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.
- *APOE ε4* 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)

Current Study

- Are there differences in dementia risk between women in same-sex and in opposite-sex twin pairs after controlling for post-natal risk factors?
- Does the interaction between sex of co-twin and *APOE ε4* 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-III-R or DSM-IV 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
- *APOE ε4*: 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 whether twin type, *APOE ε4*, 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

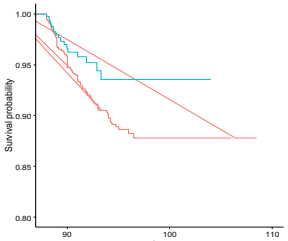
RESULTS

Dementia Rates

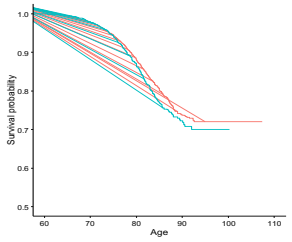
- Female twins from opposite sex pairs had significantly lower dementia rates than two randomly assigned comparison groups of females from same-sex DZ pairs (χ^2 = 78.48 and φ = -0.07, p < 0.001 for Group 1; χ^2 = 93.15 and φ = -0.08, p < 0.001 for Group 2)
- Females from opposite sex pairs did not differ in longevity from females from same sex pairs (t = -1.82, p = 0.069, d = 0.05 for Group 1; t = -1.48, p = 0.138, d = 0.04 for Group 2)
- Male twins demonstrated no statistically significant differences in dementia rates by twin type (χ^2 = 0.15 and φ = -0.003, p = 0.699 for Group 1; χ^2 = 2.77 and φ = -0.02, p = 0.096 for Group 2)

Hazard rates of dementia

- Testing from age 60, female twins from opposite-sex pairs did not show significant difference from those from same-sex pairs in dementia risks over the full follow-up (hazard ratio [HR] = 0.96, 95% confidence interval = [0.88, 1.05], p = 0.417)
- Testing from age 88 in post hoc analysis, opposite-sex females had significantly lower hazard rates than those from same-sex pairs (HR = 0.601 [0.362, 0.997], p = 0.049)
- Testing from age 60, male twins from opposite-sex pairs displayed marginally significant higher dementia risk than those from same-sex pairs (HR = 1.11 [0.99, 1.23], p = 0.062)



Survival curves for females with same-sex co-twins and females with opposite-sex co-twins tested at age 88 and beyond. Red line represents same-sex twins; blue line represents opposite-sex twins.



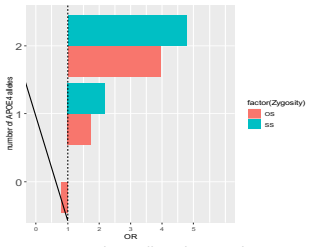
Survival curves for males with same-sex co-twins and males with opposite-sex co-twins tested at age 60 and beyond. Red line represents same-sex twins; blue line represents opposite-sex twins.

Controlling for post-natal risk factors

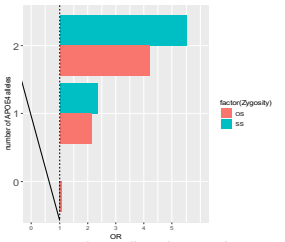
- After controlling for education, exercise, vascular risk, and post-natal hormone exposure, testing from age 88, females from opposite sex pairs had reduced but still marginally significant lower hazard rates than females from same sex pairs (HR = 0.61, p = 0.053)
- After controlling for education, exercise, and vascular risk, testing from age 60, there was little change in males in dementia risk compared to results without these covariates(HR = 1.11, p = 0.050)

Twin Type, APOE ε4 ,and Interaction

- In this reduced sample, twin type was significant (HR = 0.78 [0.63, 0.97], p = 0.026) in female twins but not significant in male twins (HR = 1.09 [0.85, 1.39], p = 0.500)
- Number of *APOE ε4* alleles also was significant in both female (HR = 2.18 [1.85, 2.57], p < 0.001) and male twins (HR = 2.35 [1.90, 2.91], p < 0.001)
- No interaction between twin type and *APOE ε4* was found in female (HR = 1.03 [0.77, 1.38], p = 0.842) or male twins (HR = 0.84 [0.61, 1.15], p = 0.271)



The hazard ratio for the effects of number of *APOE ε4* alleles compared by twin type for female twins.



The hazard ratio for the effects of number of APOE ε4 alleles compared by twin type for male twins.

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
- *APOE ε4* 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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