

# Sex and age influence the inflammatory response to vascular risk management in older adults: secondary analysis to risk reduction to Alzheimer's disease (rrAD) clinical trial

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## Background

Cardiovascular risk factors such as hypertension and dyslipidemia, in concert with inflammaging (chronic low-grade inflammation associated with aging) are significant risk factors for Alzheimer's disease and related dementias (ADRD). Evidence shows that physical exercises reduce those risk factors and may slow cognitive decline. Additionally, management of hypertension and dyslipidemia through drug therapies has also been proven to be effective. However, the effects of physical exercise and drug therapies to manage those risk factors to prevent or slow cognitive decline are not clear. While management of these vascular risks is known to reduce these factors, and may slow cognitive decline, the impact of physical exercise and drug therapies on systemic inflammation in high-risk populations remains unclear. Furthermore, potential sex-based differences in these inflammatory responses have yet to be established.

## Goal

Investigate the sex effects of independent and combined effects of Intensive pharmacological Reduction of Vascular Risk factors (IRVR) i.e. hypertension and dyslipidemia and aerobic exercise (Ex) on inflammation and cognitive function.

## Approach

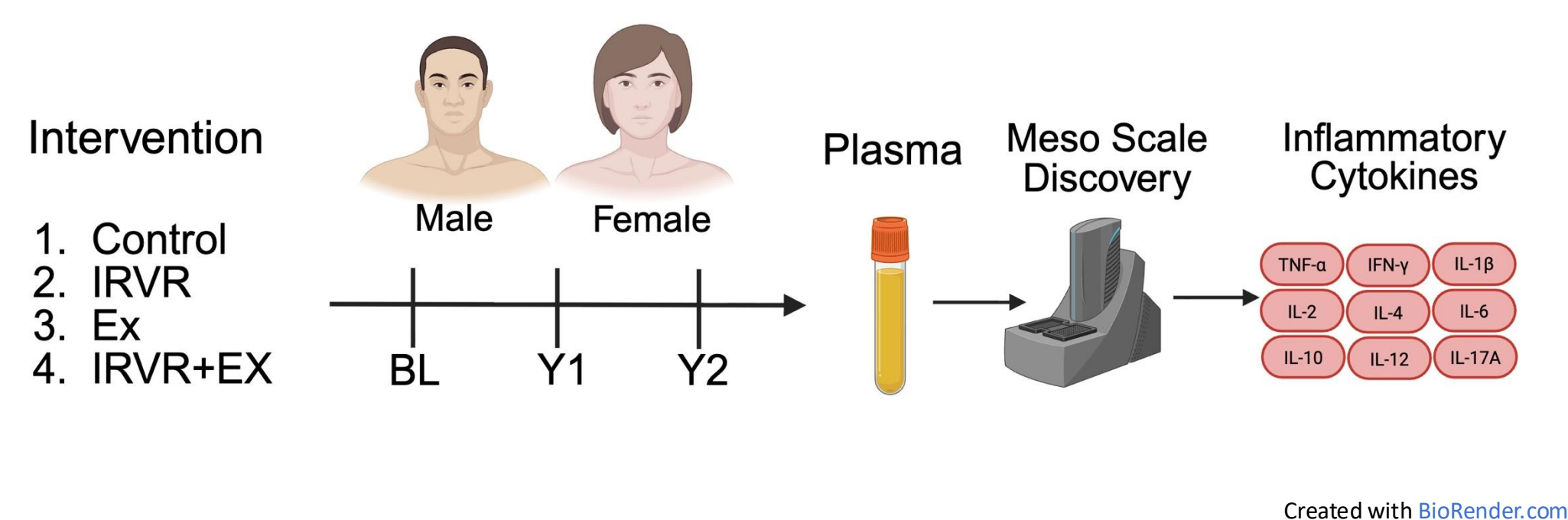


**Figure 1: Illustration of the materials and methods used for this project.** The risk reduction for Alzheimer's disease (rrAD) two-year clinical trial NCT02913664; completed Jan. 2022; n=480 total. Inflammatory cytokines were quantified using the Meso Scale Discovery S-plex proinflammatory cytokines panel 1. Participants were from four institutions: University of Texas Southwestern Medical Center/Texas Health Presbyterian Hospital Dallas, University of Kansas Alzheimer's Disease Center, Pennington Biomedical Research Center, Washington University School of Medicine in St. Louis

