

Early-Life Determinants of Dementia: The Role of Education and Genetics

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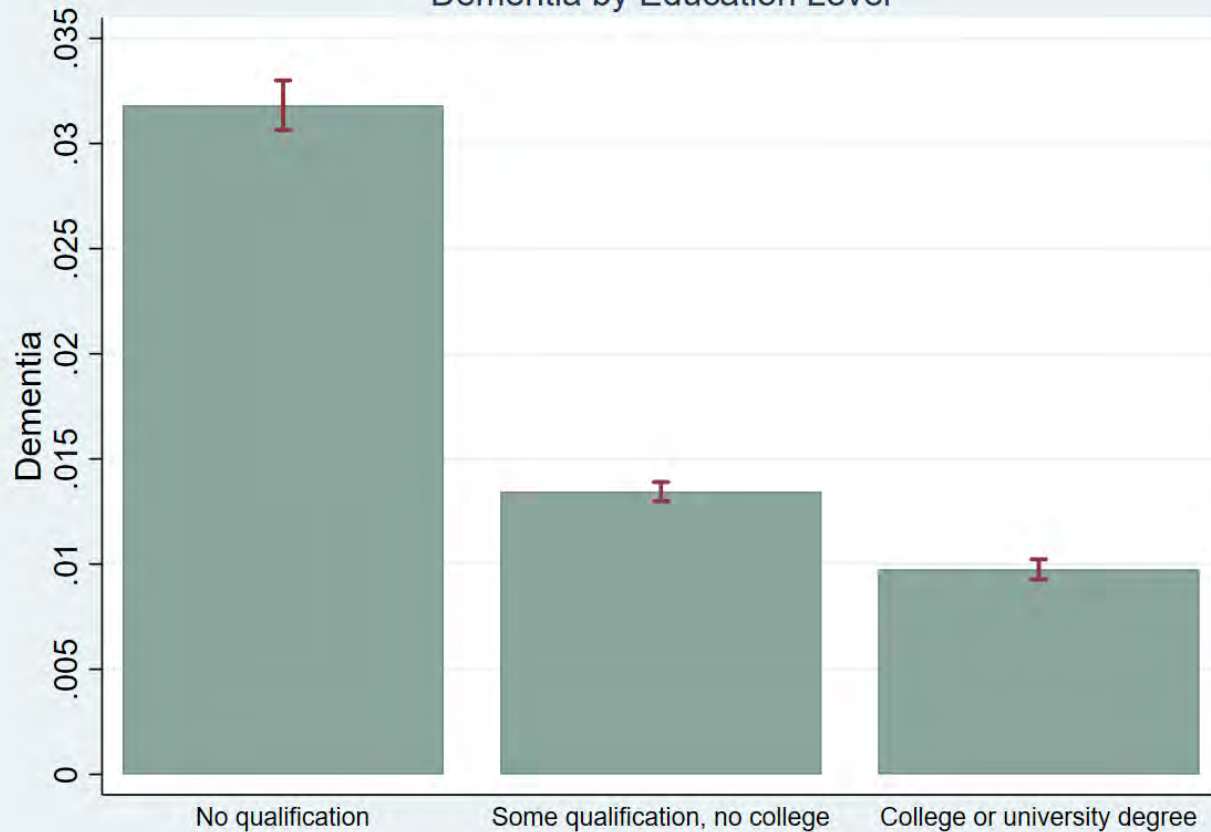
Funding from the National Institute on Aging (R01AG078522) is gratefully acknowledged.

Motivation

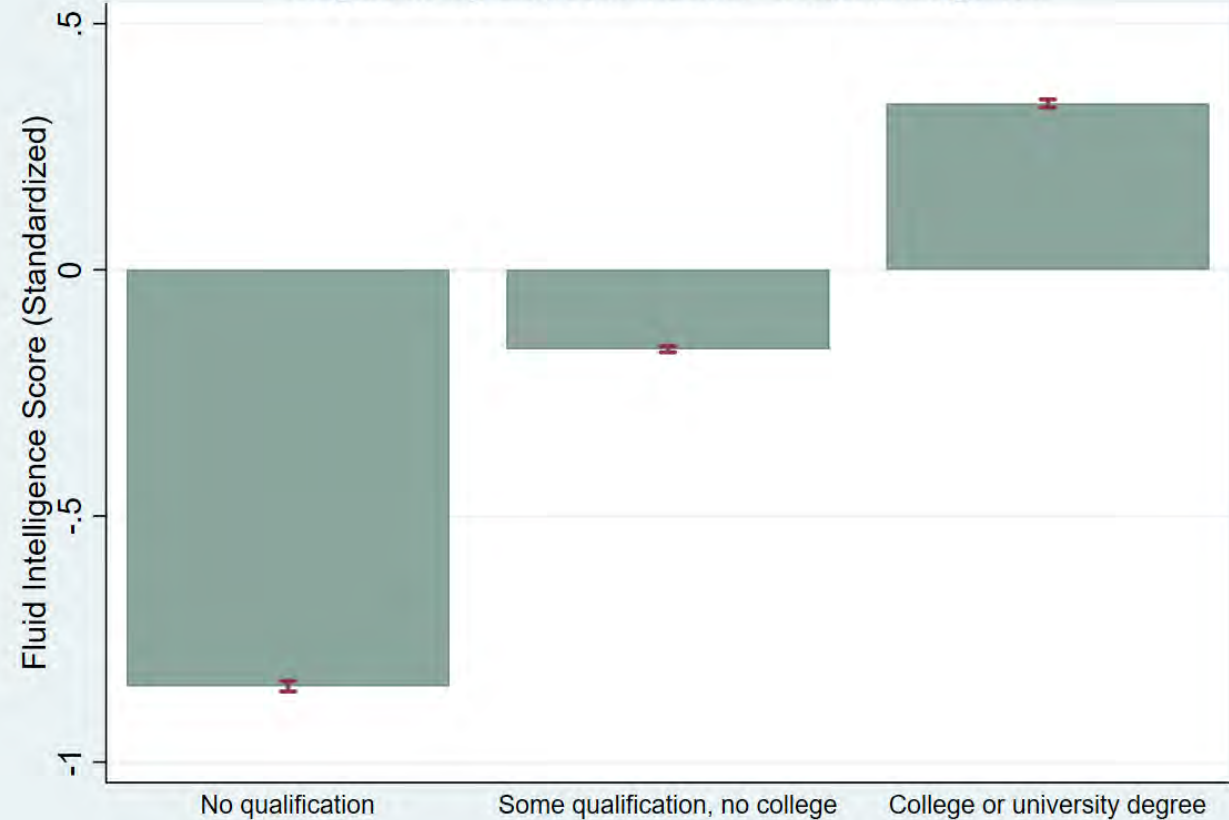
- Gains in life expectancy and population aging are driving a sharp rise in Alzheimer's Disease and Related Dementias (ADRD)
 - Predicted global prevalence of 65.7 million people by 2030 (Prince et al. 2013)
 - High direct and indirect costs associated with ADRD
- ADRD is challenging to study empirically
 - Hard to diagnose/selection into diagnosis
 - Selective attrition in surveys
- Interest in factors that can modify ADRD risk
- Education is a candidate, but little evidence of causal effect
 - Theory: Cognitive reserve hypothesis

Association between education and ADRD/cognition

Dementia by Education Level



Cognition by Education Level - Fluid Intelligence



Today

- Investigate the causal effect of education on ADRD
 - Outcome: registry-based measures of dementia (from hospital, GP, death records) linked to UK Biobank
1. Use change in compulsory schooling (1972 ROSLA)
 - In the UK, students born after Sept. 1 1957 had to stay in school until age 16
 - Regression Discontinuity Design (RDD)
 2. Use genetic data to focus on the population at risk
 - AD highly heritable
 - Due to Mendelian inheritance, the exact genes you inherit are random conditional on your parent's genes
 3. Estimate GxE
 - Are those at higher AD higher risk most affected?

Data: UK Biobank (UKB)

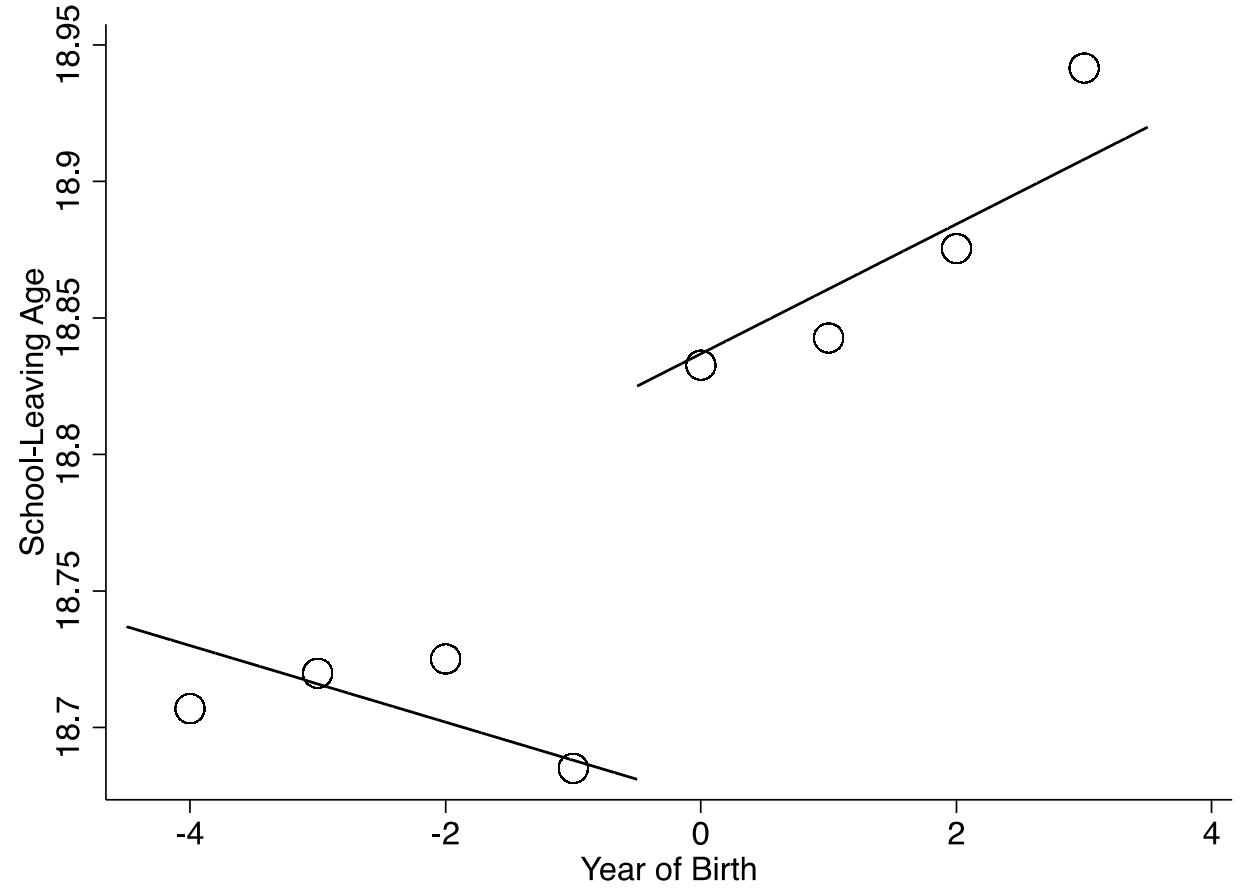
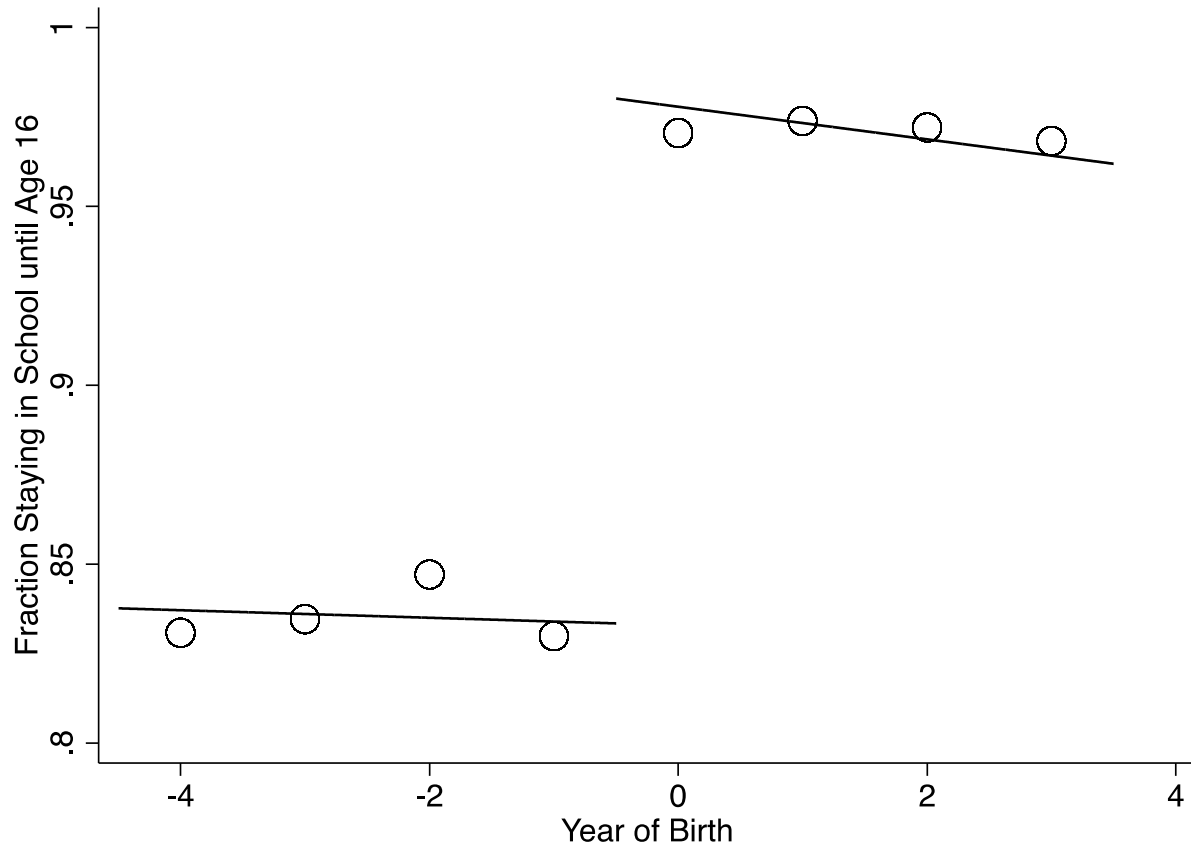
- Large, population-based prospective study initiated by the NHS
- $N \approx 500,000$; ages 40-69 in early 2000's (60-80 today)
- $N \approx 90,000$; born between 1953 and 1961 (ROSLA sample)

- Almost all participants genotyped
- Restrict to those of European Descent
- Subsample with sibling(s) or parents ($N \approx 43,000$) (Sibling Sample)

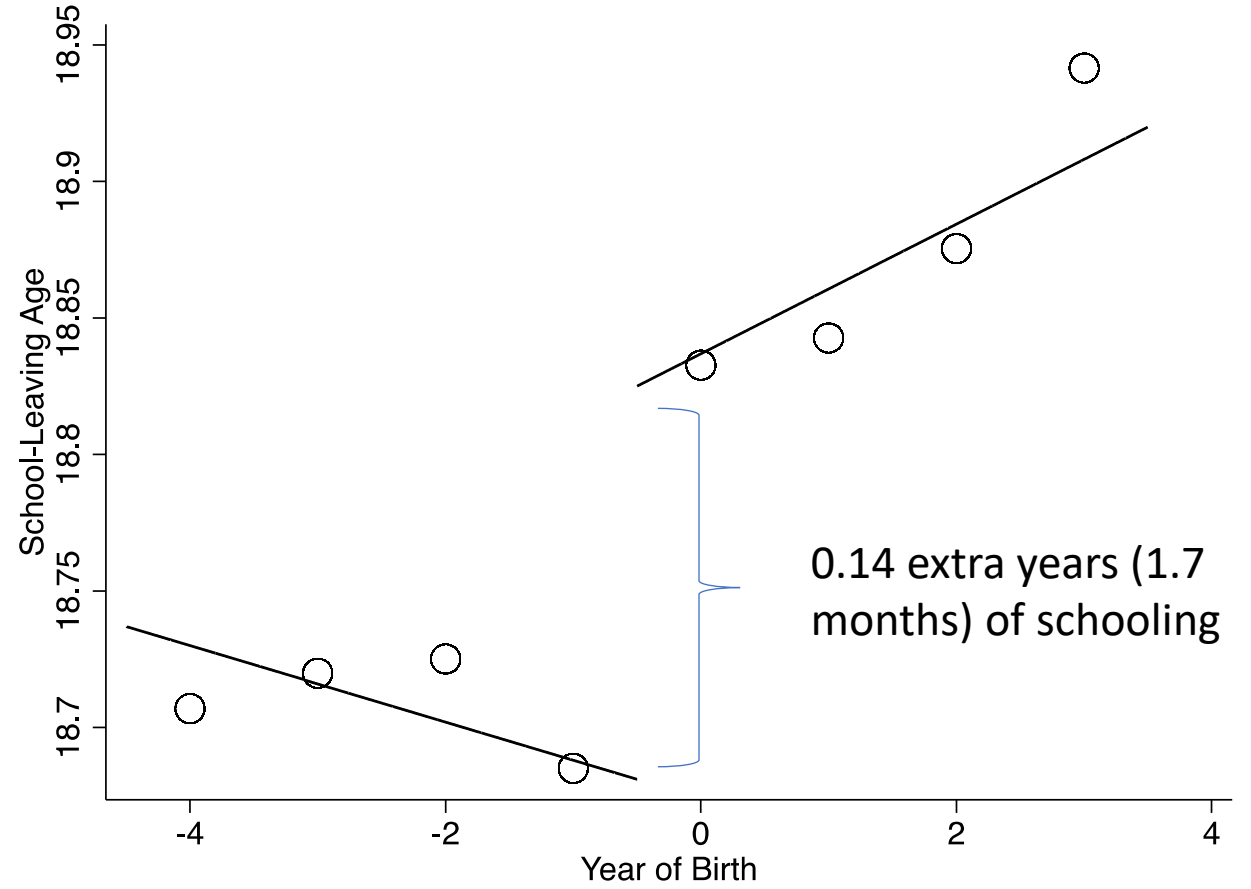
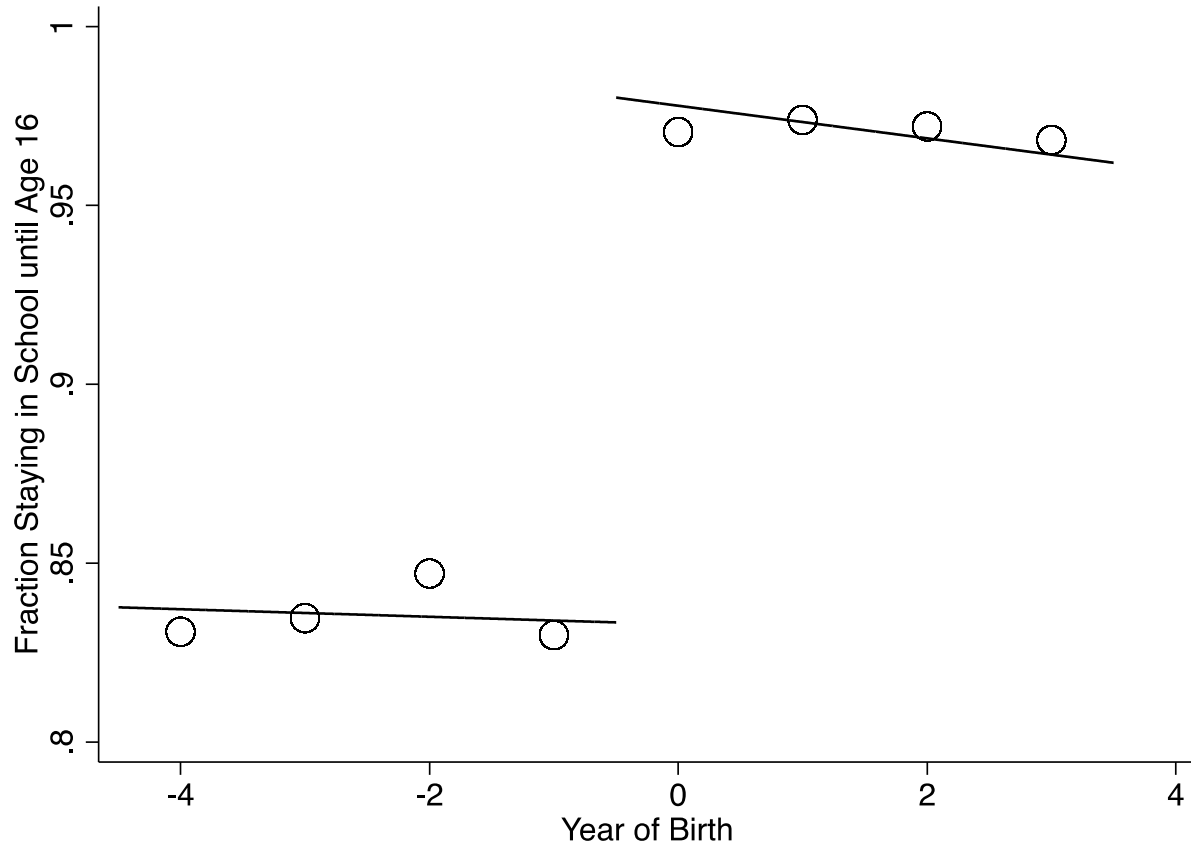
- Registry-based measure of ADRD diagnosis, age at diagnosis (about 10,000 cases, 2% prevalence full sample; 0.4% ROSLA sample, 1.7% sibling sample)

