (2018). Sex differences in cardiovascular risk factors for dementia. *Biomolecules & Therapeutics*, 26(6), 521-532
<https://doi.org/10.4062/biomolther.2018.159>
37. LaPlume, A. A., Anderson, N. D., McKetton, L., Levine, B., & Troyer, A. K. (2021). When I'm 64: Age -related variability in over 40,000 online cognitive test takers. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. Advance online publication. <https://doi.org/10.1093/geronb/gbab143>
38. Troyer, A. K., Rowe, G., Murphy, K. J., Levine, B., Leach, L., & Hasher, L. (2014). Development and evaluation of a self-administered on-line test of memory and attention for middle-aged and older adults. *Frontiers in Aging Neuroscience*, 6.
<https://doi.org/10.3389/fnagi.2014.00335>
39. Paterson, T., Sivajohan, B., Gardner, S., Binns, M. A., Stokes, K. A., Freedman, M., Levine, B., & Troyer, A. K. (2021). Accuracy of a self-administered online cognitive assessment in detecting amnesic mild cognitive impairment. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, gbab097. Advance online publication. <https://doi.org/10.1093/geronb/gbab097>
40. Grange, J. A. (2015). trimr: An implementation of common response time trimming methods. R package version 1.0.1. <https://CRAN.R-project.org/package=trimr>
41. Buchanan, E.M., & Scofield, J.E. (2018). Methods to detect low quality data and its implication for psychological research. *Behaviour Research Methods*, 50, 2586–2596.
<https://doi.org/10.3758/s13428-018-1035-6>

42. Jacoby, L. L. (1991). A process dissociation framework: Separating automatic from intentional uses of memory. *Journal of Memory and Language*, 30(5), 513–541.
[https://doi.org/10.1016/0749-596X\(91\)90025-F](https://doi.org/10.1016/0749-596X(91)90025-F)
43. Troyer, A. K., Murphy, K. J., Anderson, N. D., Craik, F. I. M., Moscovitch, M., Maione, A., & Gao, F. (2012). Associative recognition in mild cognitive impairment: Relationship to hippocampal volume and apolipoprotein E. *Neuropsychologia*, 50(14), 3721–3728.
<https://doi.org/10.1016/j.neuropsychologia.2012.10.018>
44. Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum.
45. Gravetter, F.J., & Wallnau, L.B. (2009). Statistics for the Behavioural Sciences (8th ed.). Wadsworth CENGAGE Learning: Belmont, CA, USA.
46. Georgakis, M. K., Kalogirou, E. I., Diamantaras, A. A., Daskalopoulou, S. S., Munro, C. A., Lyketsos, C. G., Skalkidou, A., & Petridou, E. T. (2016). Age at menopause and duration of reproductive period in association with dementia and cognitive function: A systematic review and meta-analysis. *Psychoneuroendocrinology*, 73, 224-243.
<https://doi.org/10.1016/j.psyneuen.2016.08.003>
47. Gurvich, C., Hoy, K., Thomas, N., & Kulkarni, J. (2018). Sex differences and the influence of sex hormones on cognition through adulthood and the aging process. *Brain Sciences*, 8(9), 163. <https://doi.org/10.3390/brainsci8090163>
48. Mielke, M. M. (2018). Sex and gender differences in Alzheimer’s disease dementia. *The Psychiatric Times*, 35(11), 14-17.
49. Buckley, R. F., Mormino, E. C., Rabin, J., S., Hohman, T. J., Landau, S., Hanseeuw, B. J., Jacobs, H. I. L., Papp, K. P., Amariglio, R. E., Properzi, M. J., Schultz, A. P., Kirn, D.,

Scott, M. R., Hedden, T., Farrell, M., Price, J., Chhatwal, J., Rentz, D., Villemagne, V. L., Johnson, K. A., & Sperling, R. A. (2019). Sex, amyloid, and APOE ϵ 4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three well-characterized cohorts. *Alzheimer's & Dementia*, 14(9), 1193-1203.

<https://doi.org/10.1001/jamaneurol.2018.4693>

50. Buckley, R. F., Scott, M. R., Jacobs, H. I., Schultz, A. P., Properzi, M. J., Amariglio, R. E., Hohman, T. J., Mayblyum, D. V., Rubinstein, Z. B., Manning, L., Hanseeuw, B. J., Mormino, E. C., Rentz, D. M., Johnson, K. A., & Sperling, R. A. (2020). Sex mediates relationships between regional tau pathology and cognitive decline. *Annals of Neurology*, 88(5), 921-932. <https://doi.org/10.1002/ana.25878>

Figure 1

Prevalence (% frequency) of Total Risk Factors per Age Period per Sex.

Figure 2

Prevalence (% frequency) of Individual Risk Factors per Age Period per Sex.

Figure 3

Dose-Response Association of Total Risk Factors and Age per Sex on a Face-Name Associative Recognition Task.

Note. Each dot shows the mean performance per number of risk factors. The lines show fitted polynomial curves. The grey shading around the curves indicates a 95% confidence interval envelope. Smaller scores indicate worse performance on the Face-Name Task.

Table 1*Regression Estimates for Age, Sex, and Total Risk Factors on the Face-Name Association Task*

	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Age	-0.88	0.02	-60.0	<.0001***
Age ²	-0.01	0.0005	-25.9	<.0001***
Total Risk Factors	-3.32	0.21	-16.0	<.0001***
Sex	3.64	0.44	8.45	<.0001***
Age x Sex	0.09	0.02	4.49	<.0001***
Age x Total Risk Factors	0.06	0.01	4.64	<.0001***
Sex x Total Risk Factors	0.45	0.28	1.60	.11
Age x Sex x Total Risk Factors	-0.06	0.02	-3.75	.0002**

*** $p < .0001$, ** $p < .001$, * $p < .05$

Table 2*Regression Estimates for Age, Sex, and Adjusted Risk Amount on the Face-Name Association**Task*

	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Age	-0.93	0.02	-44.1	<.0001***
Age ²	-0.01	0.0006	-21.5	<.0001***
Adjusted Risk Amount	-0.24	1.56	-15.1	<.0001***
Sex	3.60	0.47	7.60	<.0001***
Age x Sex	0.10	0.02	4.23	<.0001***
Age x Adjusted Risk Amount	0.58	0.11	5.32	<.0001***
Sex x Adjusted Risk Amount	7.27	2.07	3.52	.0004**
Age x Sex x Adjusted Risk Amount	-0.33	0.14	-2.39	.017*

*** $p < .0001$, ** $p < .001$, * $p < .05$

Supplemental Figure 1

Dose-Response Association of Adjusted Risk Amount and Age on Cognitive Performance per Sex.

Note. Each dot shows the mean performance per number of risk factors. The lines show fitted polynomial curves. The grey shading around the curves indicates a 95% confidence interval envelope. Smaller scores indicate worse performance on the Face-Name Task.