## Selected References

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- Merz, A. and S. Cheng, Regarding sex differences in cardiovascular ageing: let us not forget iron. Heart, 2016. **102**(17): p. 1418-9
- Zhang, R., et al., Effects of Exercise and Intensive Vascular Risk Reduction on Cognitive Function in Older Adults: A Randomized Clinical Trial. JAMA Neurol, 2026. **83**(5): p. 424-434

## Acknowledgements

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## Participants

Table 1: Participants Demographics

| Interventions                               | Standard Care (n=129) | Exercise (n=122) | IRVR (n=109) | IRVR+Exercise (n=120) |
|---------------------------------------------|-----------------------|------------------|--------------|-----------------------|
| <b>Characteristics</b>                      |                       |                  |              |                       |
| Age (years) mean (SD)                       | 69.4(6.4)             | 68.2(5.8)        | 68.6(6.3)    | 68.9(5.6)             |
| Years of education, mean (%)                | 16.5(2.2)             | 16.4(2.2)        | 16.2(2.1)    | 16.1(2.4)             |
| Sex                                         |                       |                  |              |                       |
| Female, n(%)                                | 79(61.2)              | 78(63.9)         | 69(63.3)     | 76(63.3)              |
| Male, n(%)                                  | 50(38.6)              | 44(36.1)         | 40(36.7)     | 44(36.7)              |
| Ethnicity                                   |                       |                  |              |                       |
| Hispanic, n(%)                              | 3(2.3)                | 5(4.1)           | 3(2.8)       | 7(5.8)                |
| Non-hispanic, n(%)                          | 126(97.7)             | 117(95.9)        | 106(97.2)    | 113(94.2)             |
| Race                                        |                       |                  |              |                       |
| White, n(%)                                 | 107(82.9)             | 108(88.5)        | 91(83.5)     | 102(85.0)             |
| Black or African American, n(%)             | 18(13.9)              | 12(9.8)          | 14(12.8)     | 14(11.7)              |
| Other, n(%)                                 | 4(3.1)                | 2(1.6)           | 4(3.7)       | 4(3.3)                |
| BMI, mean (SD)                              | 30.3(5.0)             | 30.4(5.7)        | 30.1(5.5)    | 30.4(5.3)             |
| MMSE, mean (SD)                             | 28.8(1.1)             | 29.1(1.0)        | 29.2(1.0)    | 29.1(1.0)             |
| Hypertension, n(%)                          | 50(38.8)              | 47(38.5)         | 49(45.0)     | 44(36.7)              |
| Hypercholesterolemia, n(%)                  | 7(5.4)                | 7(5.7)           | 2(1.8)       | 4(3.3)                |
| Hypertension and hypercholesterolemia, n(%) | 63(48.8)              | 58(47.5)         | 51(46.8)     | 63(52.5)              |
| Family history of dementia, n(%)            | 14(10.9)              | 25(20.5)         | 25(22.9)     | 12(10.0)              |

Inclusion criteria: history of hypertension, hypercholesterolemia and family history of AD  
Modified from Zhang et al. JAMA 2026