PART I: ROSLA RESULTS

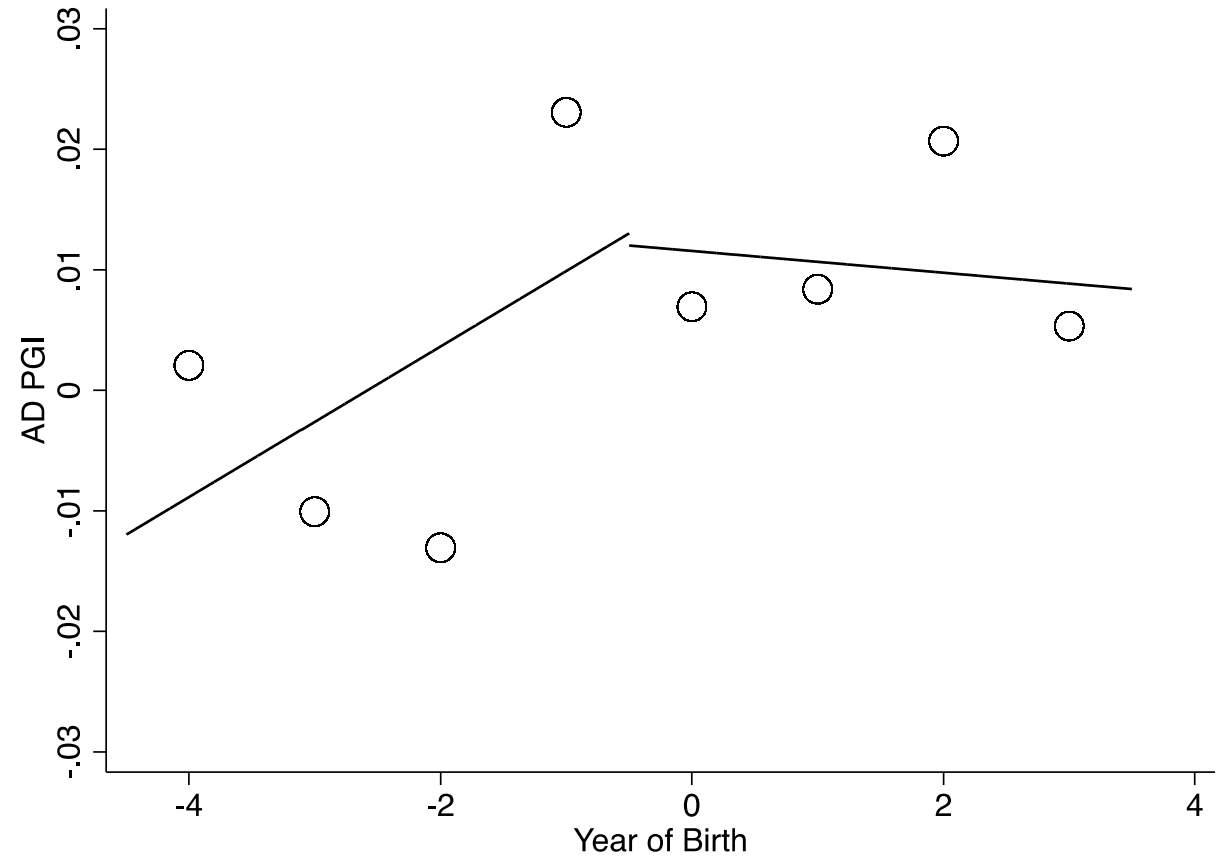
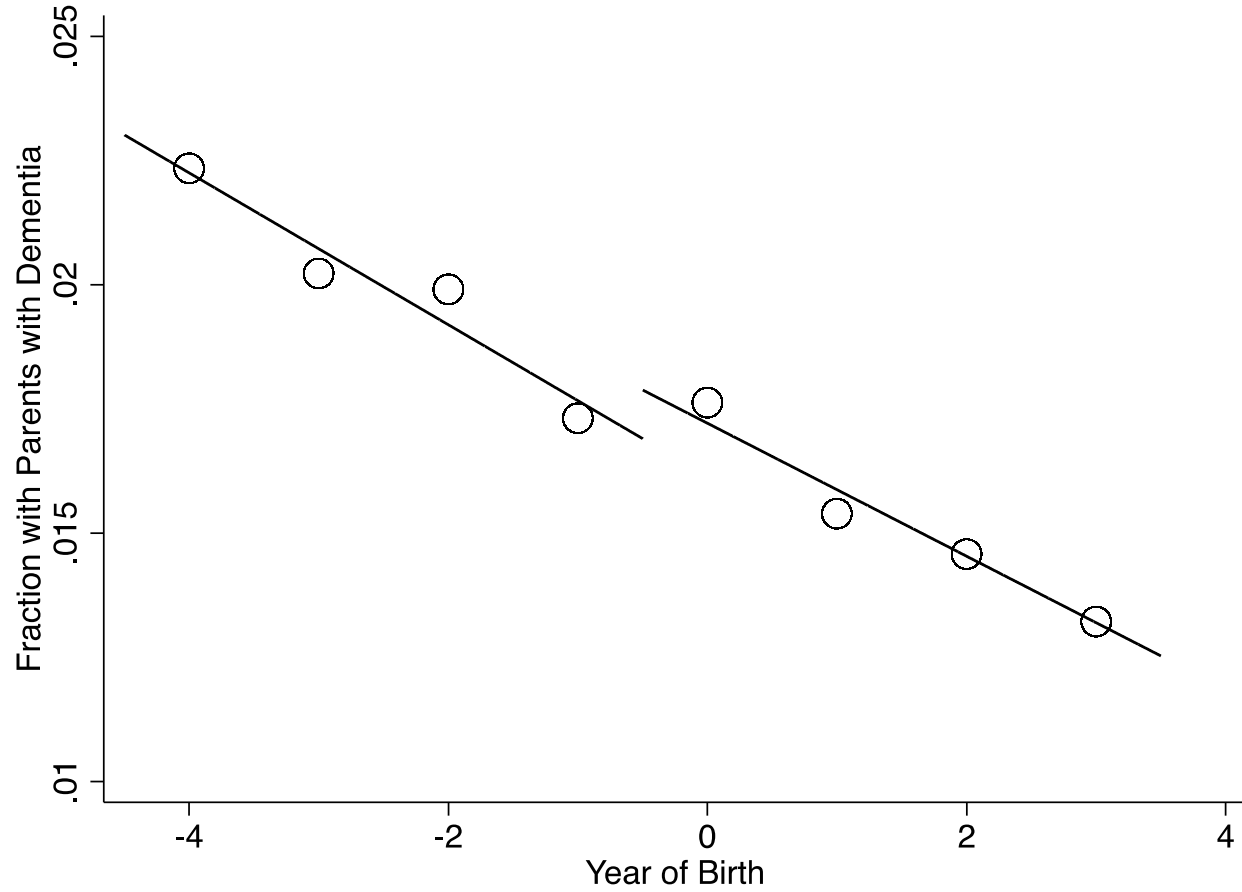
The 1972 ROSLA Increased Education



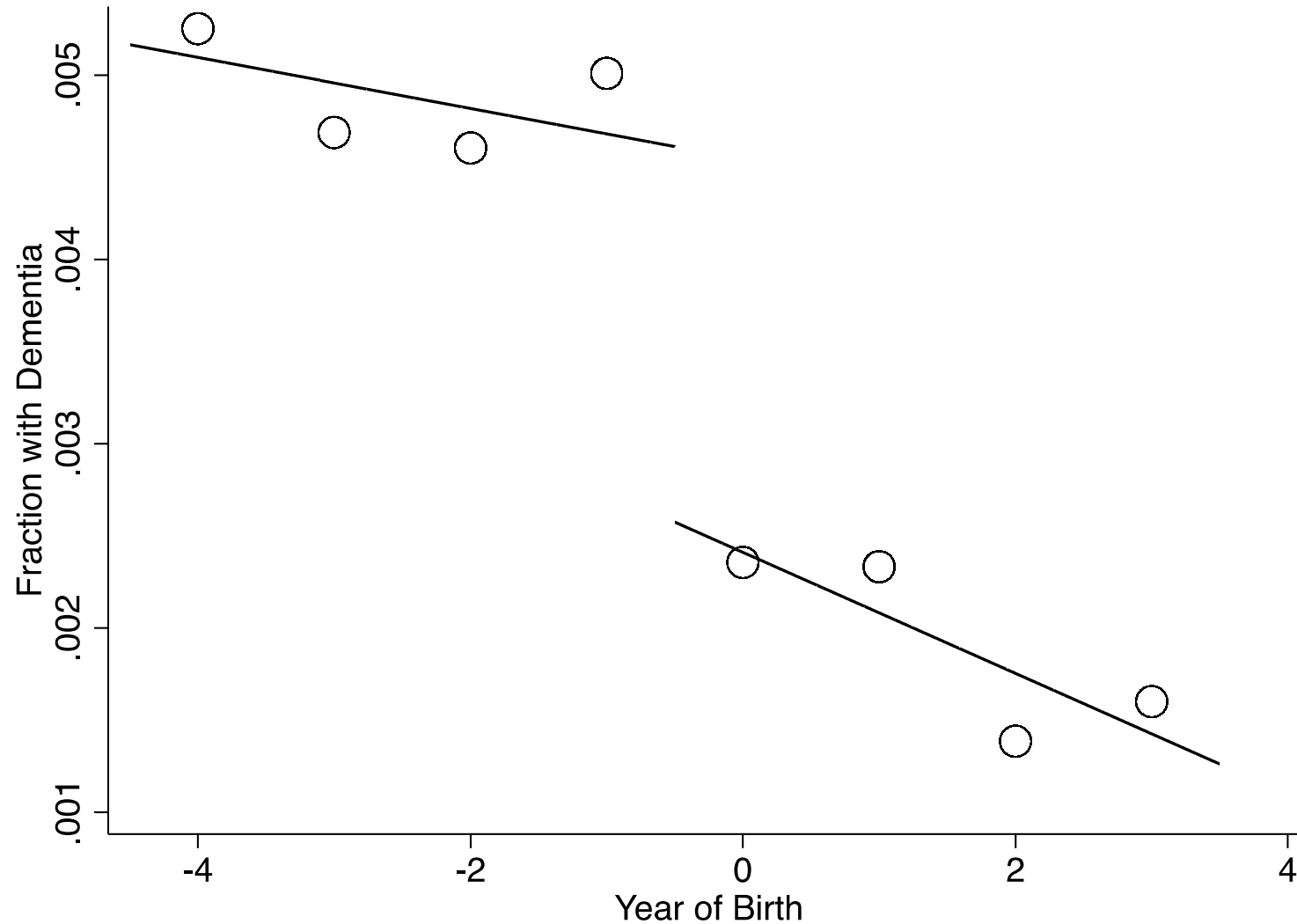
The 1972 ROSLA Increased Education



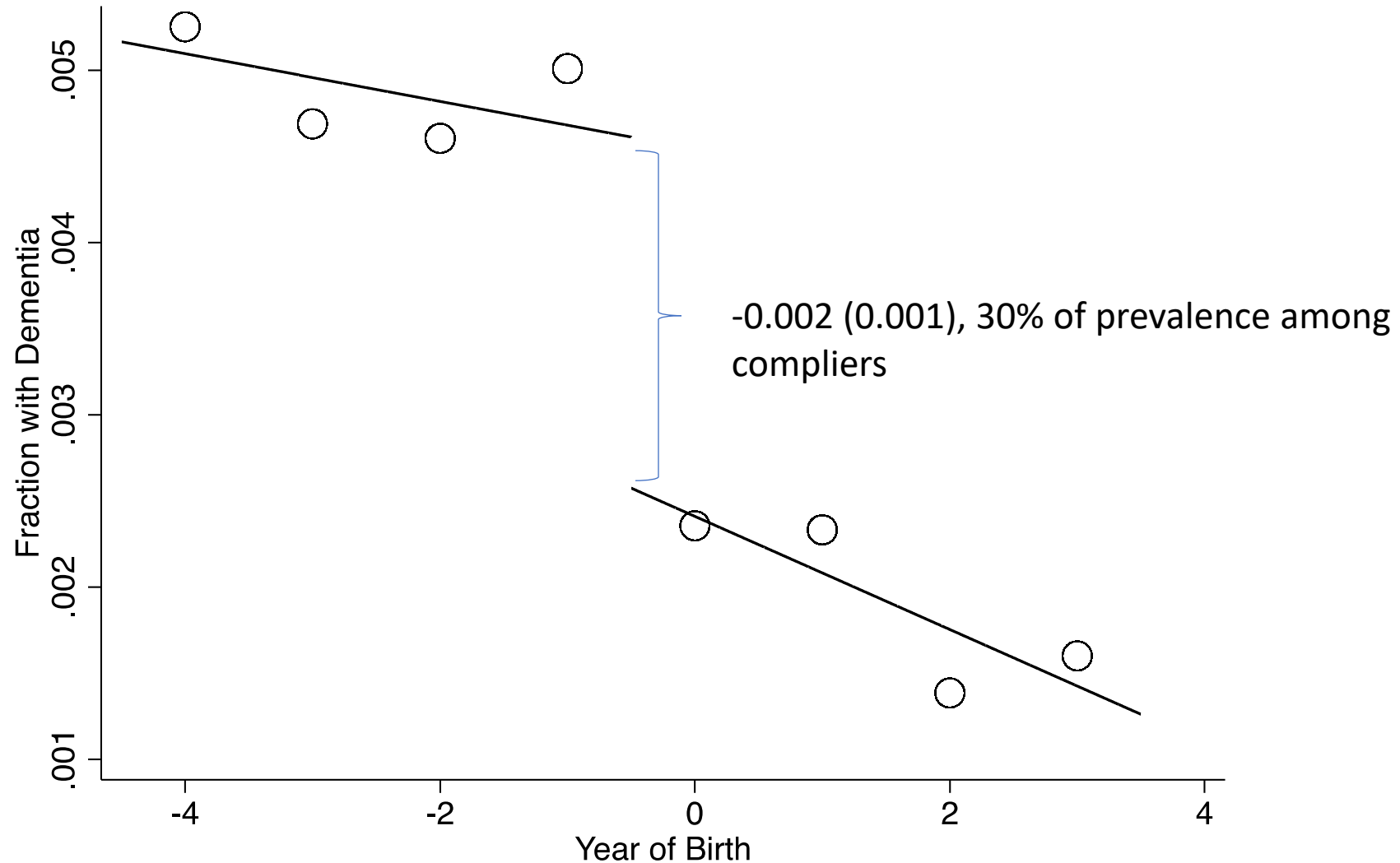
Those to the left and right of threshold have similar ADRD risk



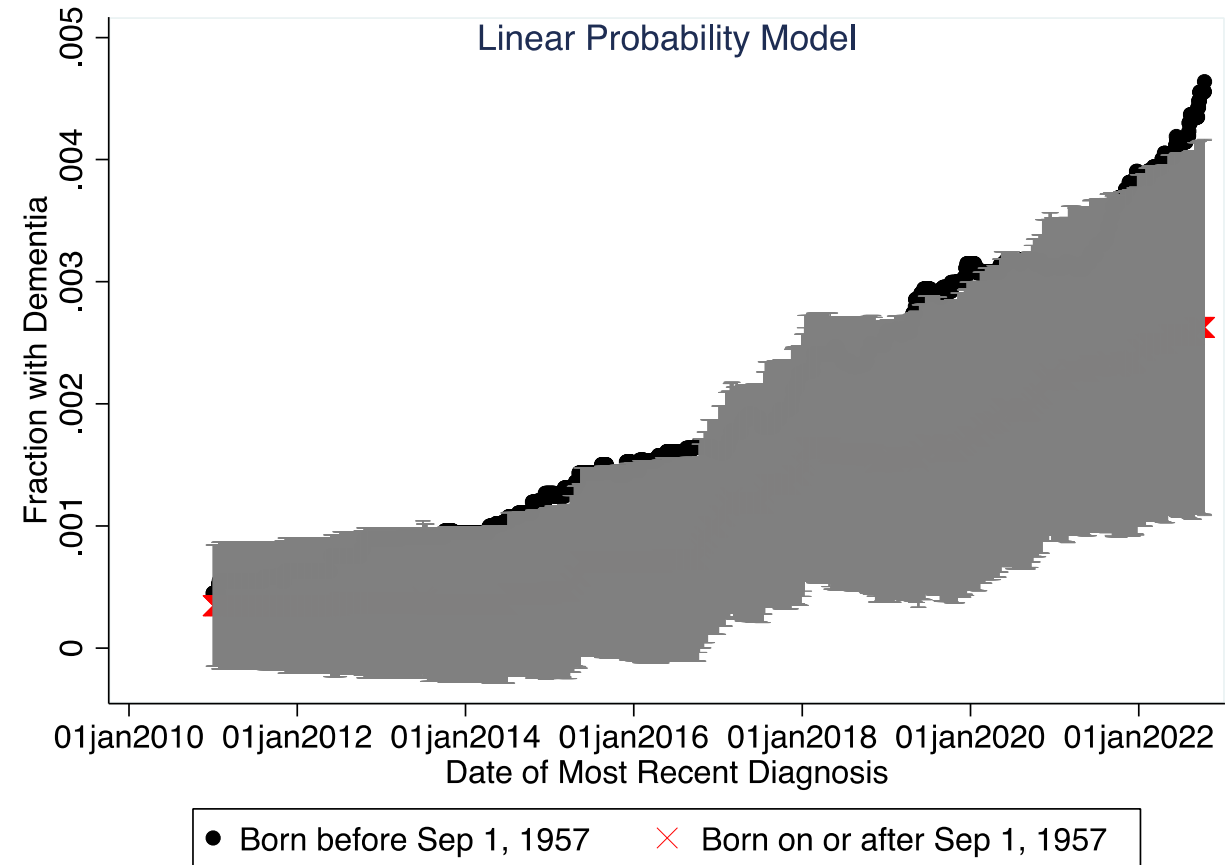
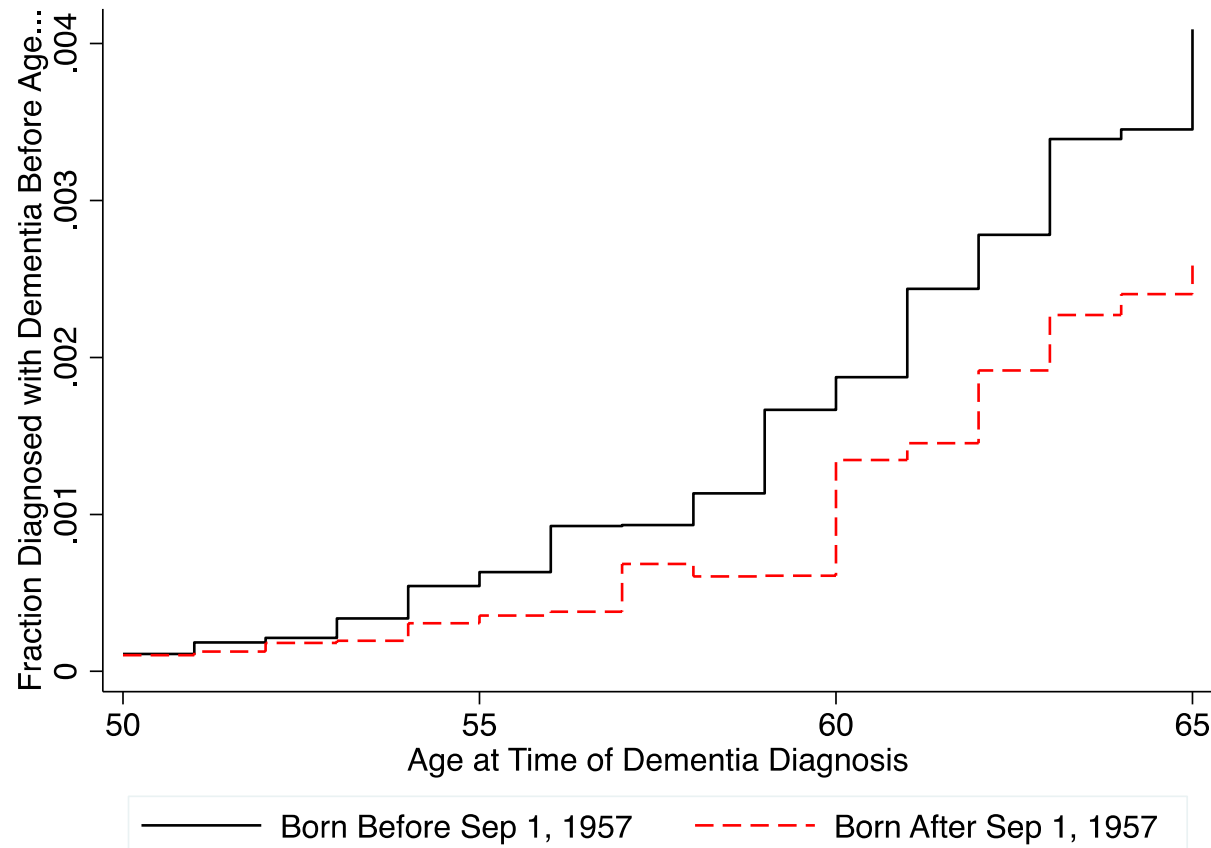
Effect of ROSLA on ADRD Diagnosis



Effect of ROSLA on ADRD Diagnosis



ROSLA delays onset – effects grow over time



PART II: ADDING GENETICS

Genetics significantly affects dementia hazard

Cox Hazard model with (Residualized) AD PGI

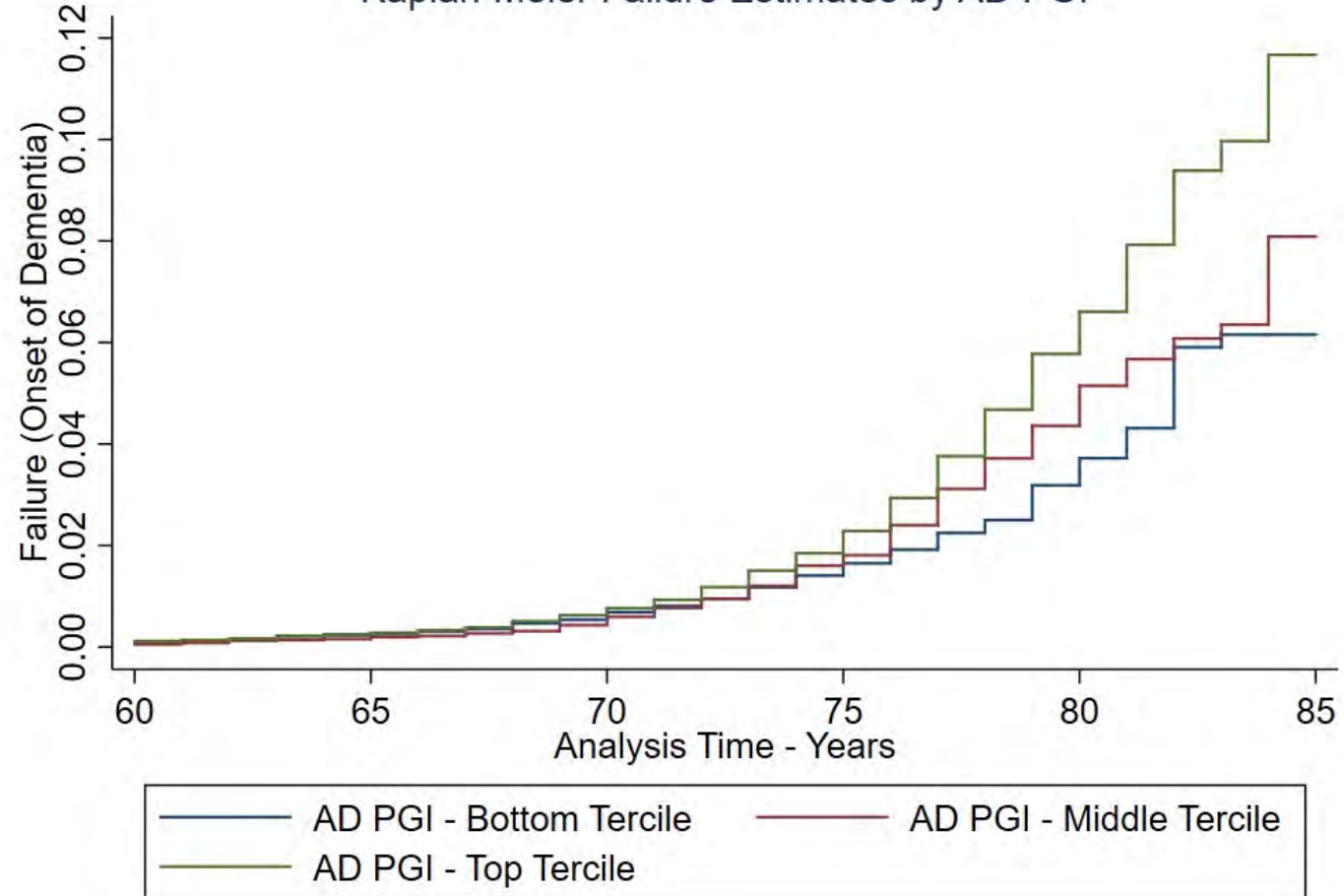
VARIABLES	(1) HR	(2) Coef.	(3) HR	(4) Coef.
AD PGI	1.483 (0.099)	0.394 (0.067)		
AD PGI - Middle Tercile			1.189 (0.115)	0.173 (0.096)
AD PGI - Top Tercile			1.599 (0.145)	0.470 (0.091)
Observations	43,990	43,990	43,990	43,990

