The Effects of Prenatal Testosterone Exposure, APOE4, and Their Interaction on Dementia Risk

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INTRODUCTION
- Evidence has been reported for higher incidence rates of dementia in women than men, with hormones as one possible contributor.
- Effects of prenatal testosterone exposure on dementia risk can be studied by comparing twins from same-sex and opposite-sex pairs.
- APOE4 has been suggested to be a more potent risk factor to Alzheimer’s disease for women than men, but remains as an open question (Farrer et al., 1997)
- Does the interaction between sex of co-twins and APOE4 predict dementia risk?

METHOD
- **Participants**
  - 15,096 female same-sex dizygotic (DZ) twins, 12,627 male same-sex DZ twins, 7,322 female twins from opposite-sex pairs, and 6,682 male twins from opposite-sex pairs, including twins from complete and incomplete pairs.
  - APOE allele data were available for 4,957 individual female twins and 4,264 individual male twins.
- **Measures**
  - Dementia: Clinical diagnosis according to DSM-IV or DSM-III-R criteria for dementia or International Classification of Disease codes for dementia in the Swedish National Health Register (12% and 8% demented cases in female and male twins).
  - Age at onset: In-person assessment and medical records.
- **APOE4**: Either directly genotyped or imputed
- **Statistical Analysis**
  - Chi-square tests were conducted for men and women separately to compare dementia rates in same-sex and opposite-sex DZ pairs
  - Cox Proportional Hazard Regression was conducted to estimate twin type, APOE4, and their interaction predict hazard rates of dementia in male and female twins.
  - Covariates were controlled to test whether the effects of twin type was explained by post-natal risk factors.

RESULTS
- **Dementia Rates**
  - Female twins from opposite-sex pairs had significantly lower dementia rates than two randomly assigned comparison groups of females from same-sex DZ pairs ($\chi^2 = 78.48$ and $p < 0.001$ for Group 1; $\chi^2 = 93.15$ and $p = 0.08$ for Group 2).
- **Controlling for post-natal risk factors**
  - After controlling for education, exercise, vascular risk, and post-natal hormone exposure, testing from age 88, females from opposite sex pairs had reduced but still marginally significant lower hazard rates than females from same sex pairs ($HR = 0.61$, $p = 0.053$).

SUMMARY
- Overall, females from opposite-sex pairs displayed lower dementia rates when compared to females from same-sex pairs, and the discrepancy was not explained by differences in longevity, education, exercise, vascular risk, or post-natal hormone exposure.
- APOE4 did not show a statistically significant interaction with twin type on dementia risk.
- The results provide support for a relatively masculine prenatal hormone milieu as a possible factor lowers dementia risk.

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