## Results

IL-12 higher in female in the 60-70 age group after Exercise

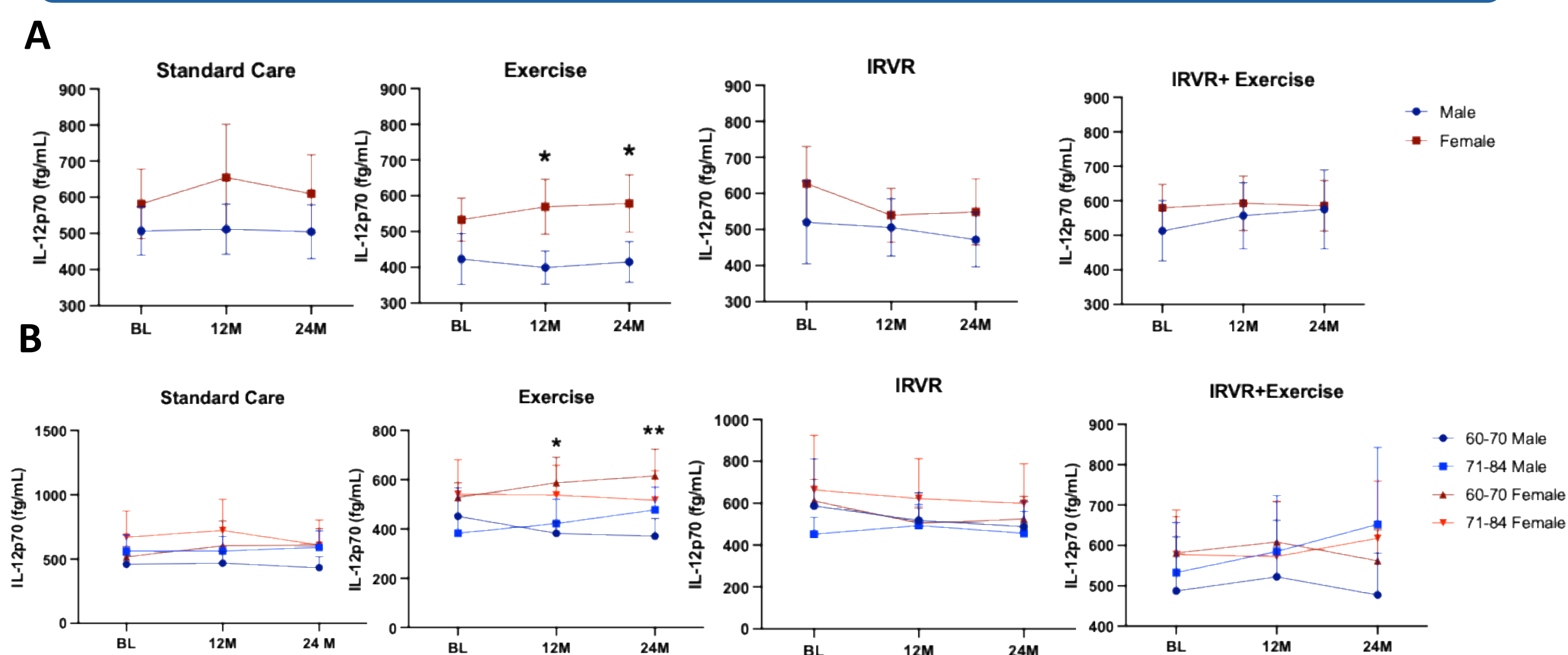


**Figure 2: (A)** Proinflammatory cytokines IL12p70 is higher in female in the exercise group. **(B)** IL-12p70 is higher in female in the 60-70 age group after exercise. \*  $p < 0.05$