Dependent variable: Age in years

Robust standard errors in parentheses

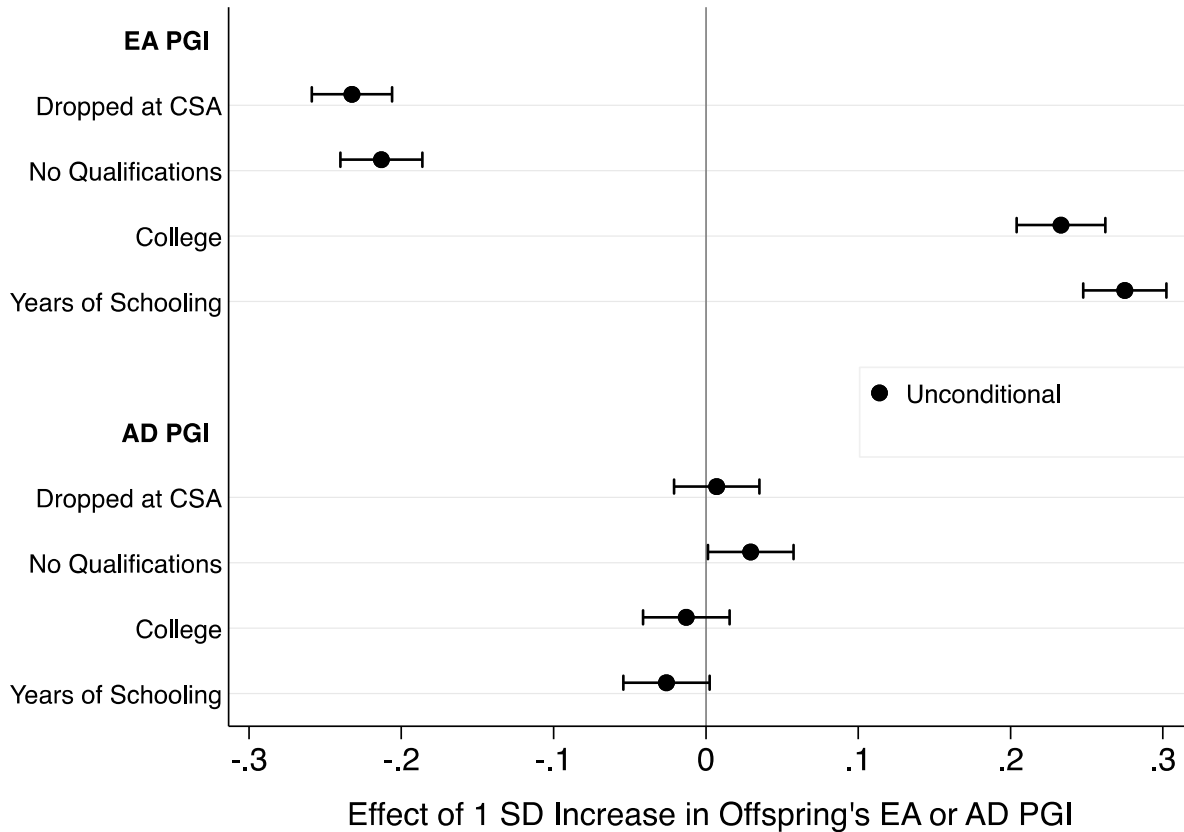
AD PGI is residualized using Parental AD PGI and then divide into terciles

Kaplan-Meier Failure Estimates by AD PGI

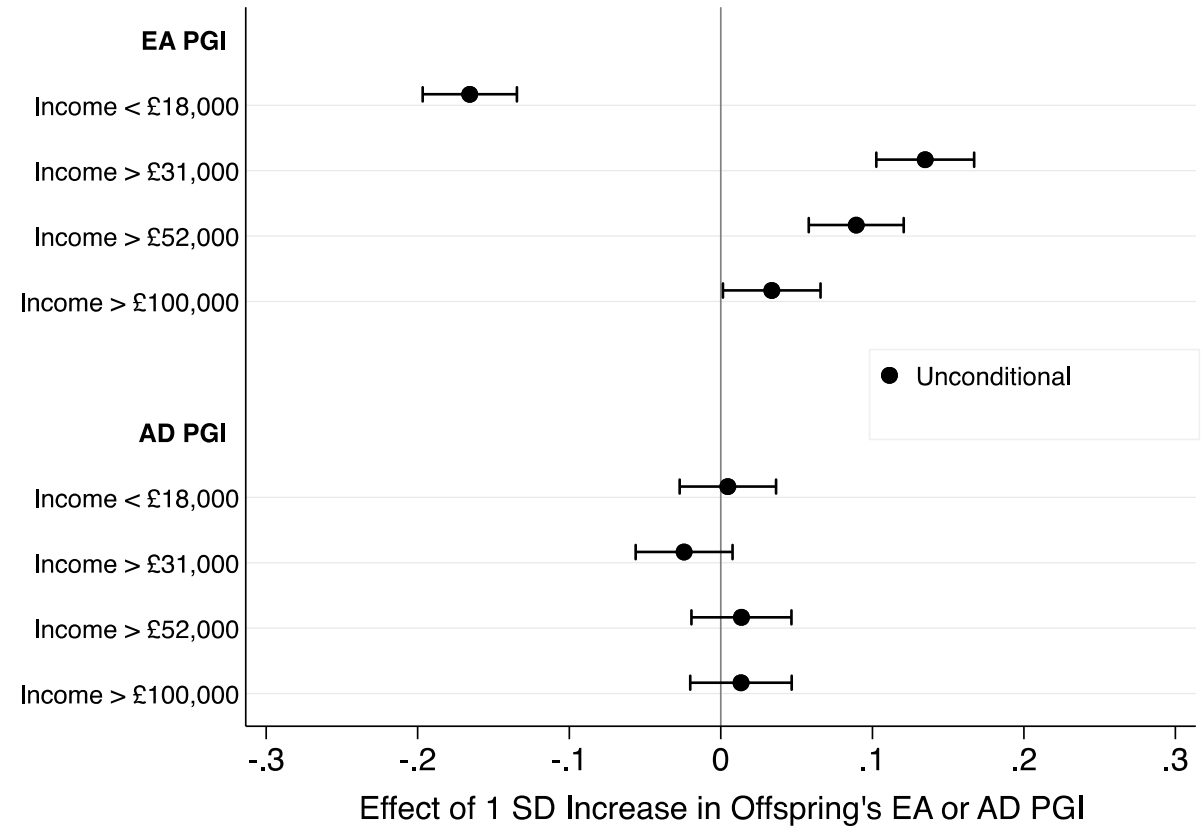


AD PGI less confounded by parental SES than EA PGI

Effects on Parental Education

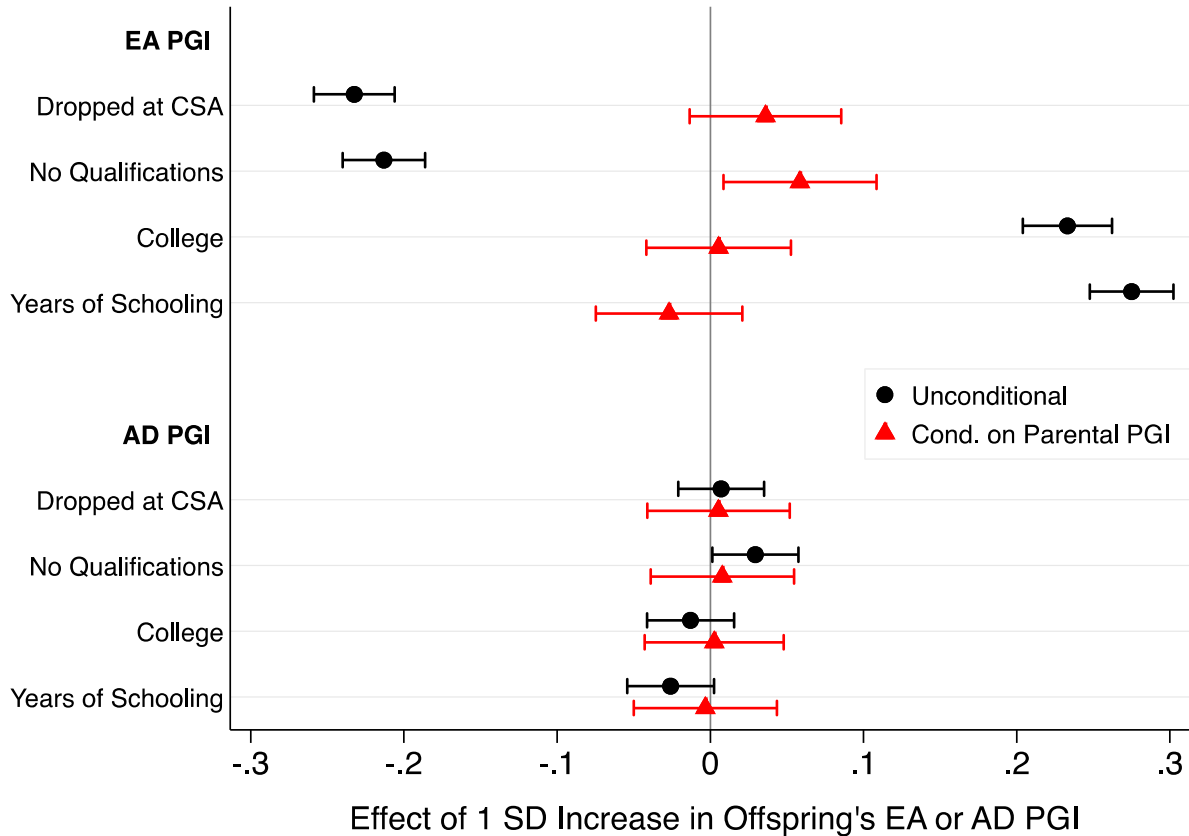


Effects on Parental Income

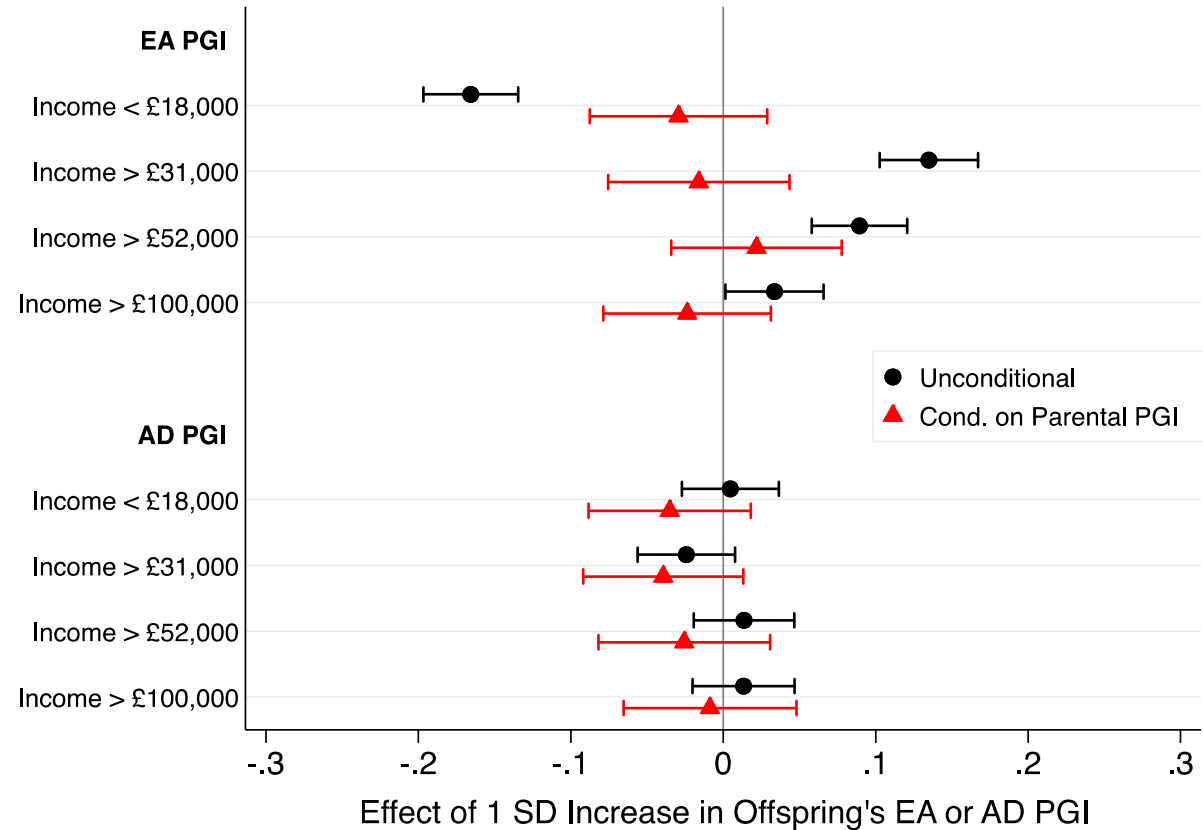


AD PGI less confounded by parental SES than EA PGI

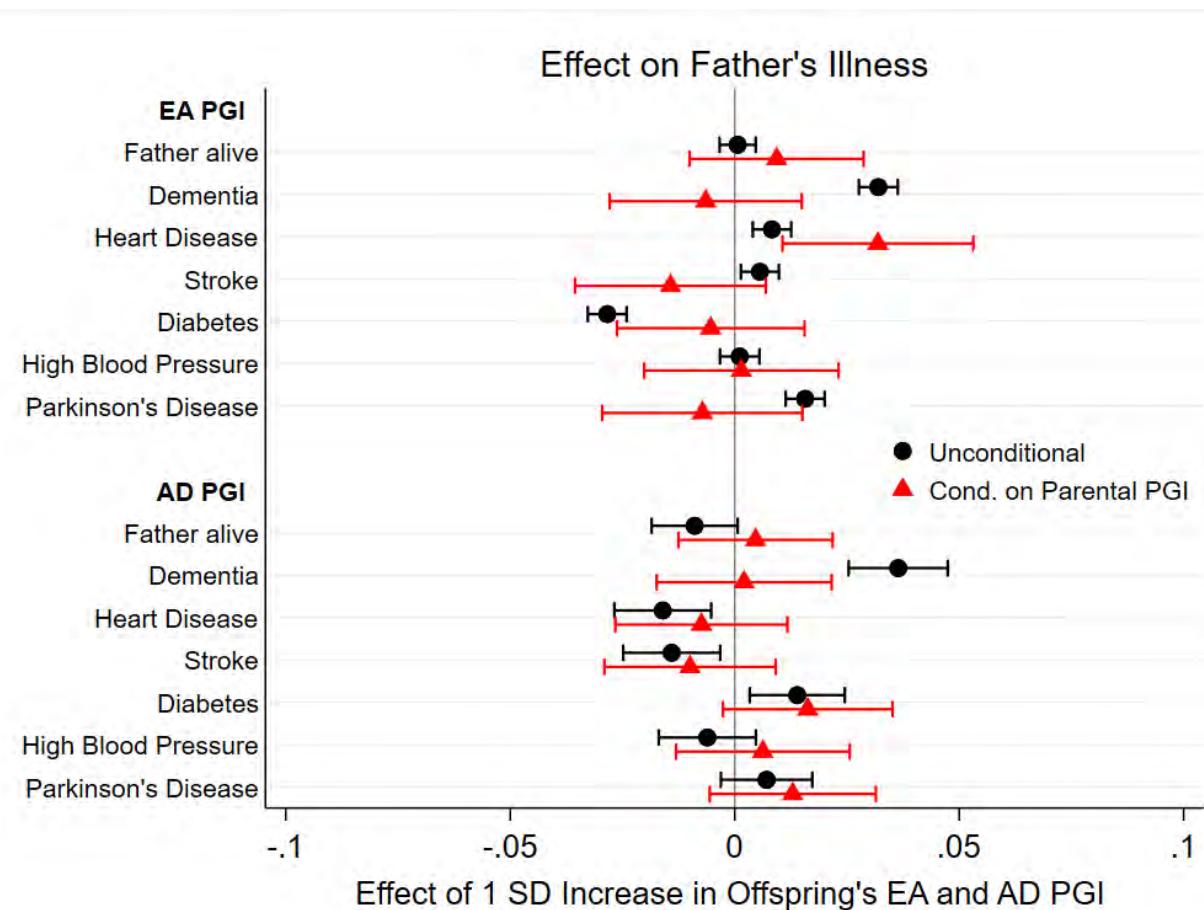
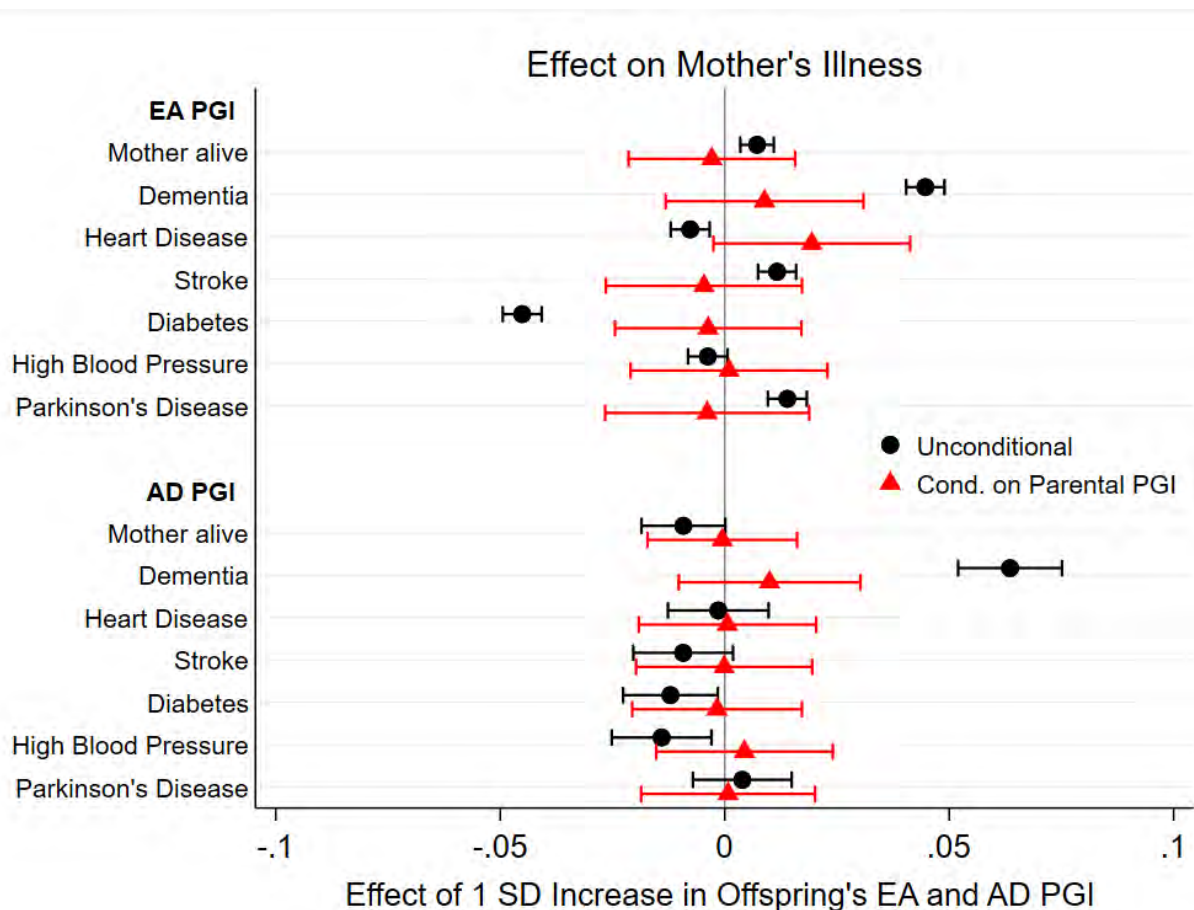
Effects on Parental Education