Higher IL-10 level in female in the standard care group

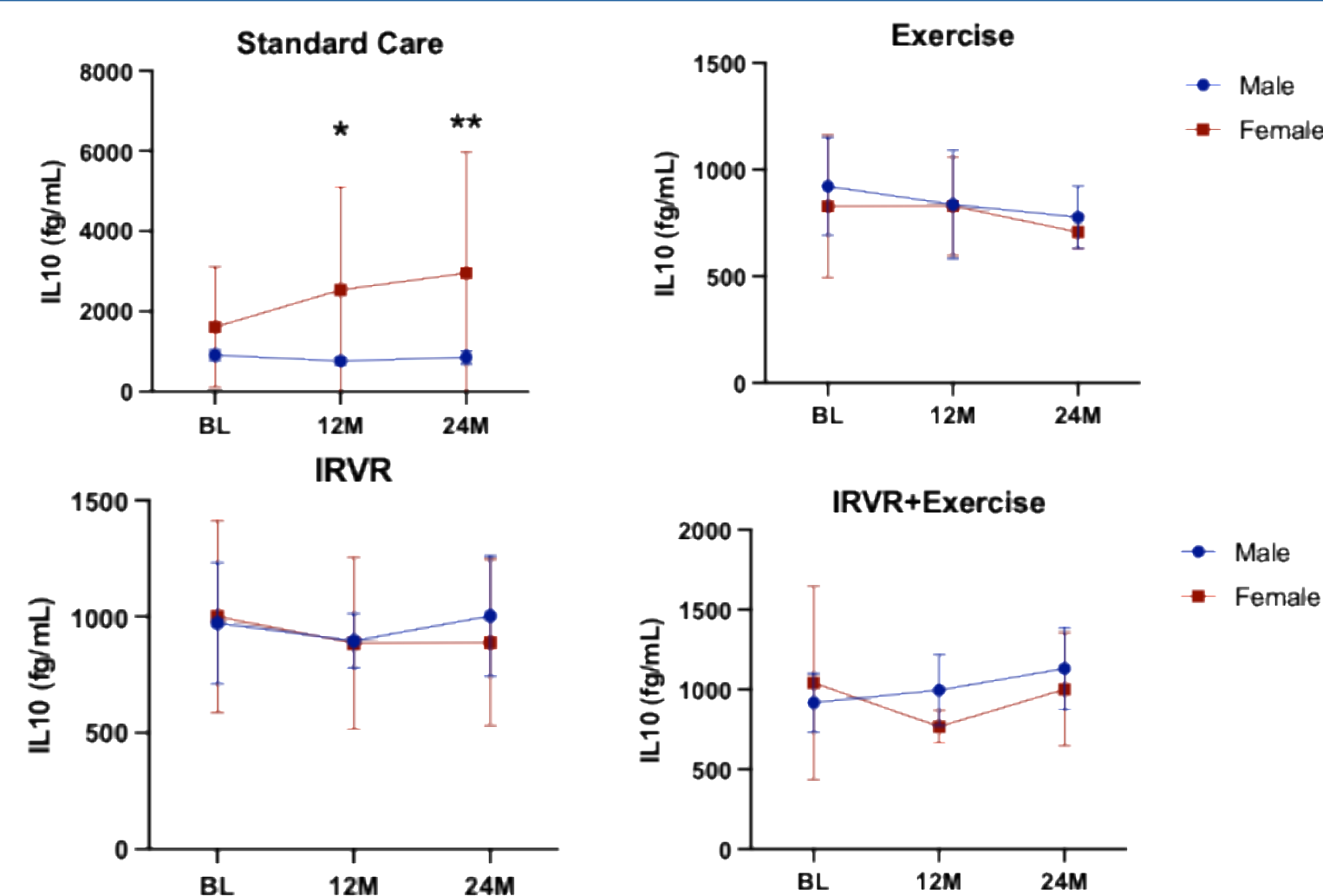


**Figure 3:** Anti-inflammatory cytokines IL-10 is elevated in female only in the standard care group over time. \*  $p < 0.05$ , \*\*  $p < 0.01$

## Results

Sex differences in IL-17A in the standard care group at 24M

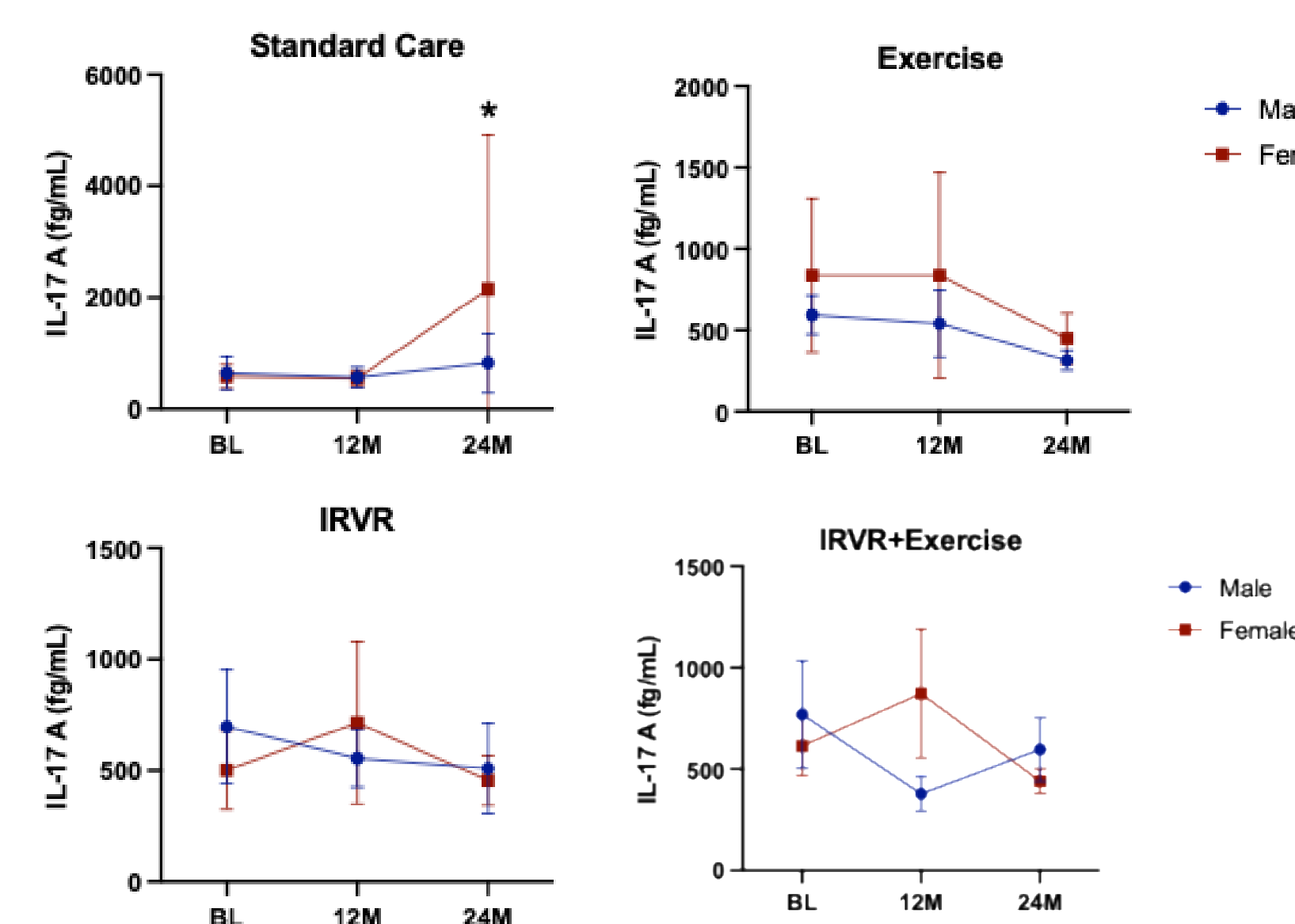


**Figure 4:** Proinflammatory cytokine IL-17A shows sex differences only in the standard care group at 24 months \*  $p < 0.05$ , \*\*  $p < 0.01$