Effects on Parental Income

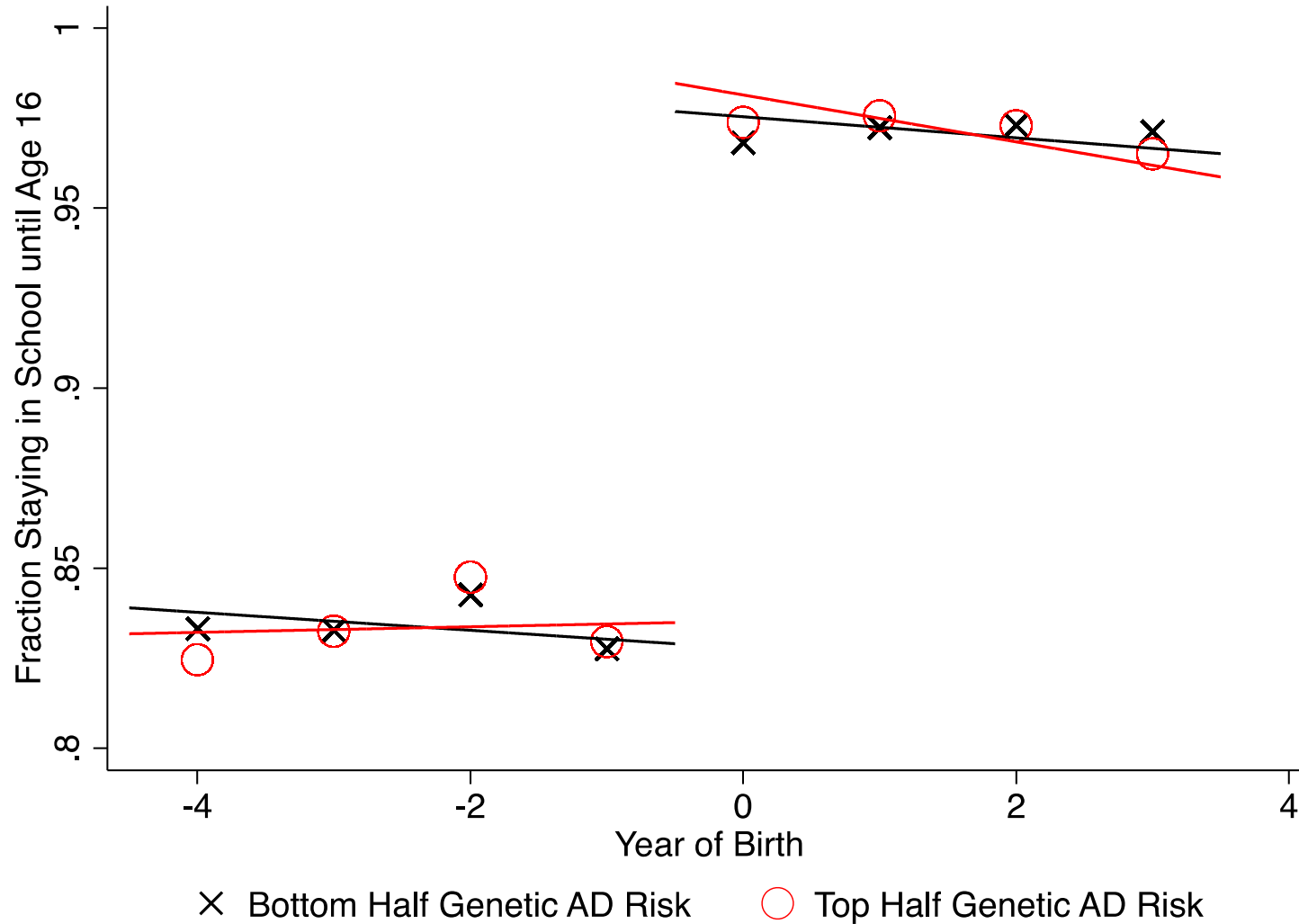


AD PGI less confounded by parental health than EA PGI

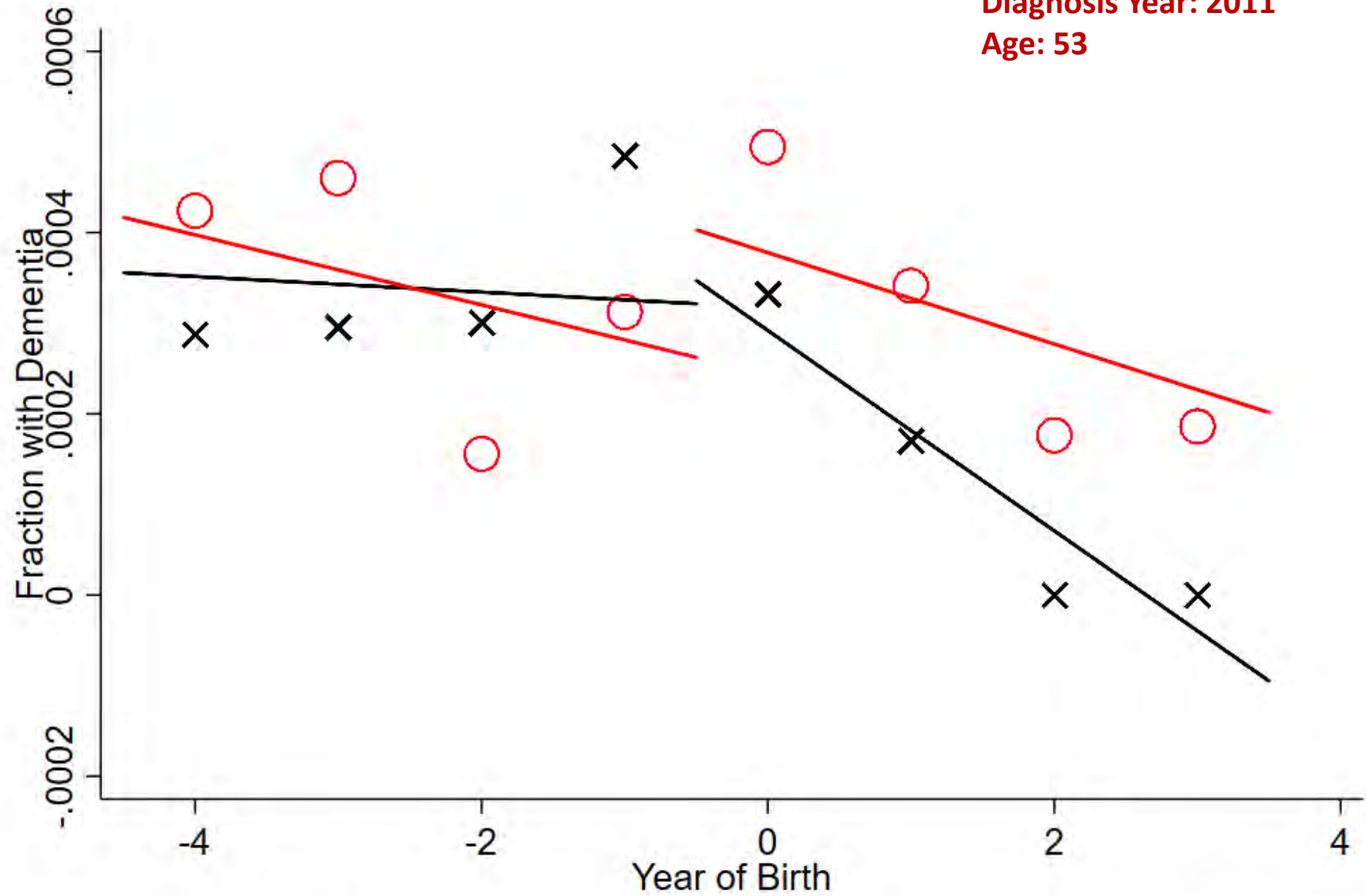


PART III: PUTTING ROSLA AND GENETICS TOGETHER

Effect of ROSLA on education is similar for those with high and low AD risk

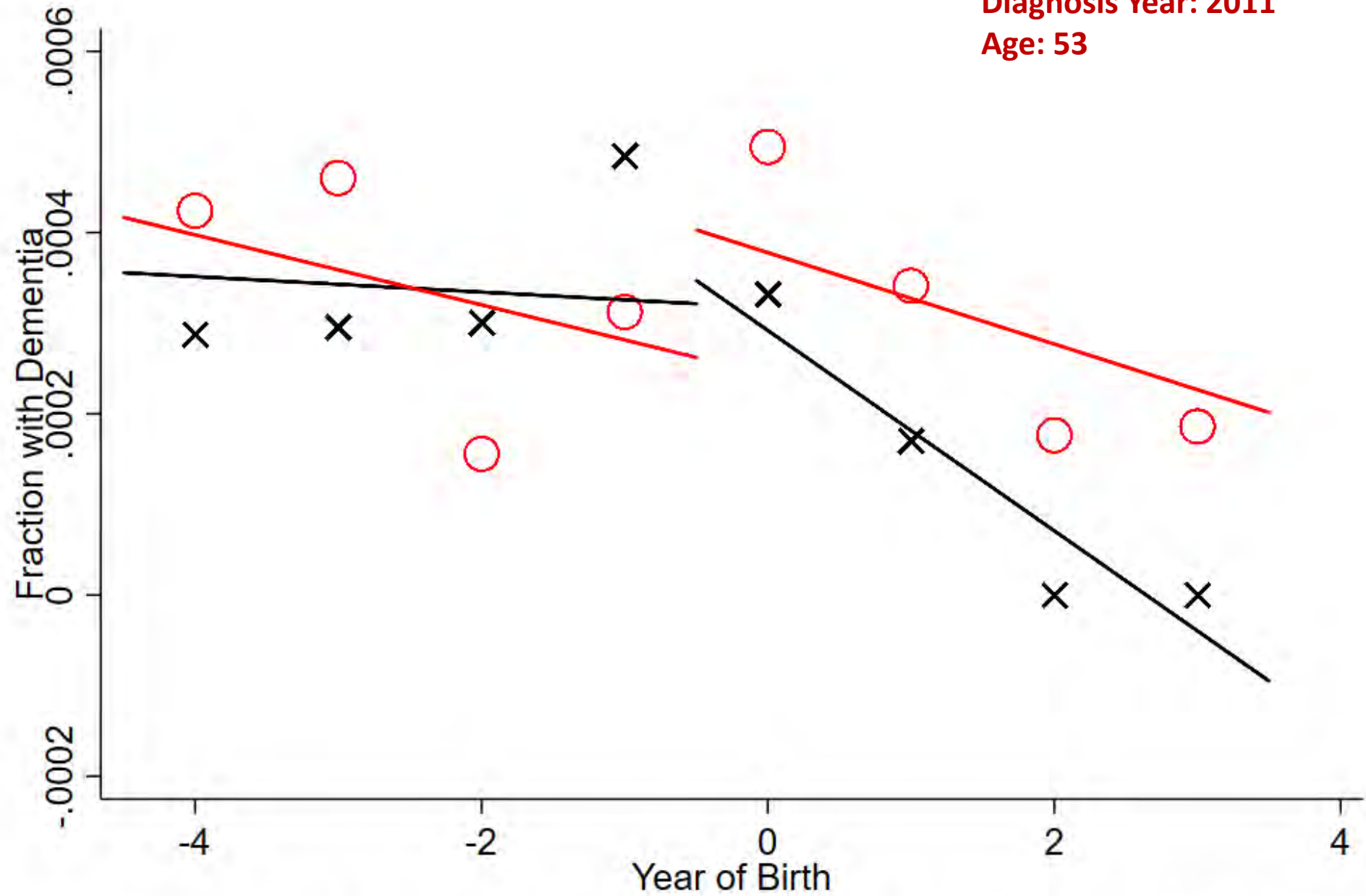


Diagnosis Year: 2011
Age: 53

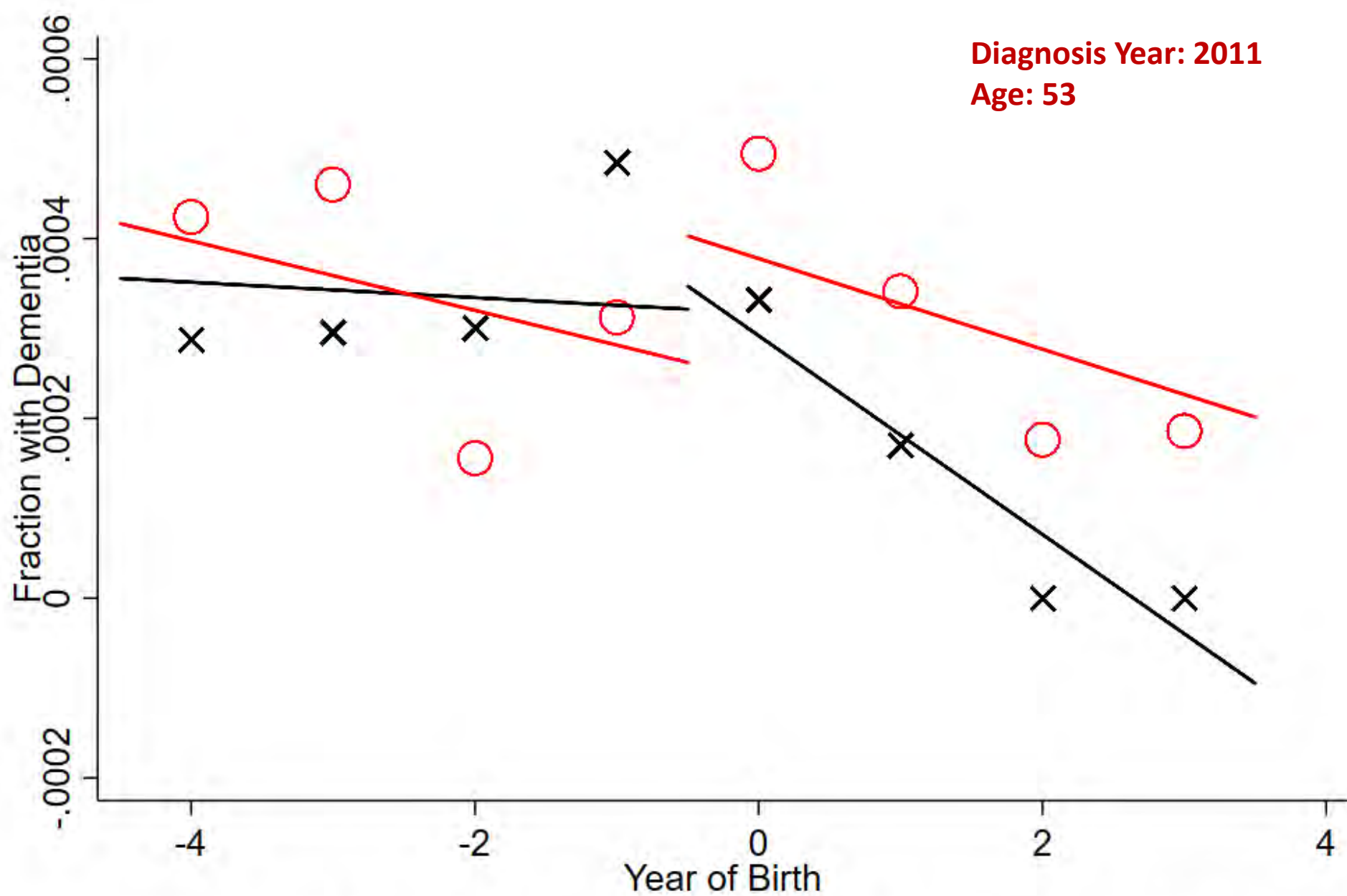


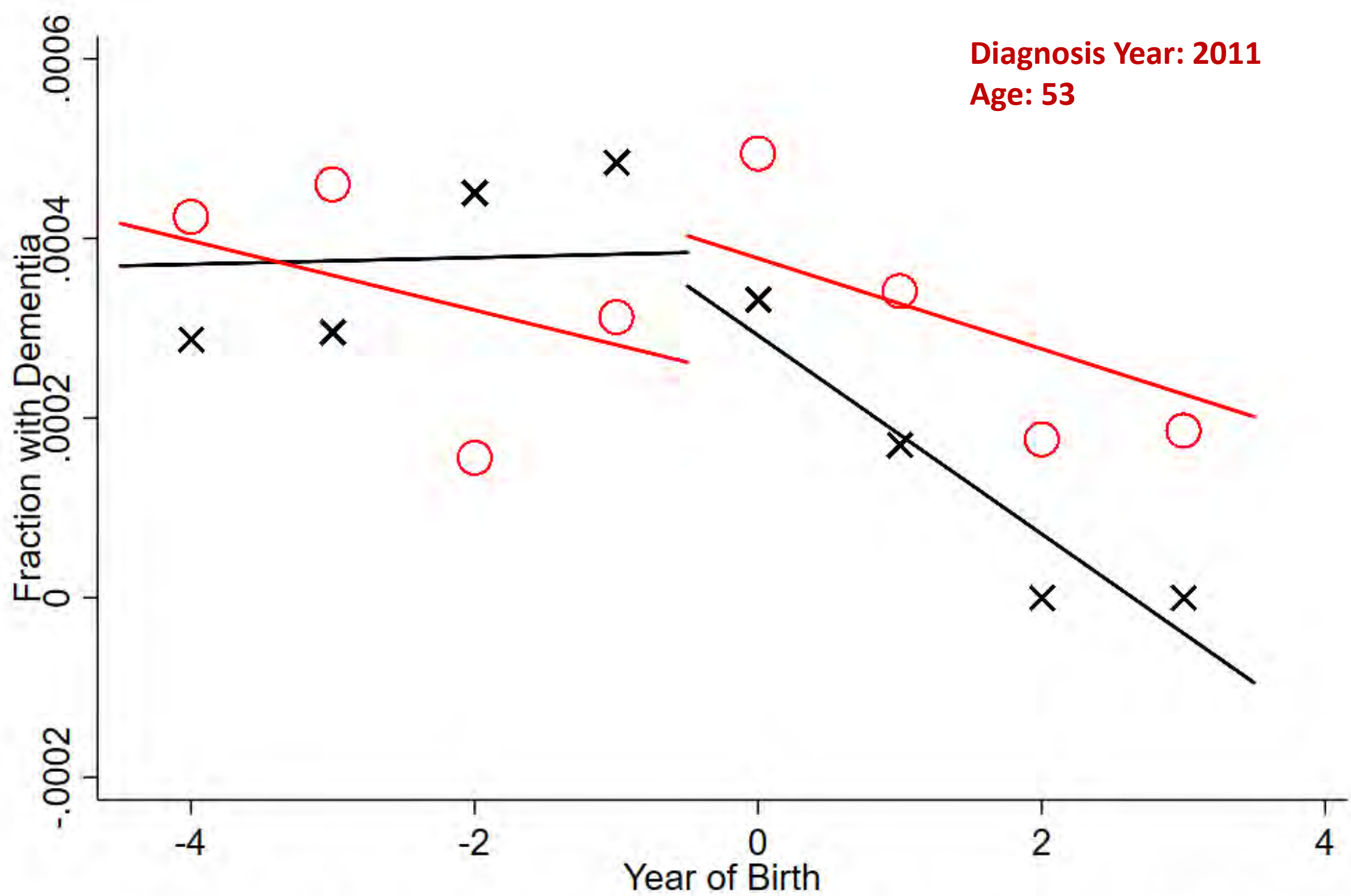
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

Diagnosis Year: 2011
Age: 53

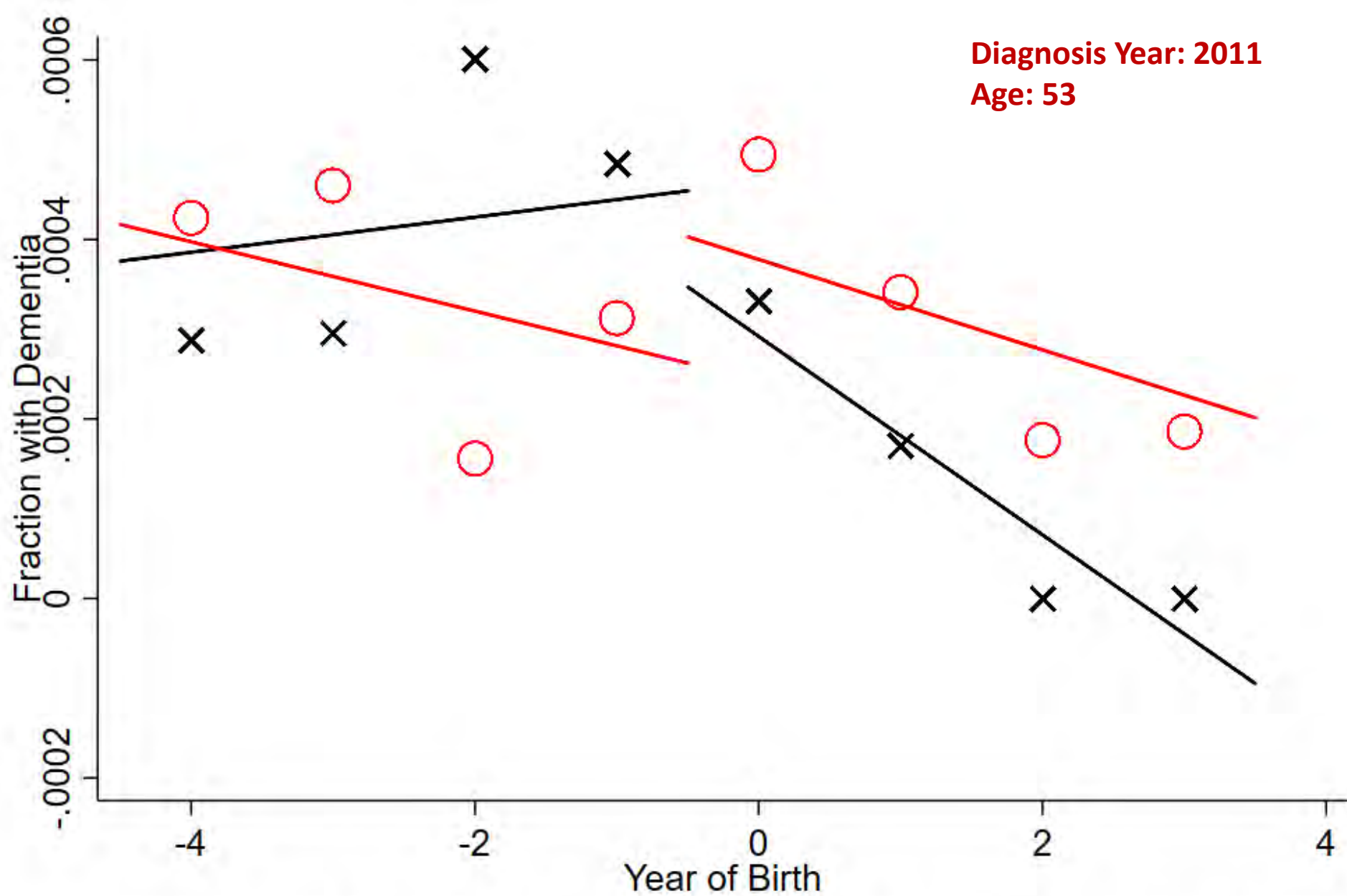


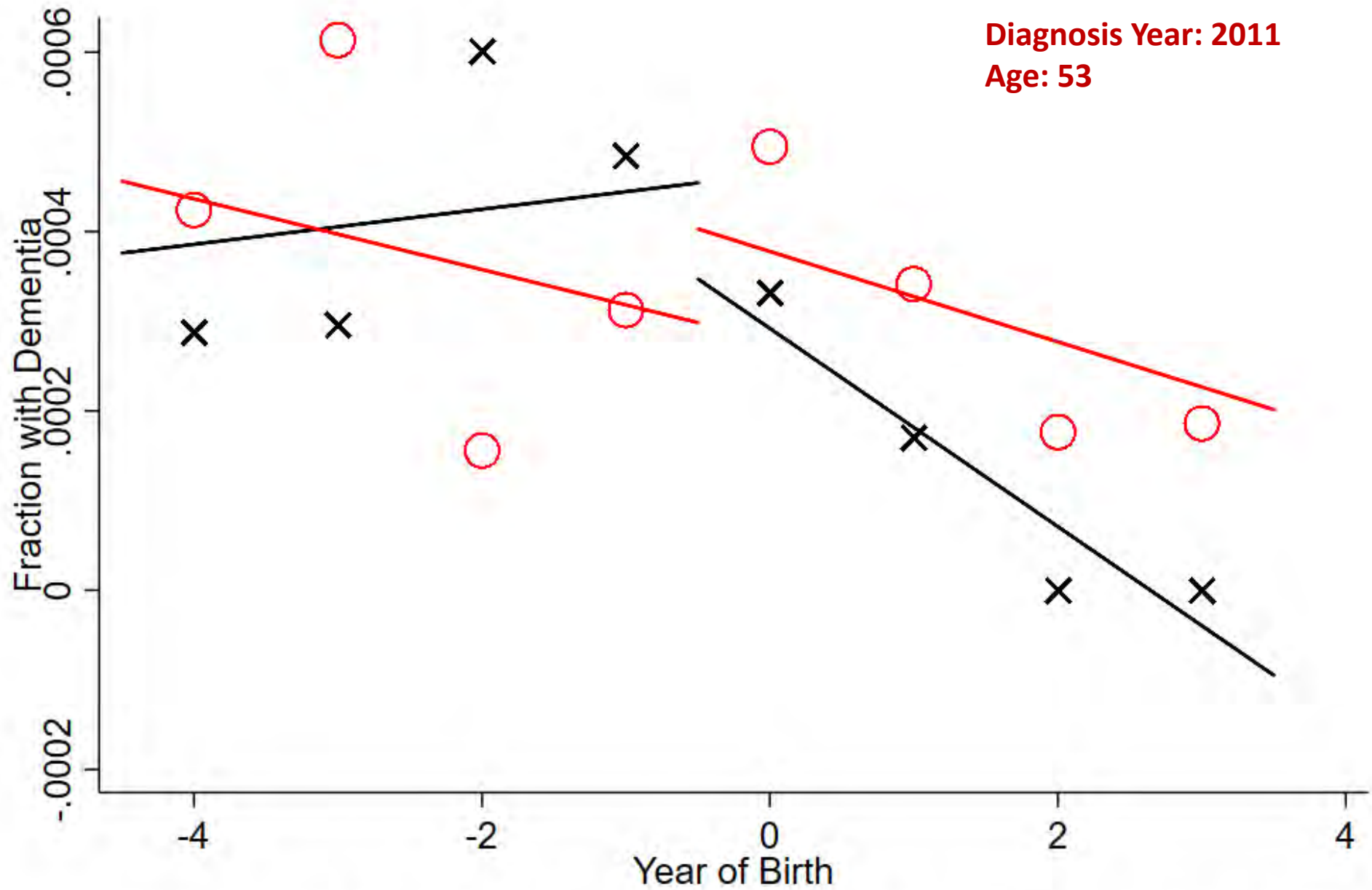
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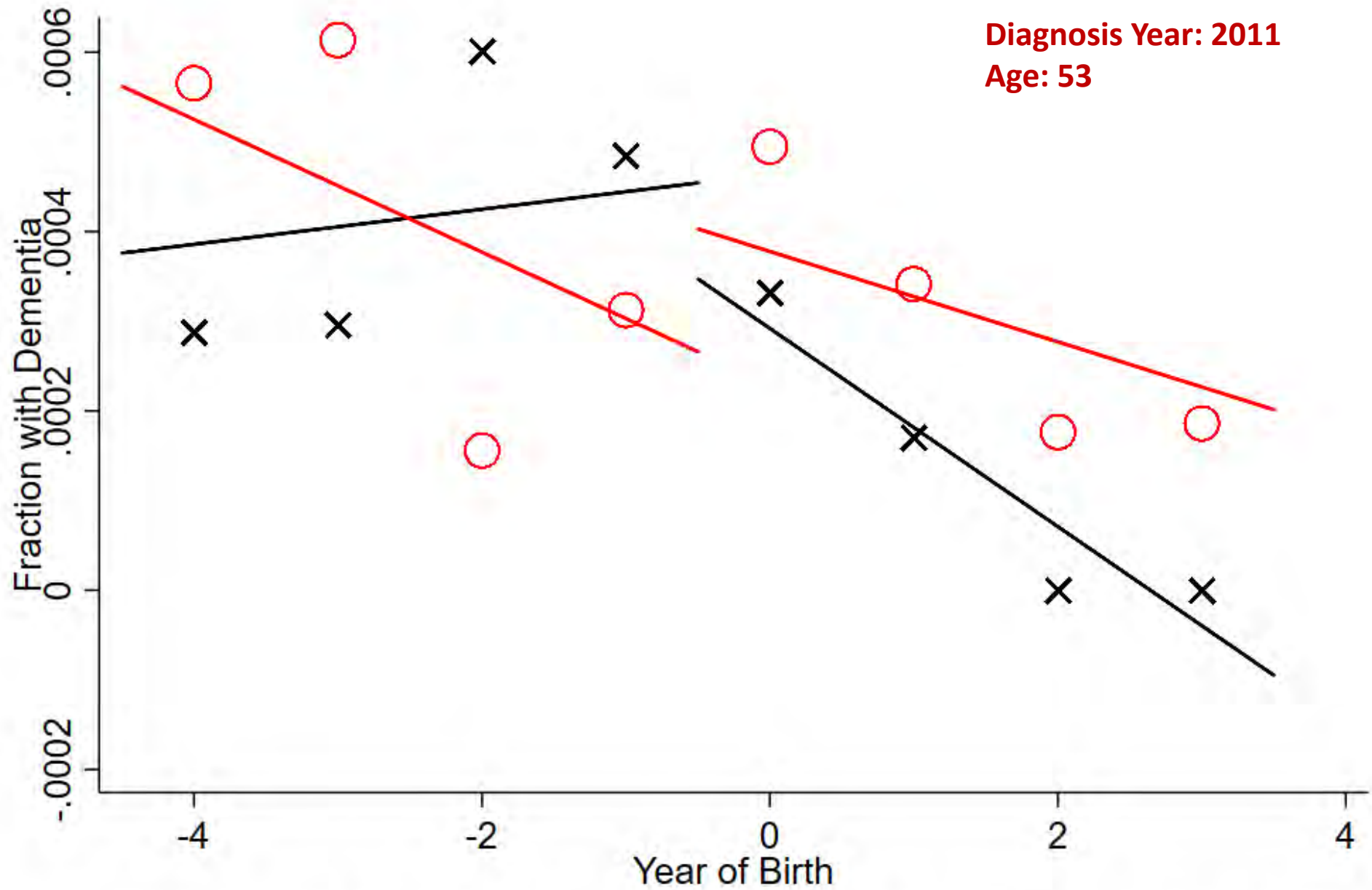