Sex differences and age effect on IL-6 levels in the IRVR+ Exercise only at 12M

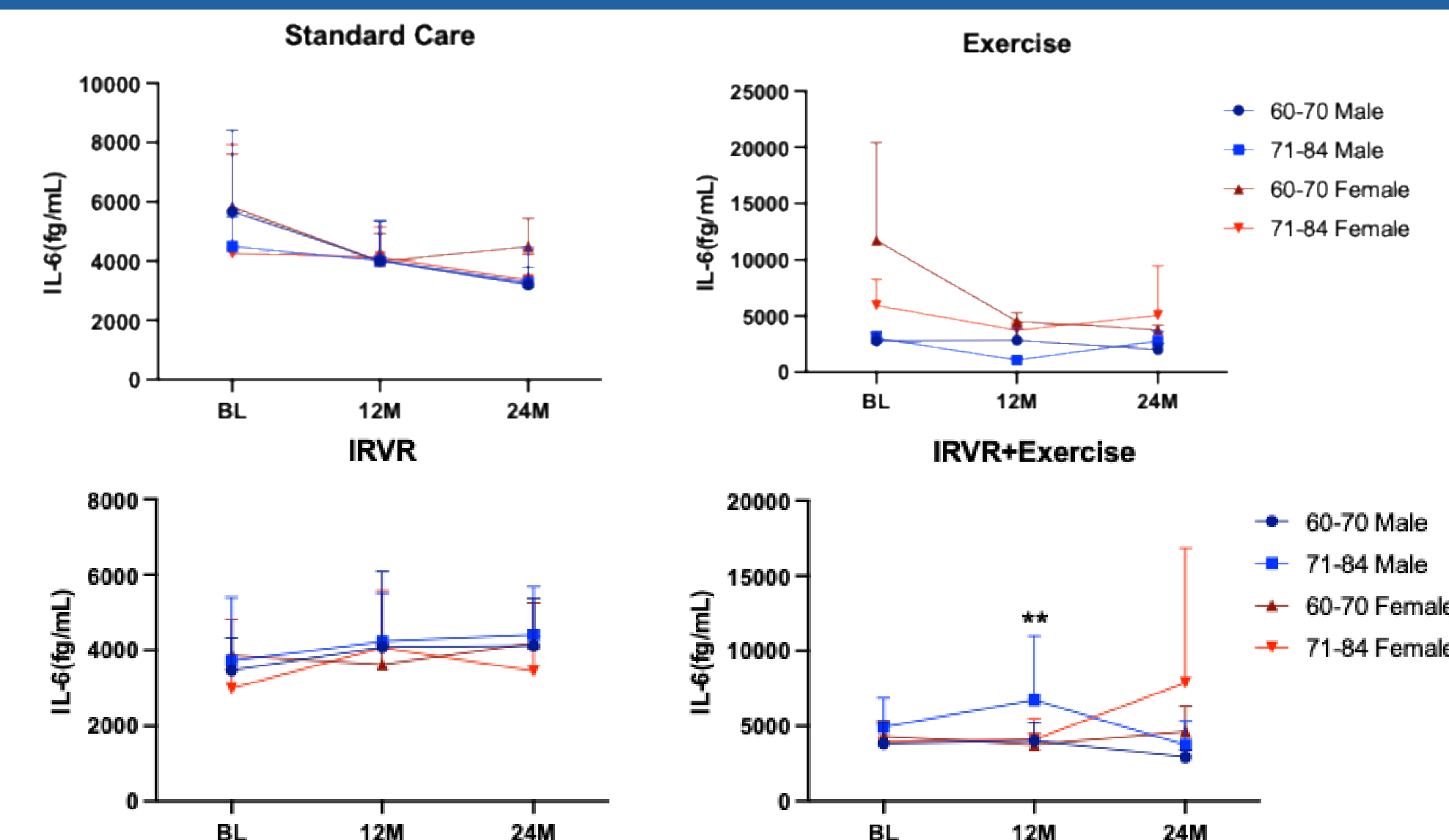


**Figure 5:** Proinflammatory cytokine IL-6 show sex differences only in the 71-84 age group after IRVR + exercise at 12 months \*\*  $p < 0.01$

## Conclusion

- Alzheimer's disease risk factor management affects inflammation in a sex and age dependent manner.
- These differences suggest involvement of different inflammatory pathways between both males and females

## Future Directions

- Determine whether sex will modify the association between AD plasma biomarkers (pTau217, Total Tau and Aβ42/40) and inflammatory cytokines with the cardiovascular risk management
- Determine whether sex will modify the association between white matter hyperintensities and inflammatory cytokines with the cardiovascular risk management