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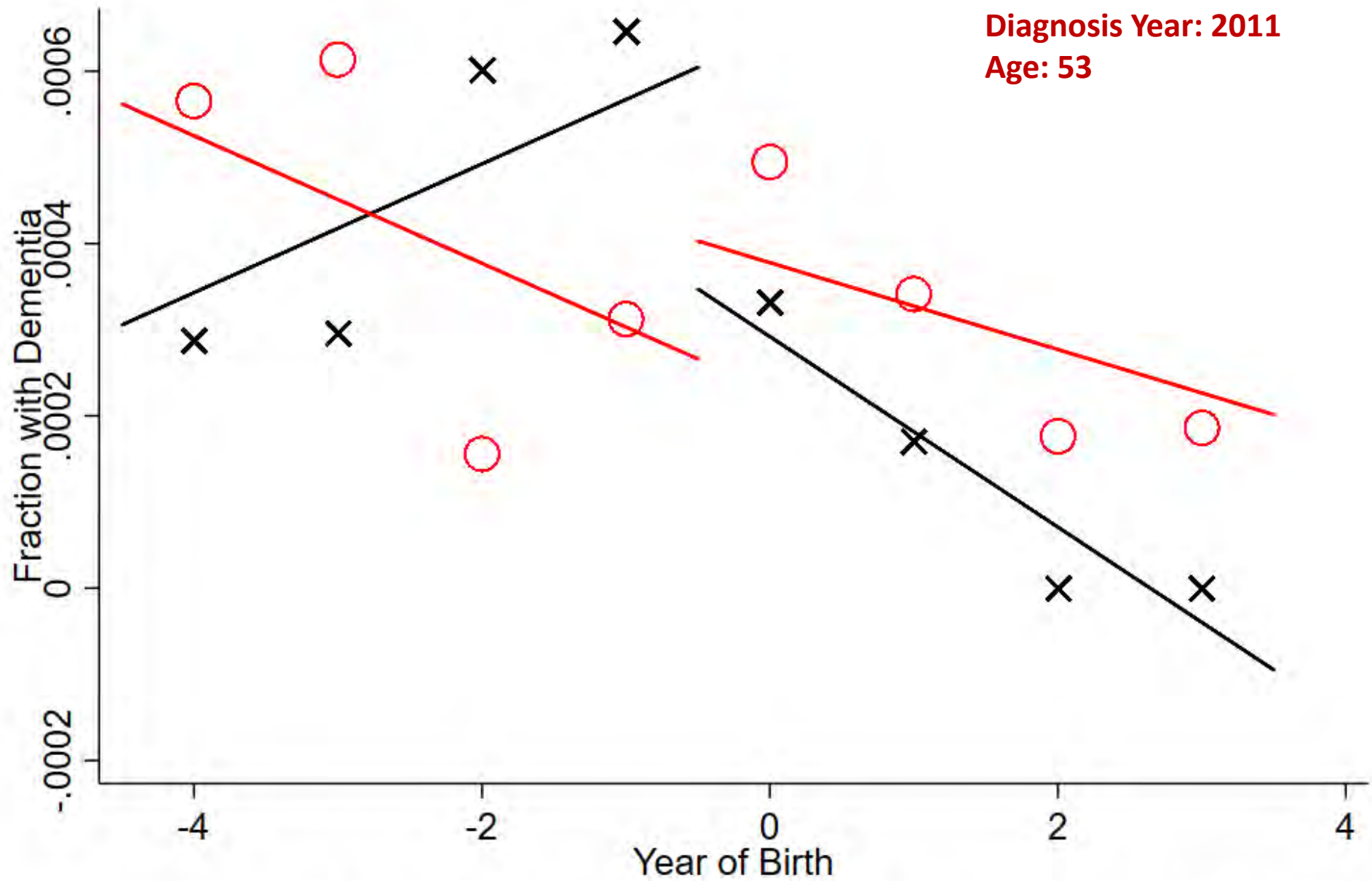




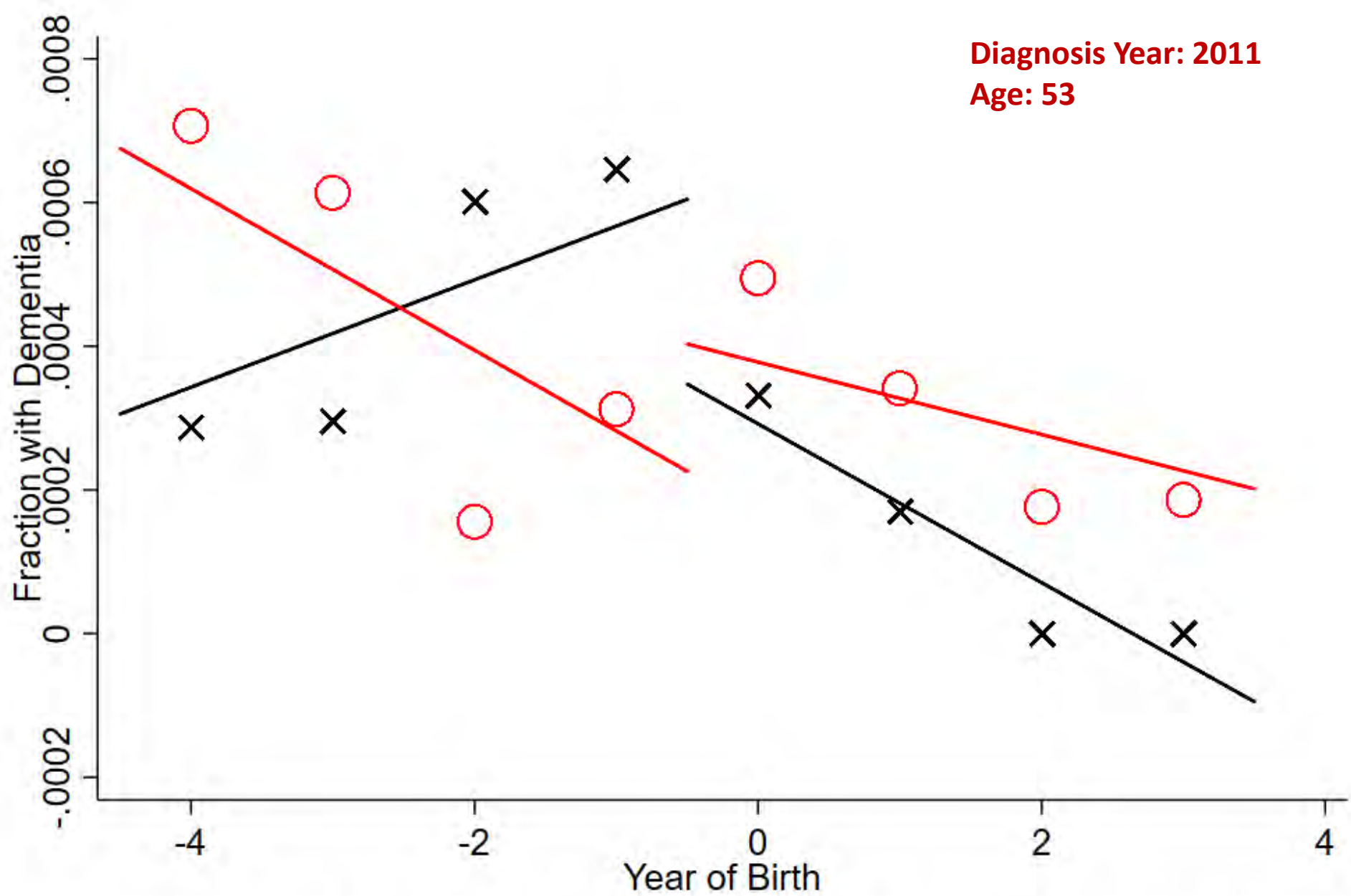
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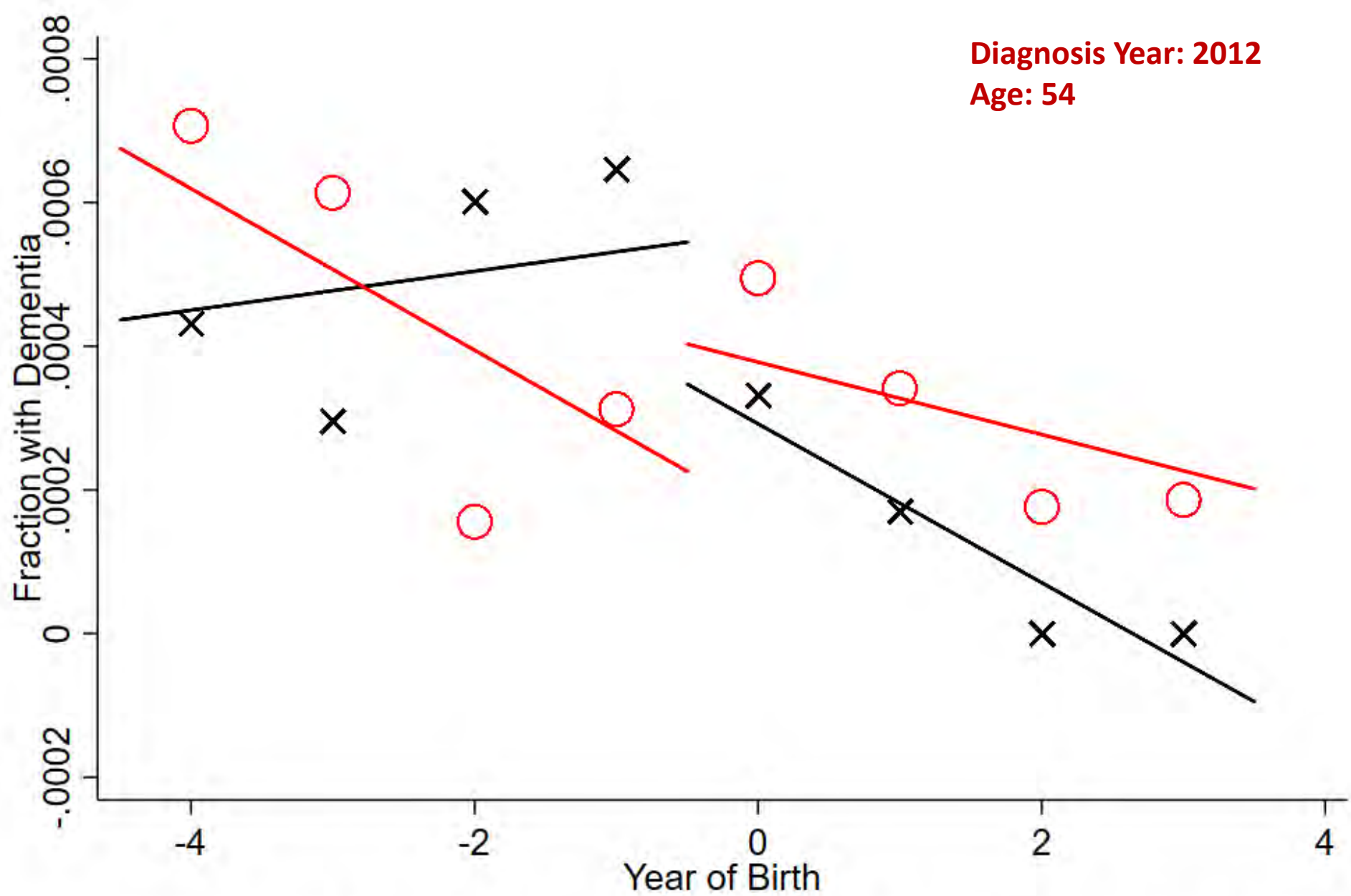
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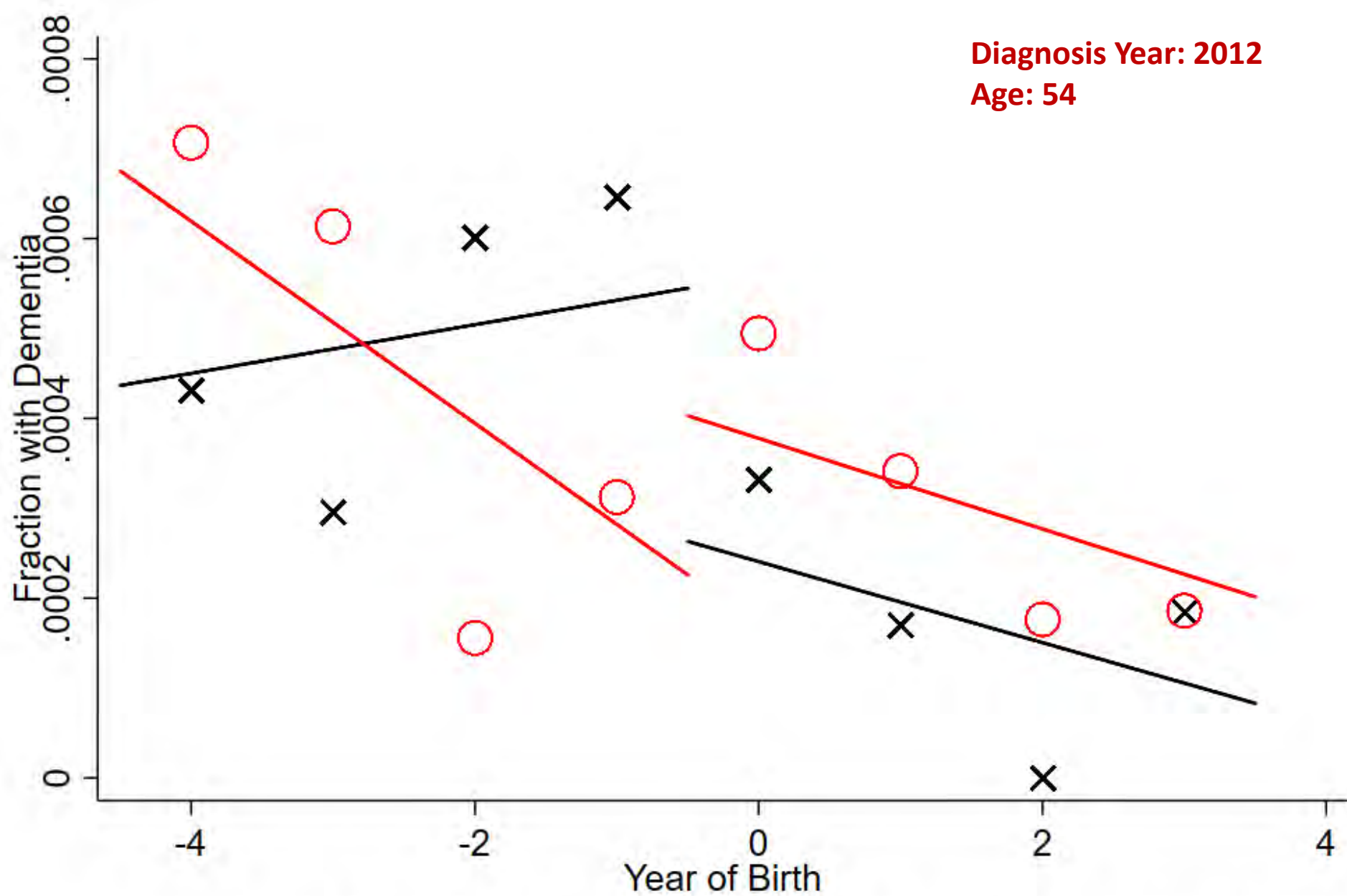


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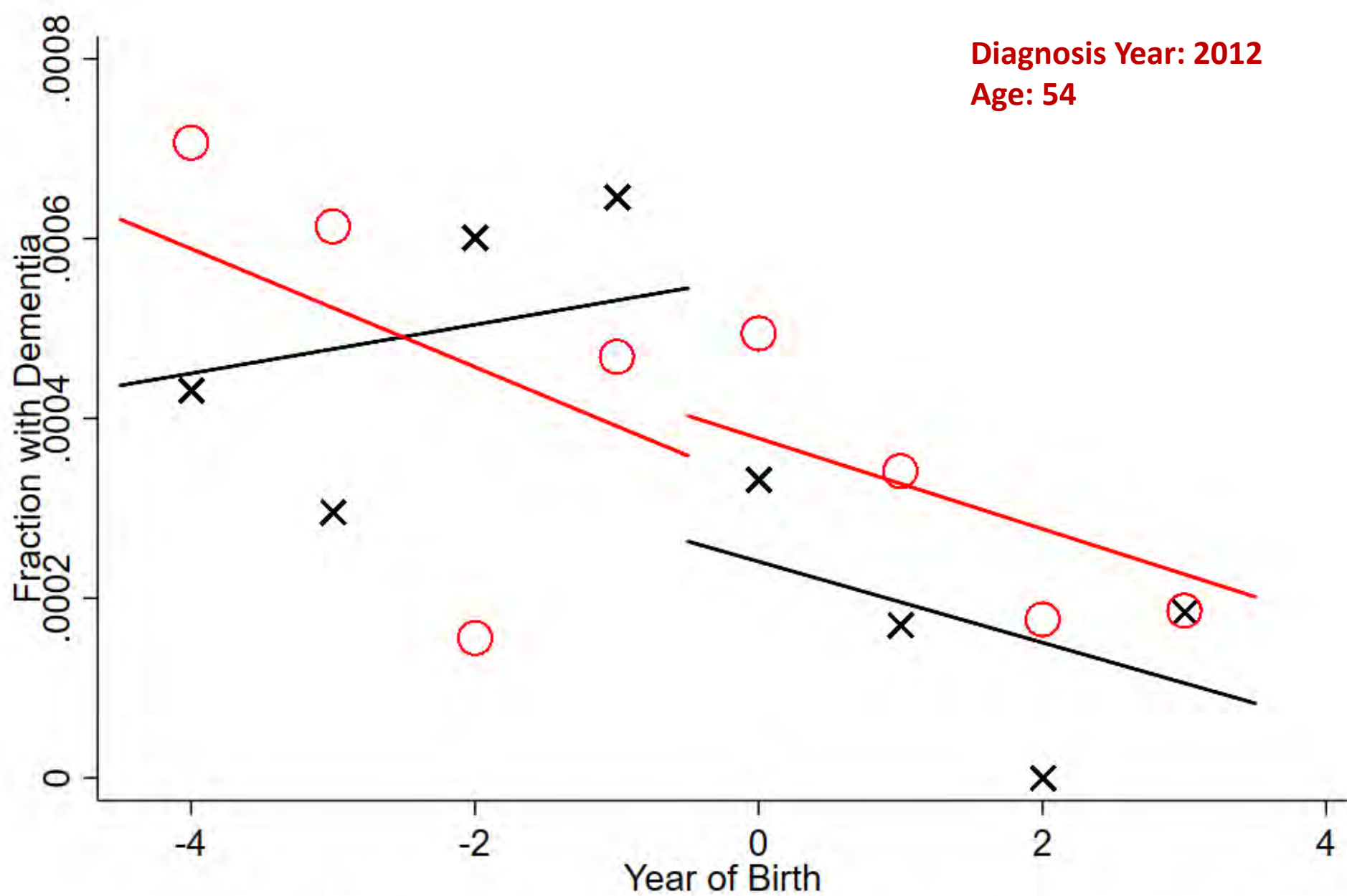
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Diagnosis Year: 2012
Age: 54

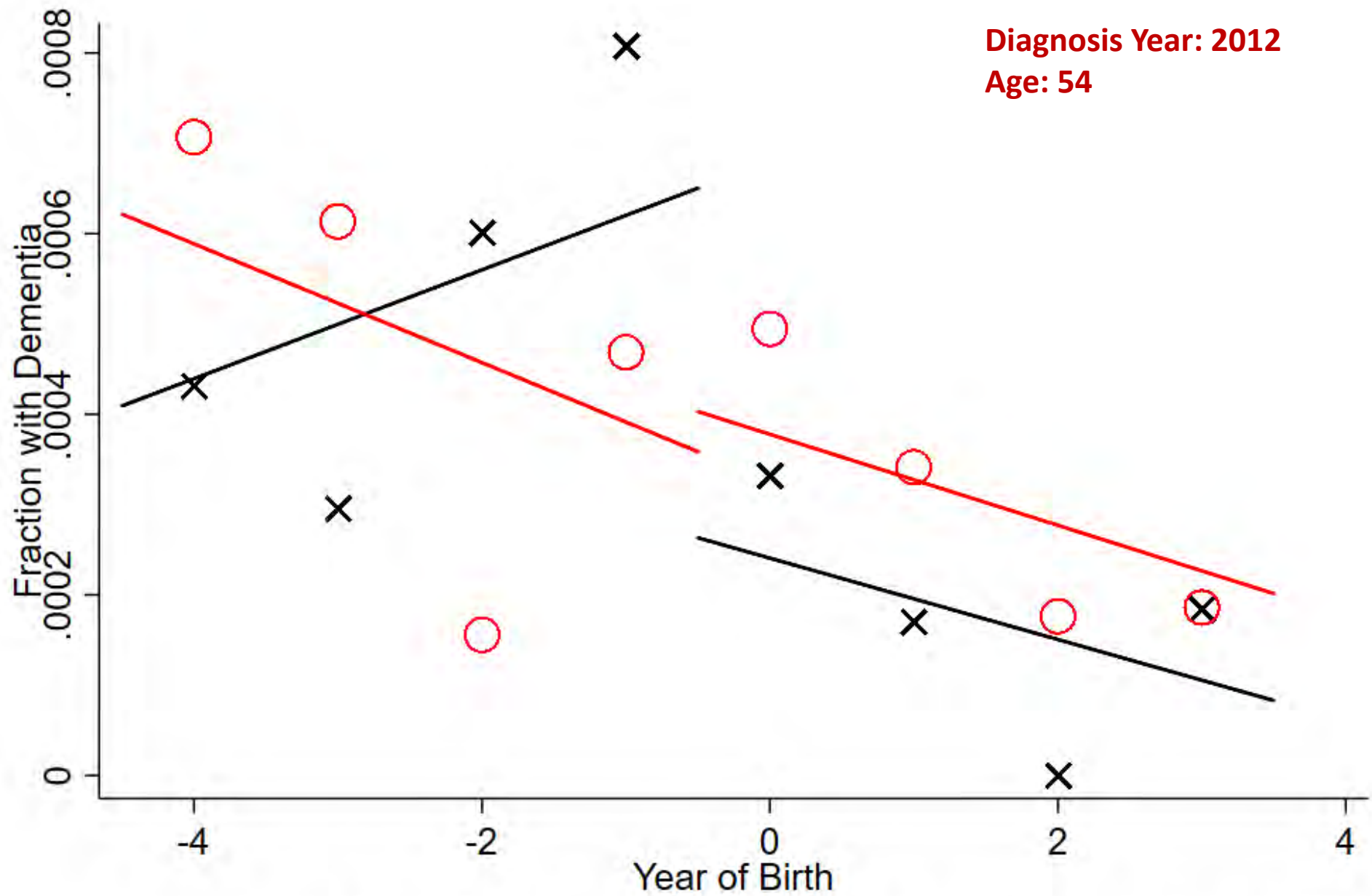


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Diagnosis Year: 2012
Age: 54

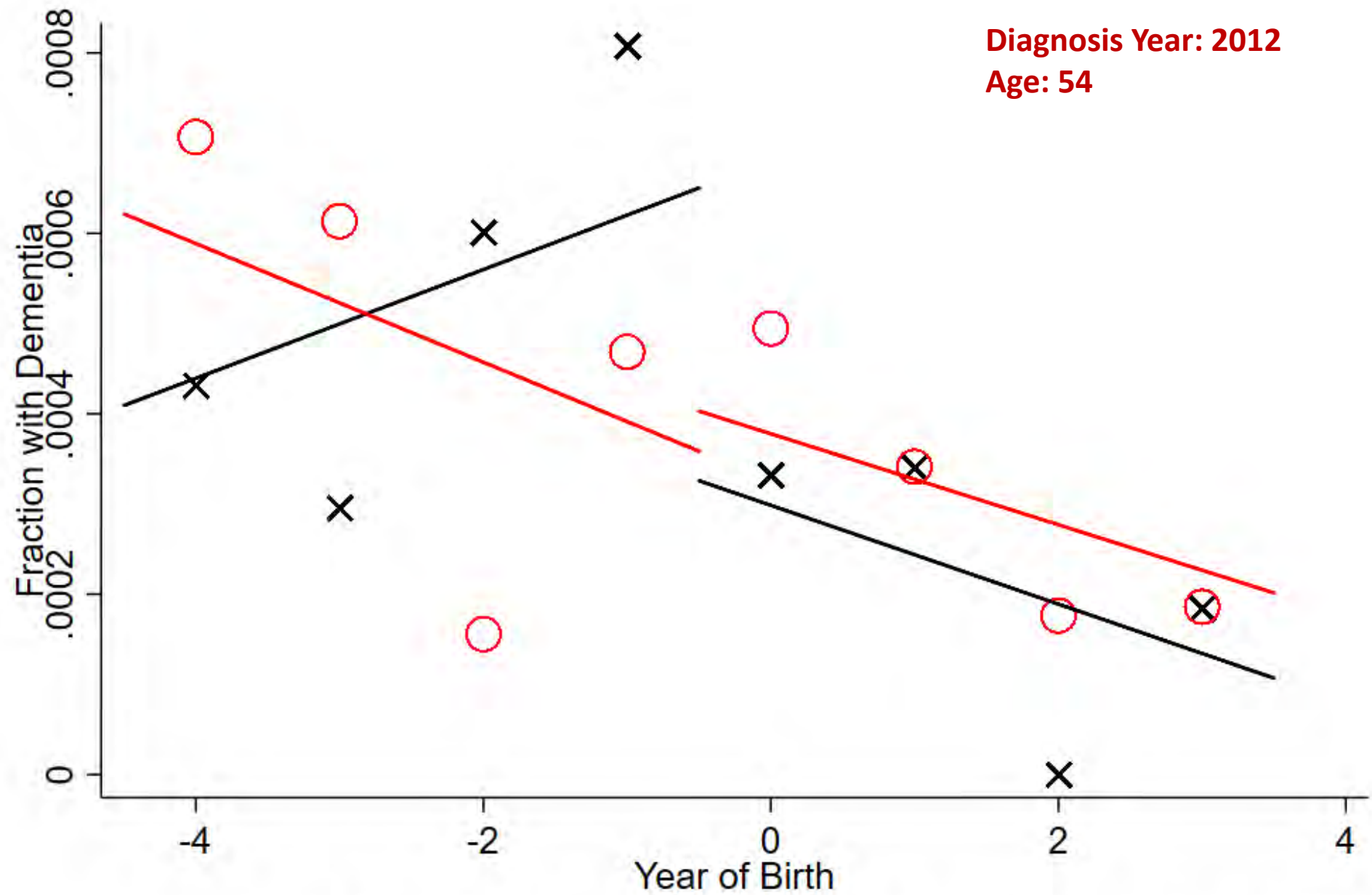


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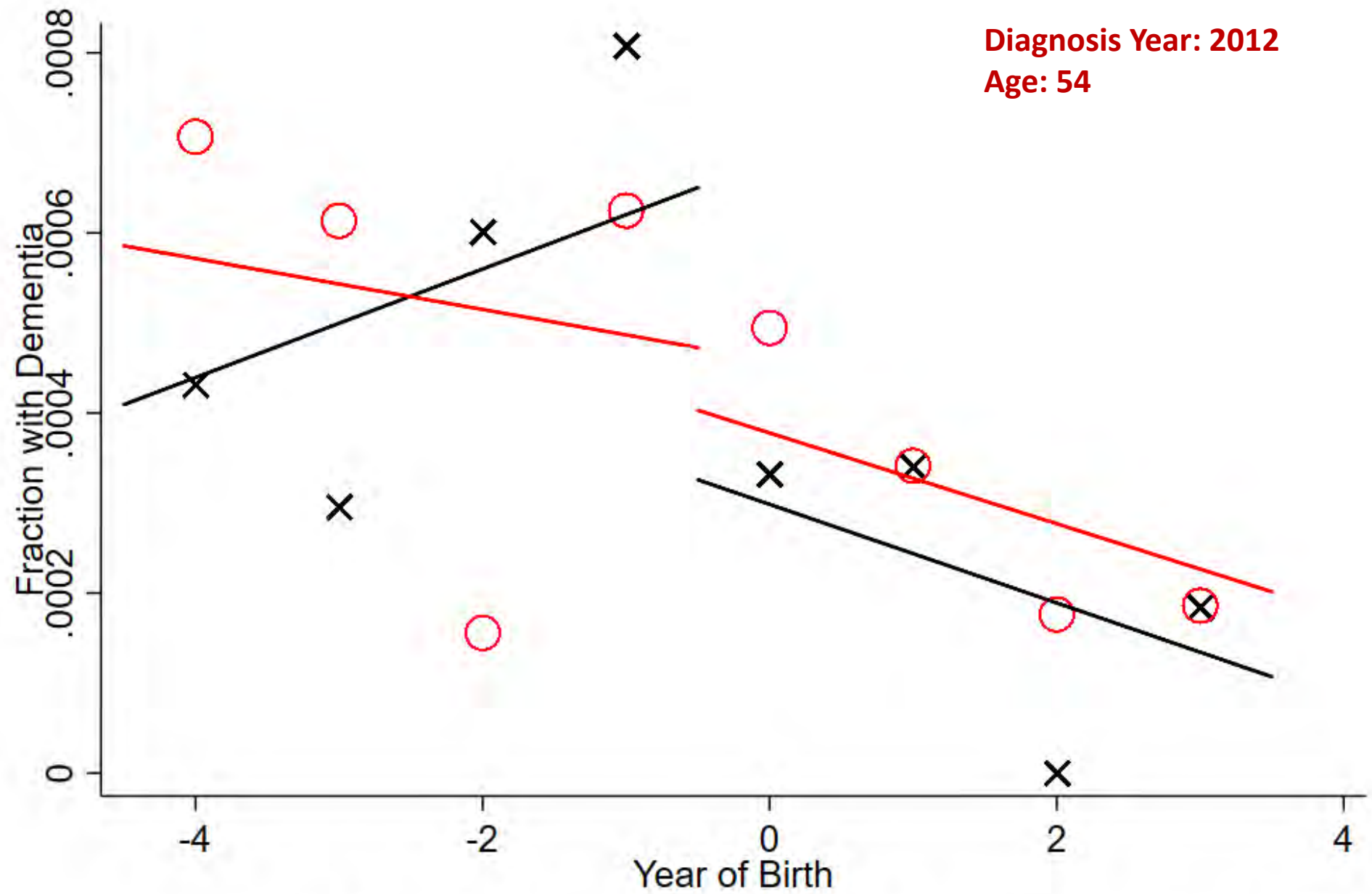
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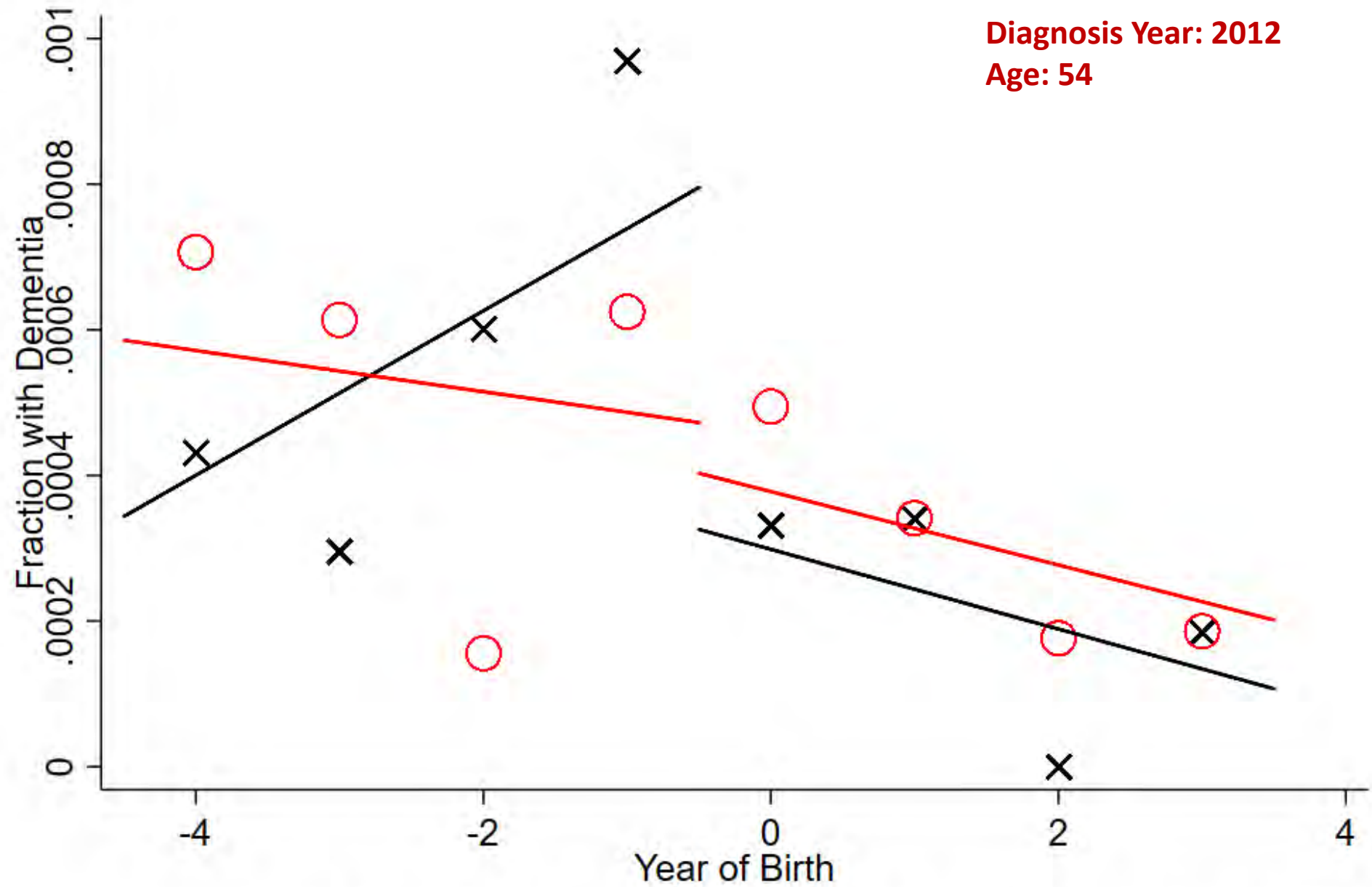
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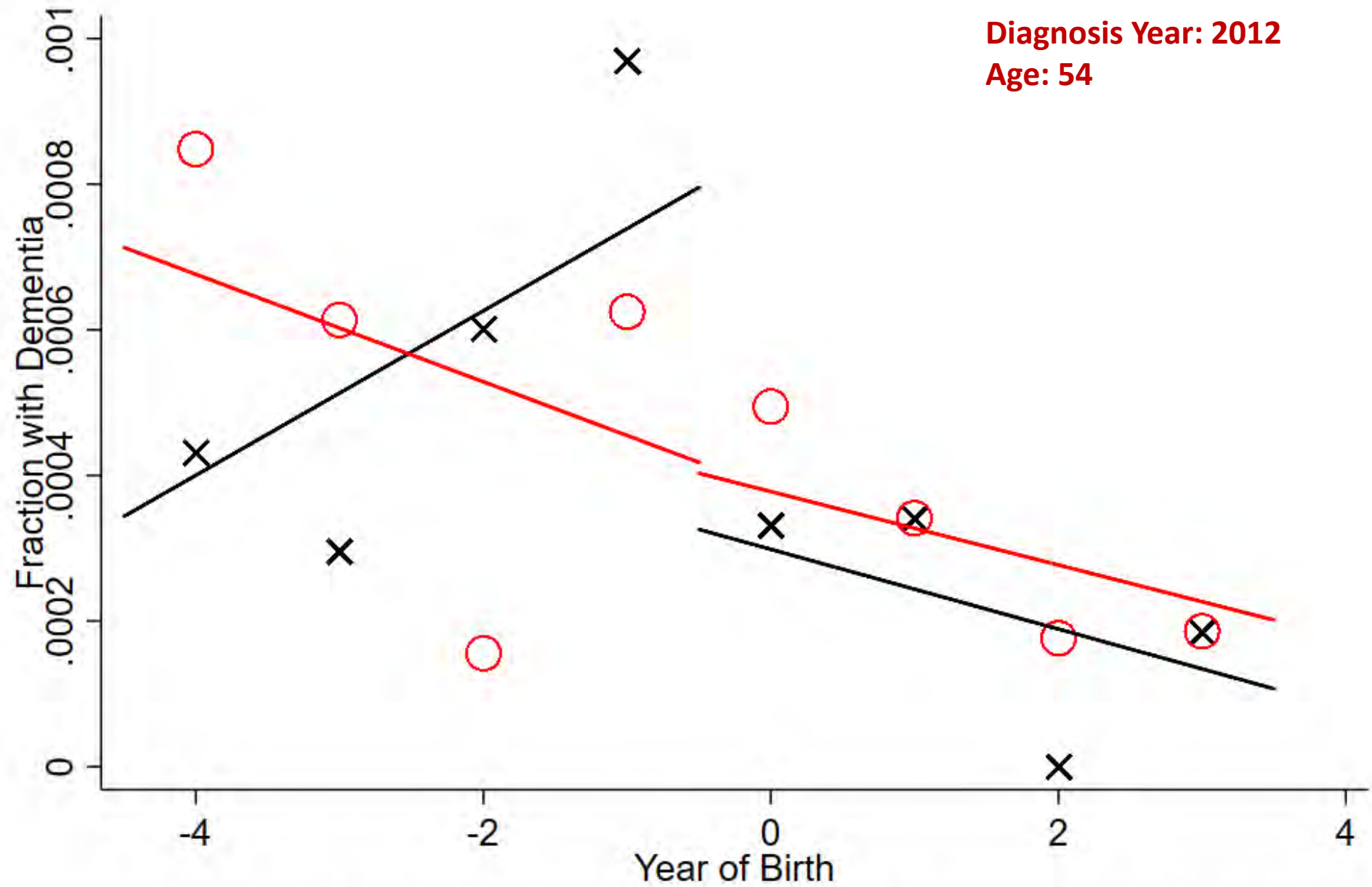
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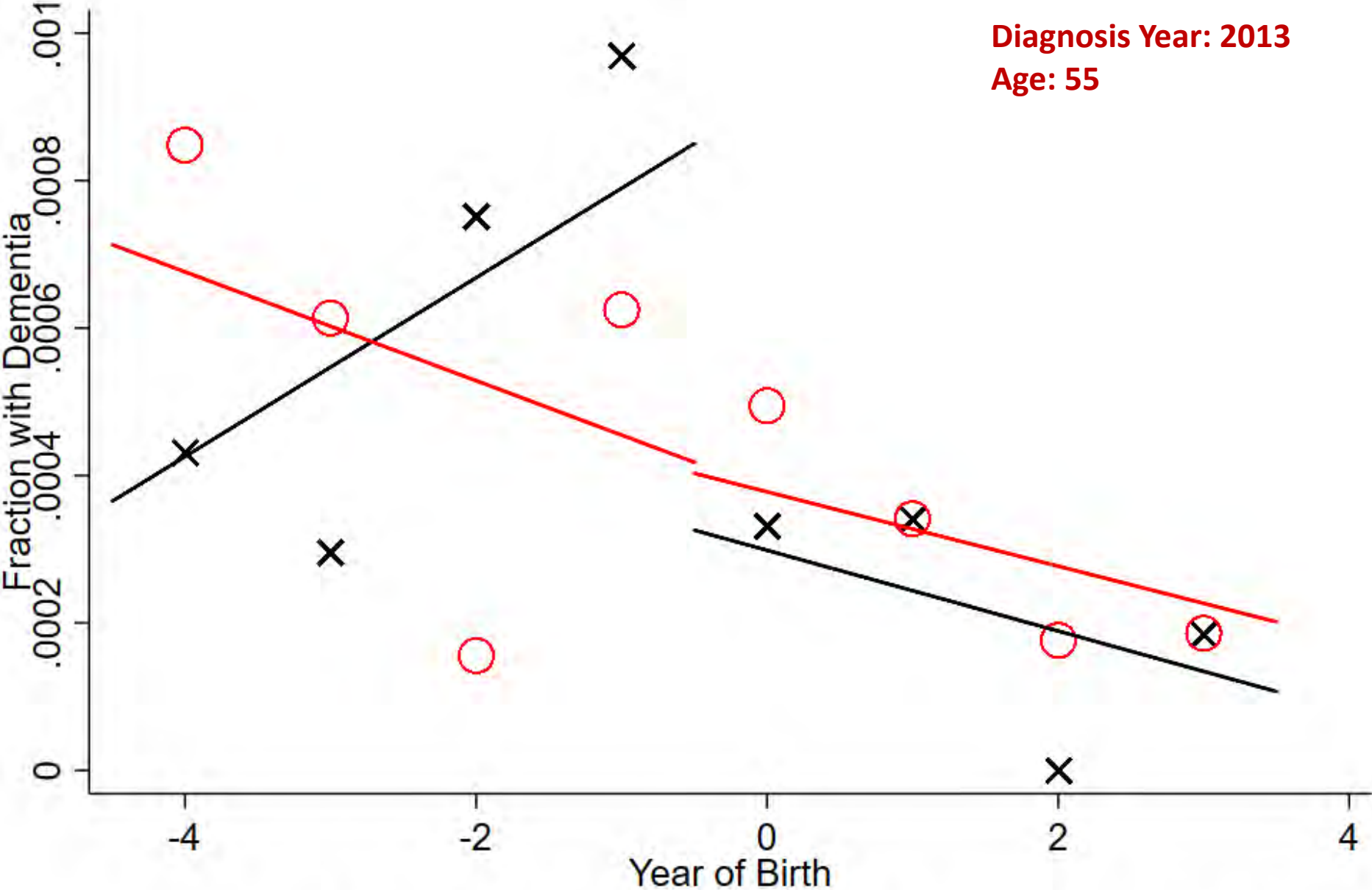
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Age: 54



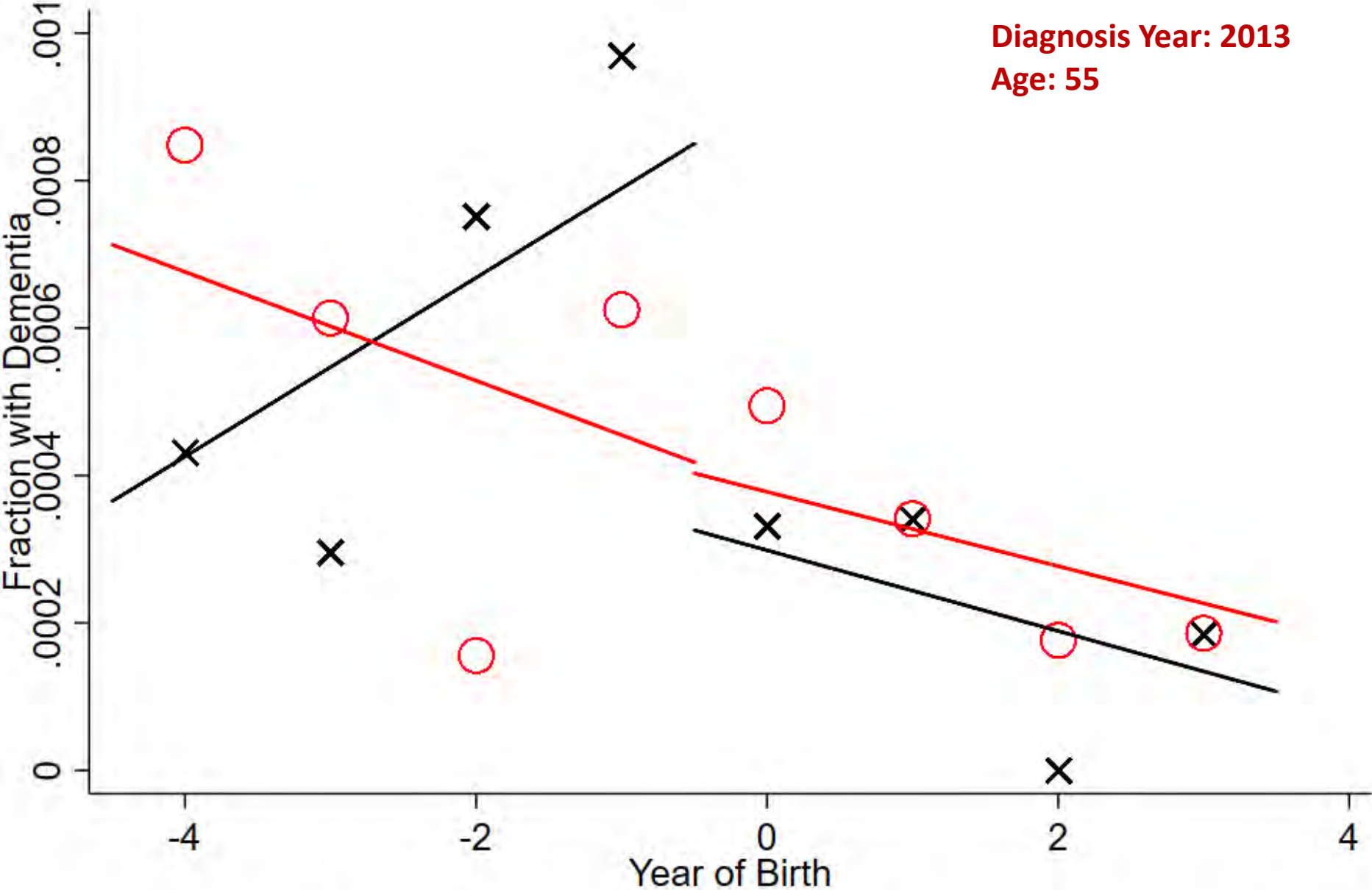
X Bottom Half Composite Genetic Risk O Top Half Composite Genetic Risk

Diagnosis Year: 2013
Age: 55



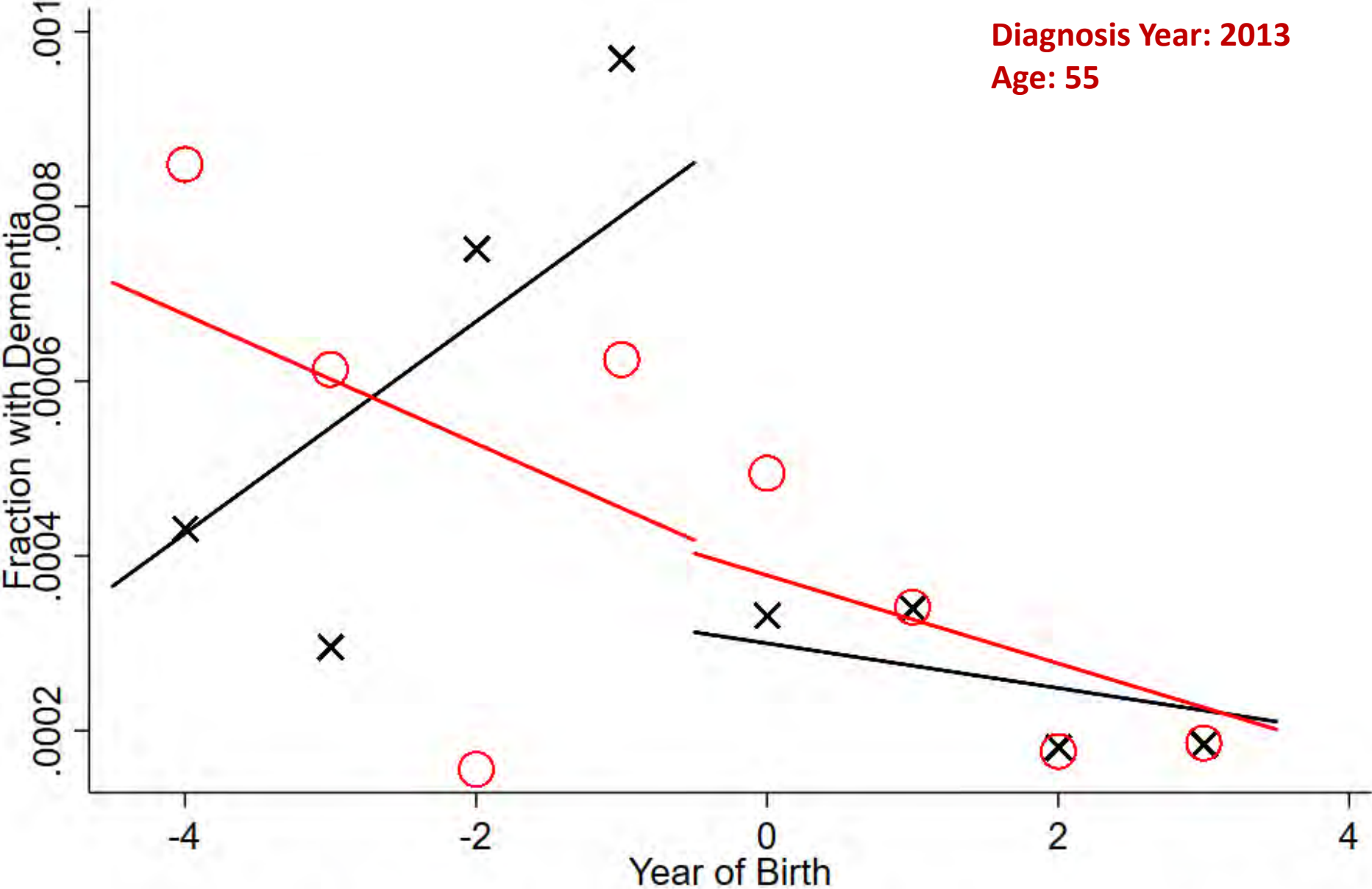
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Diagnosis Year: 2013
Age: 55



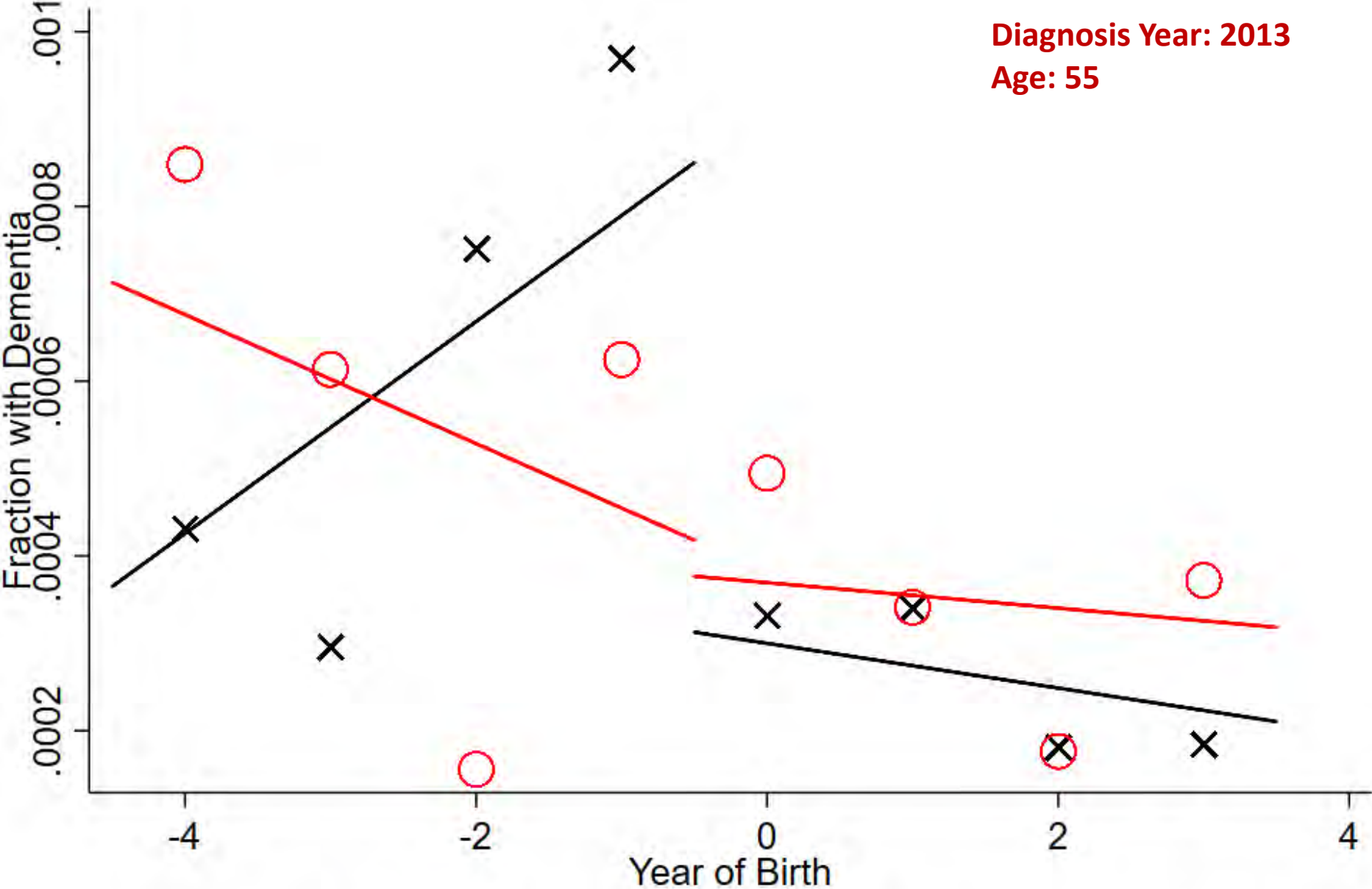
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Diagnosis Year: 2013
Age: 55

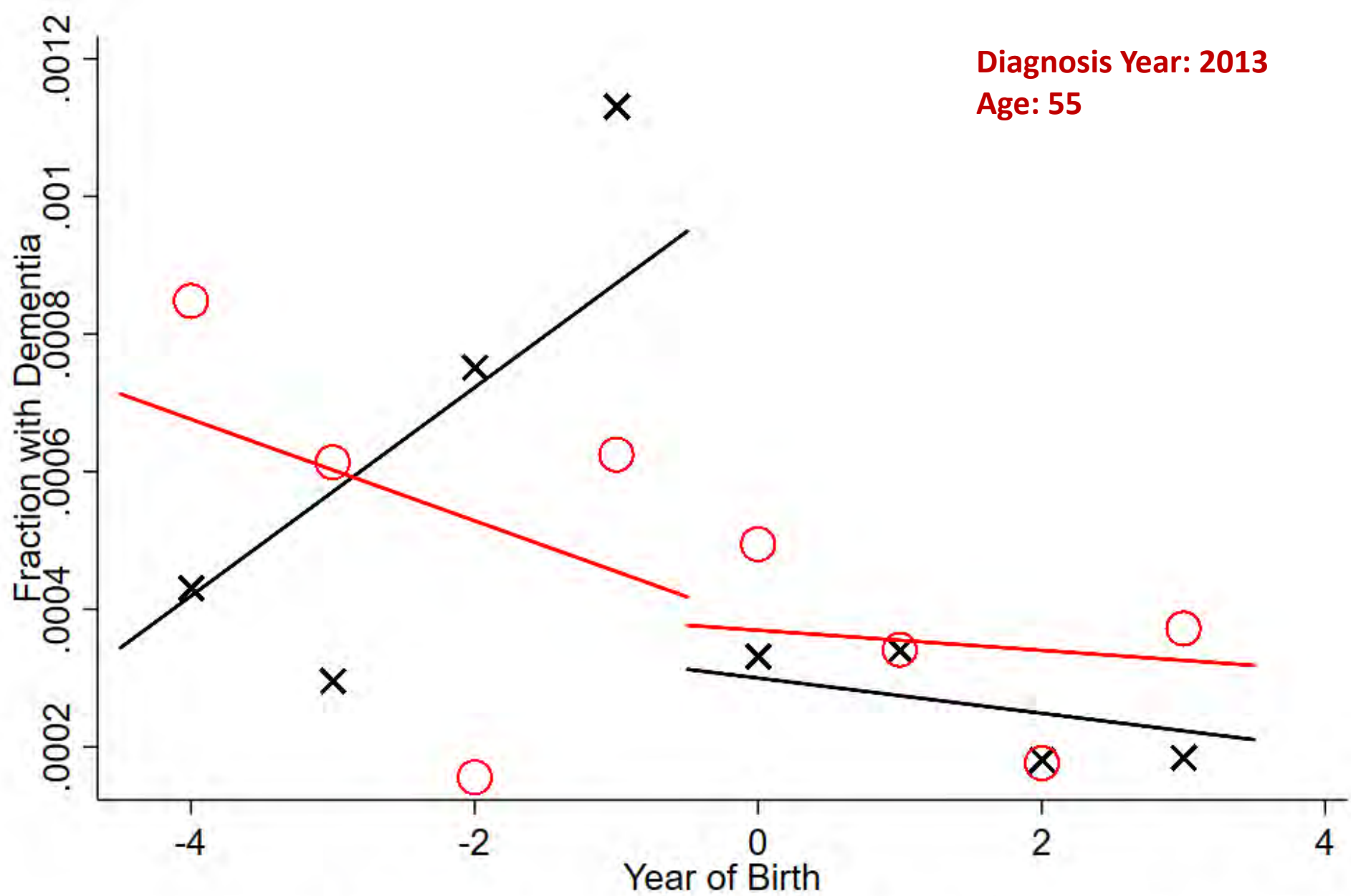


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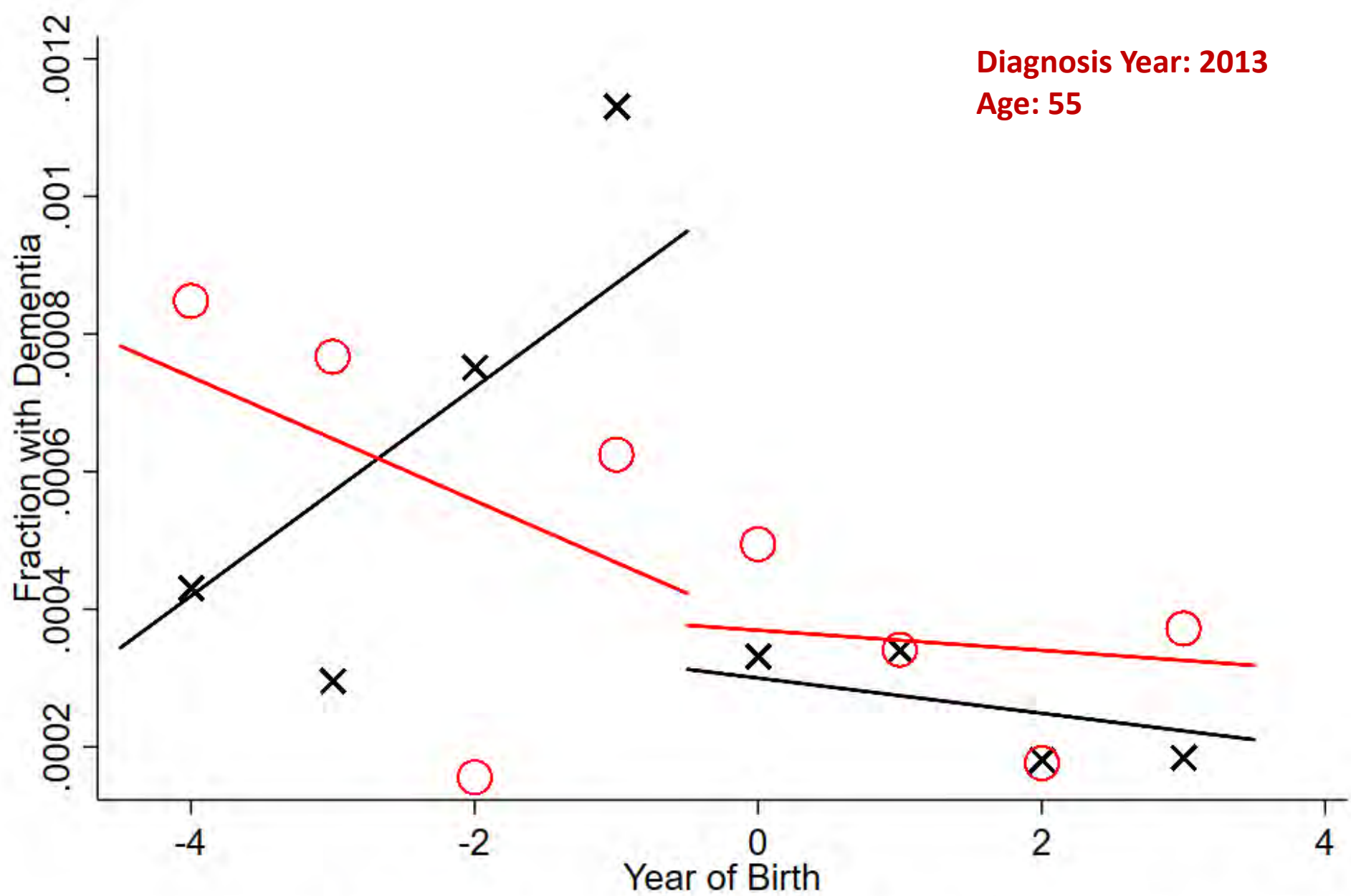
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Age: 55



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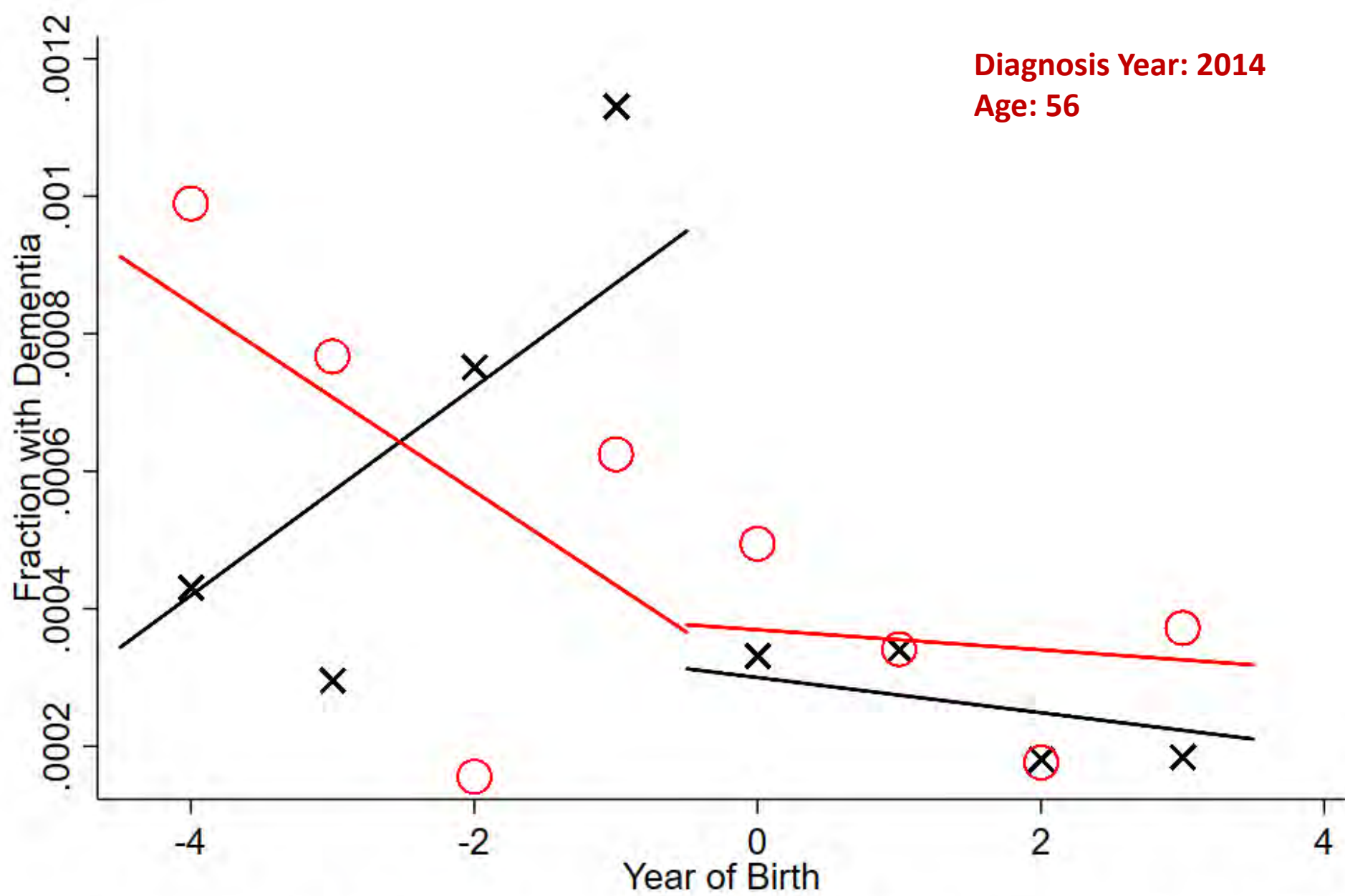


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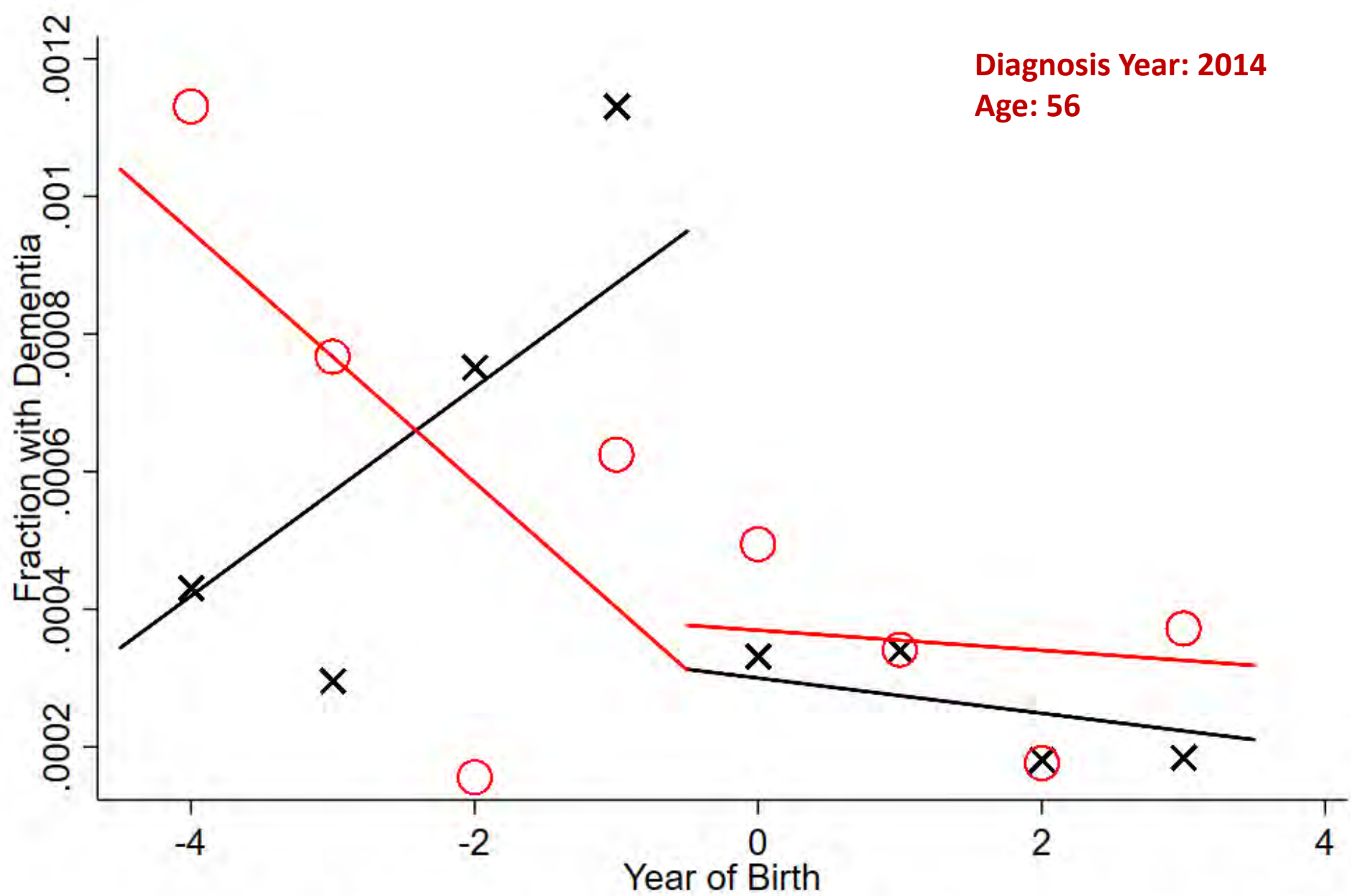


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Diagnosis Year: 2014
Age: 56

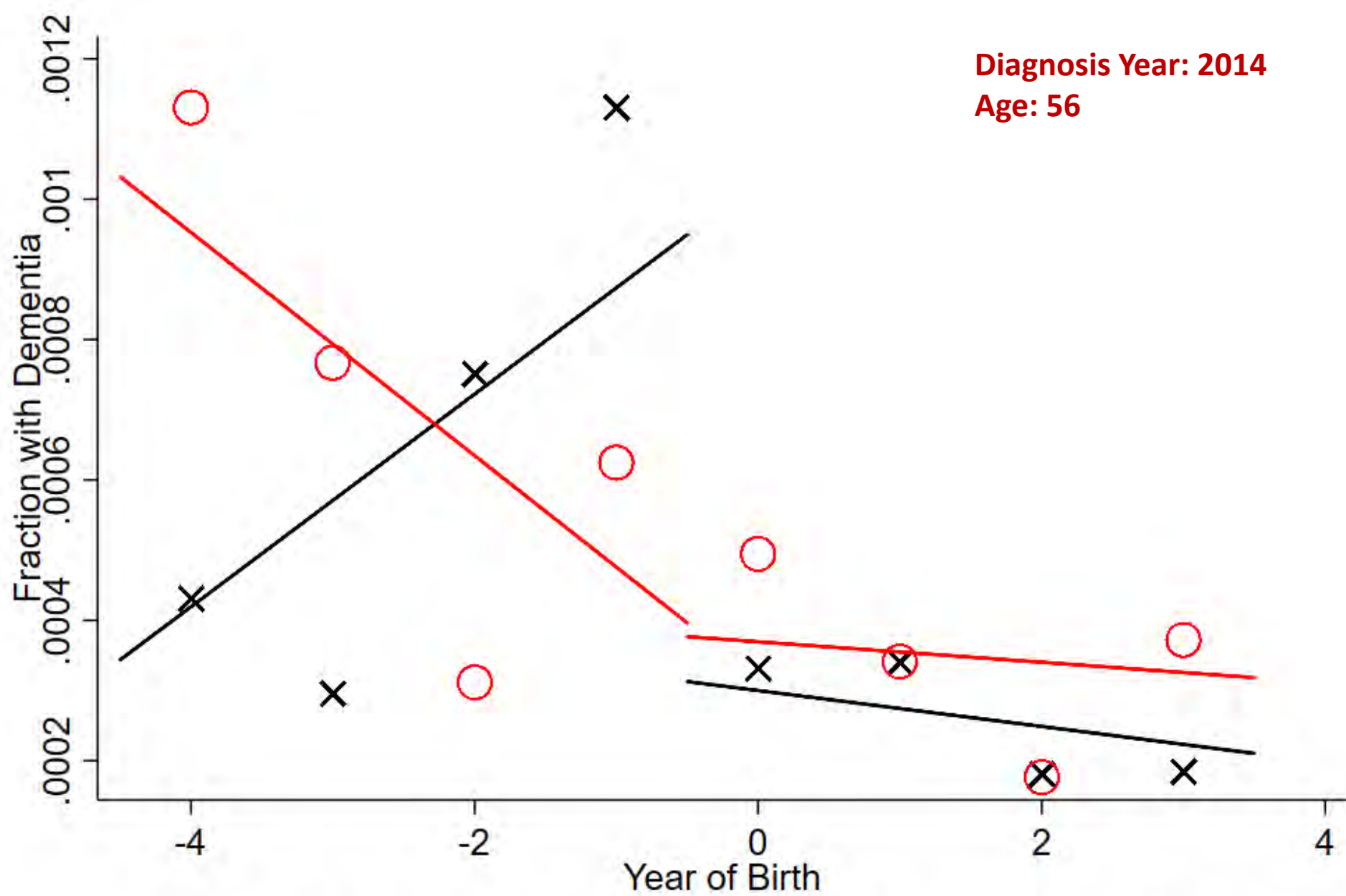


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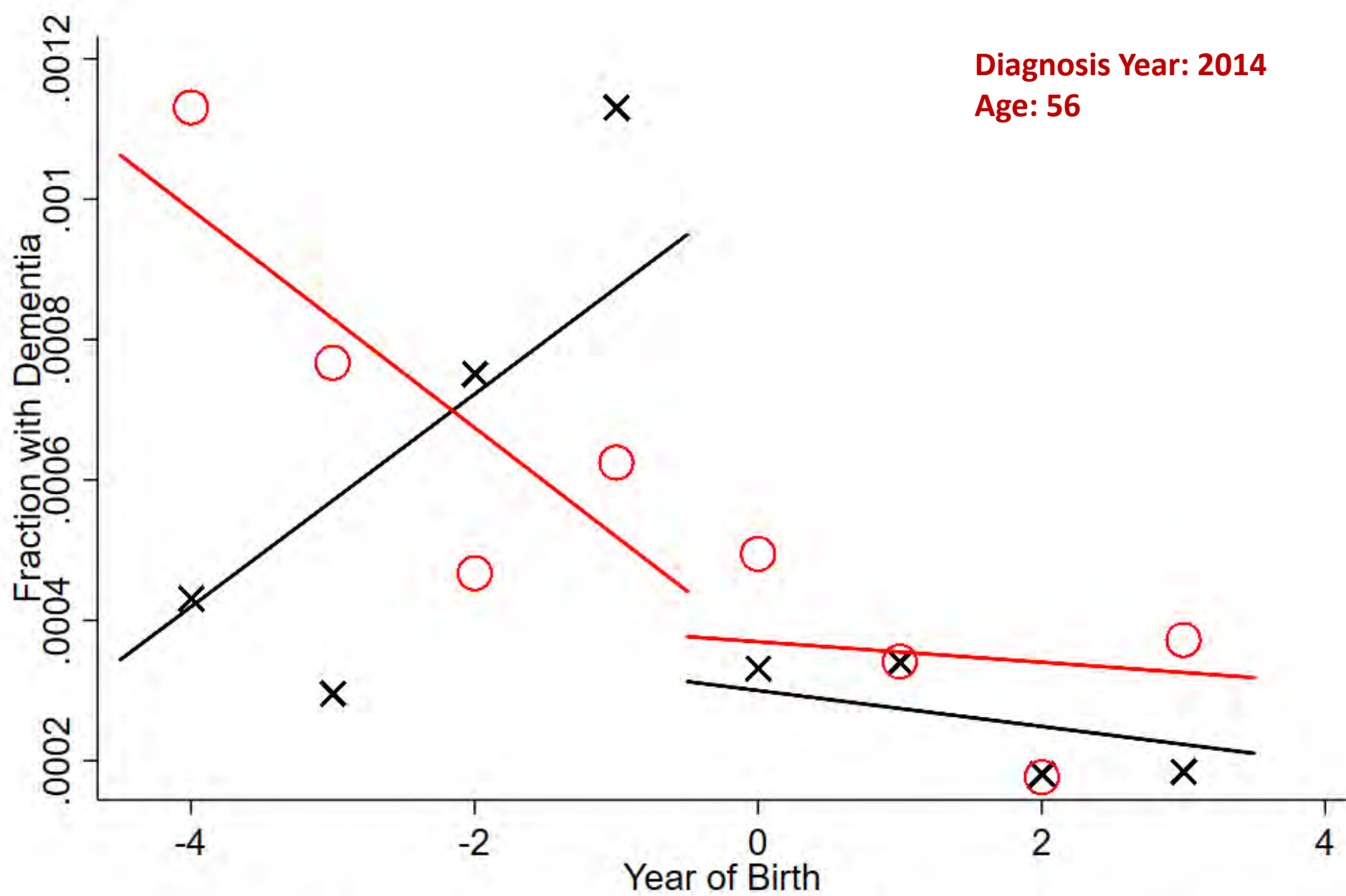
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Diagnosis Year: 2014
Age: 56

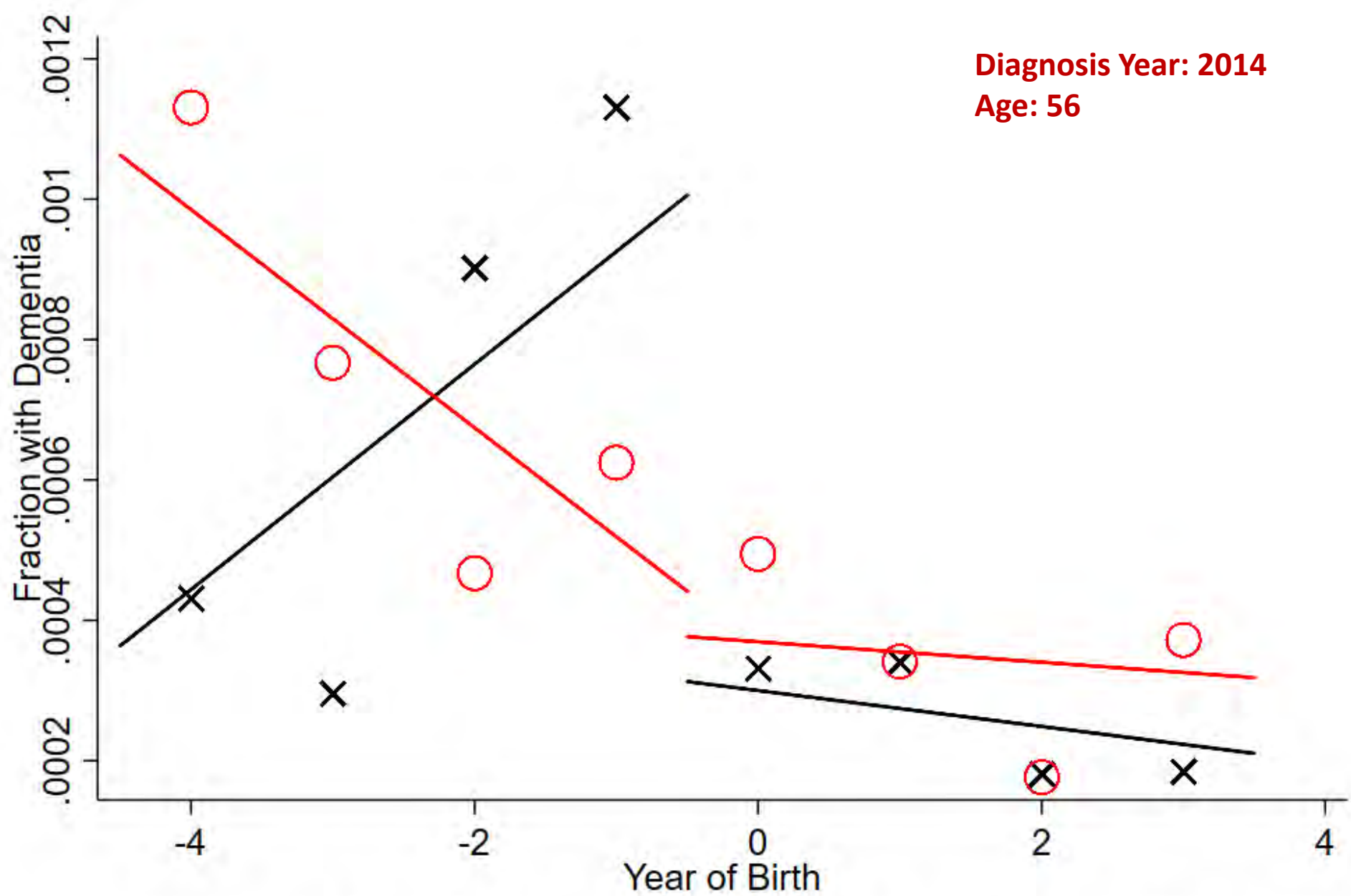


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Diagnosis Year: 2014
Age: 56

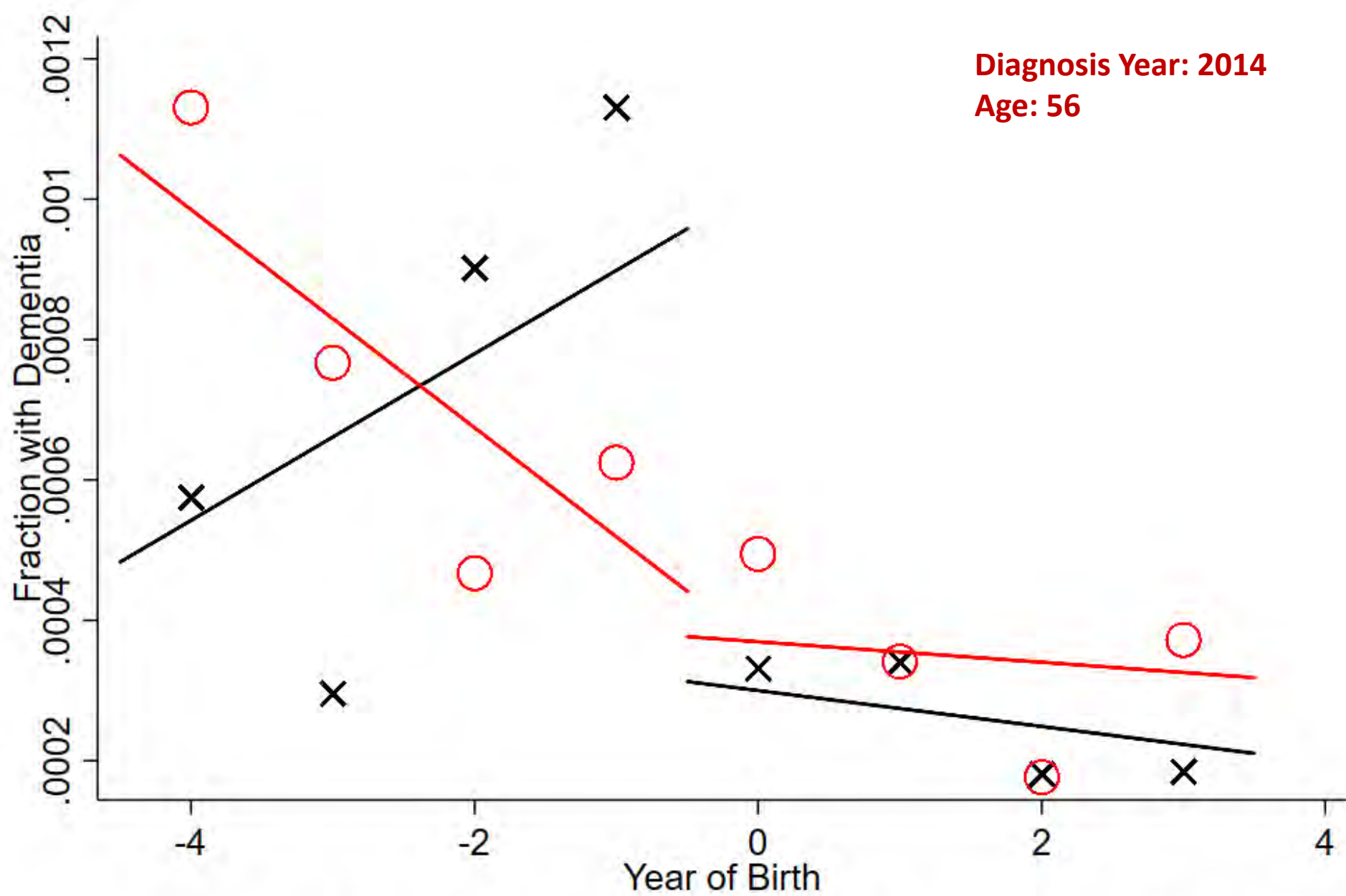


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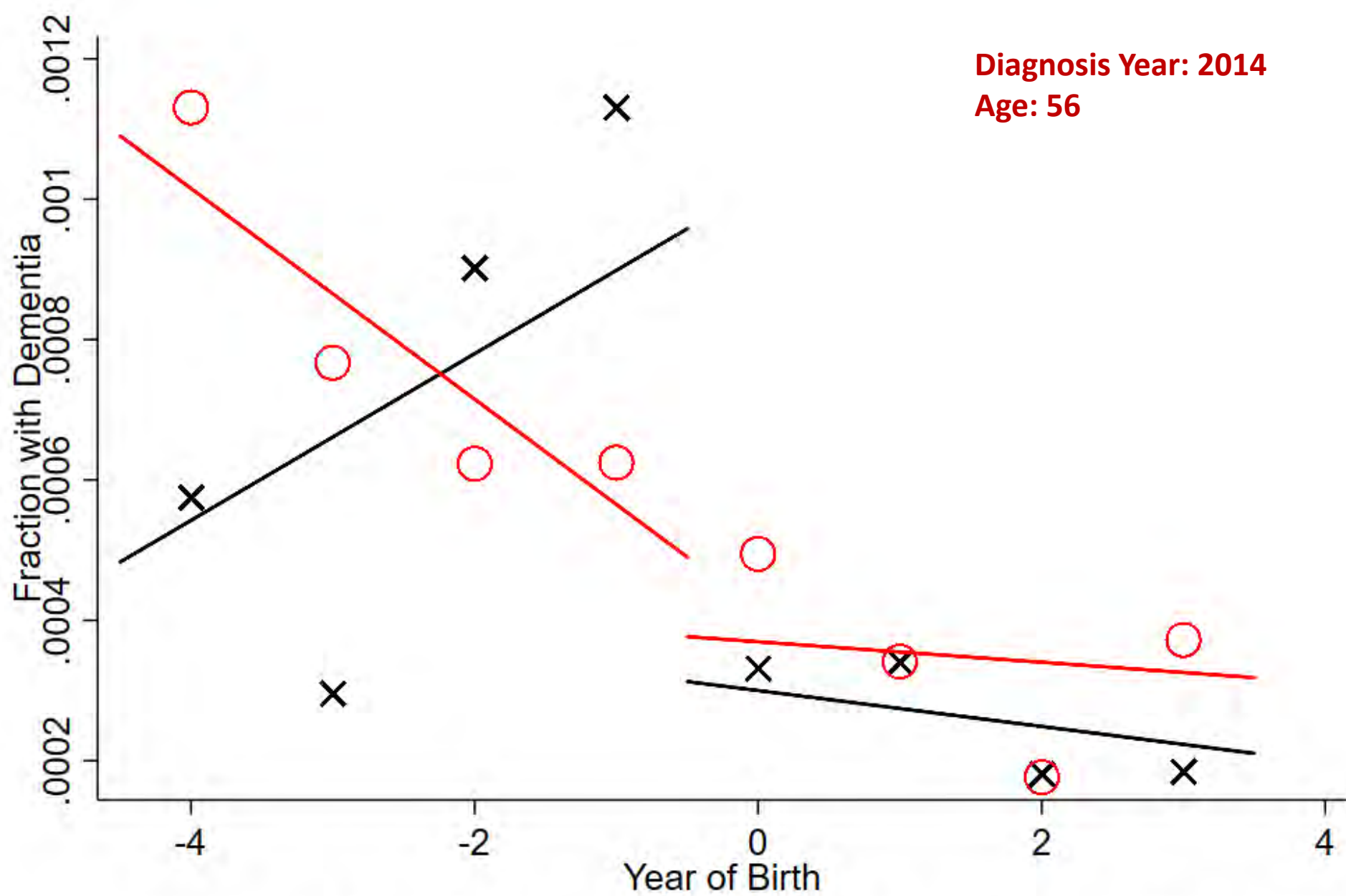
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Diagnosis Year: 2014
Age: 56

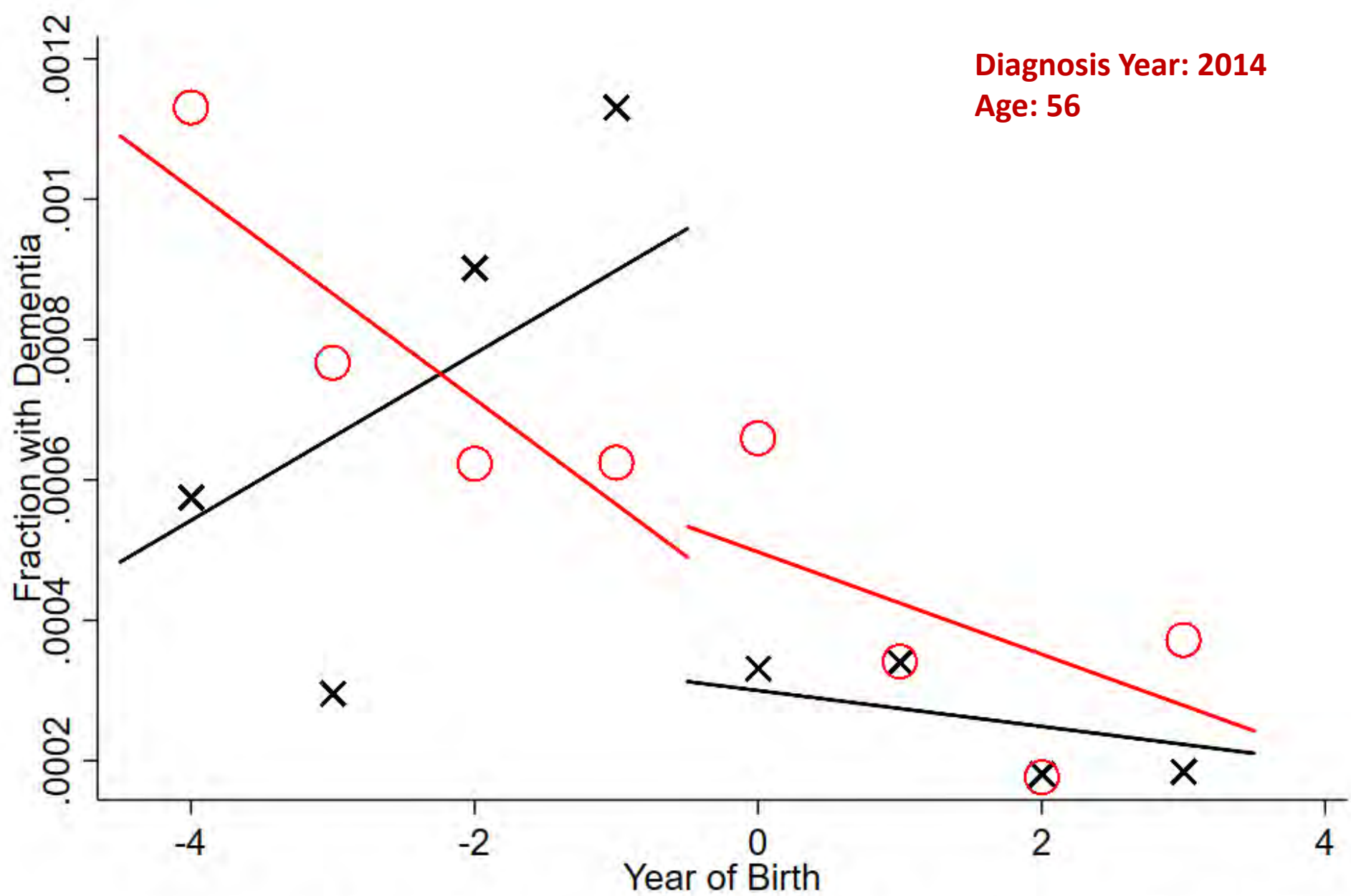


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Diagnosis Year: 2014
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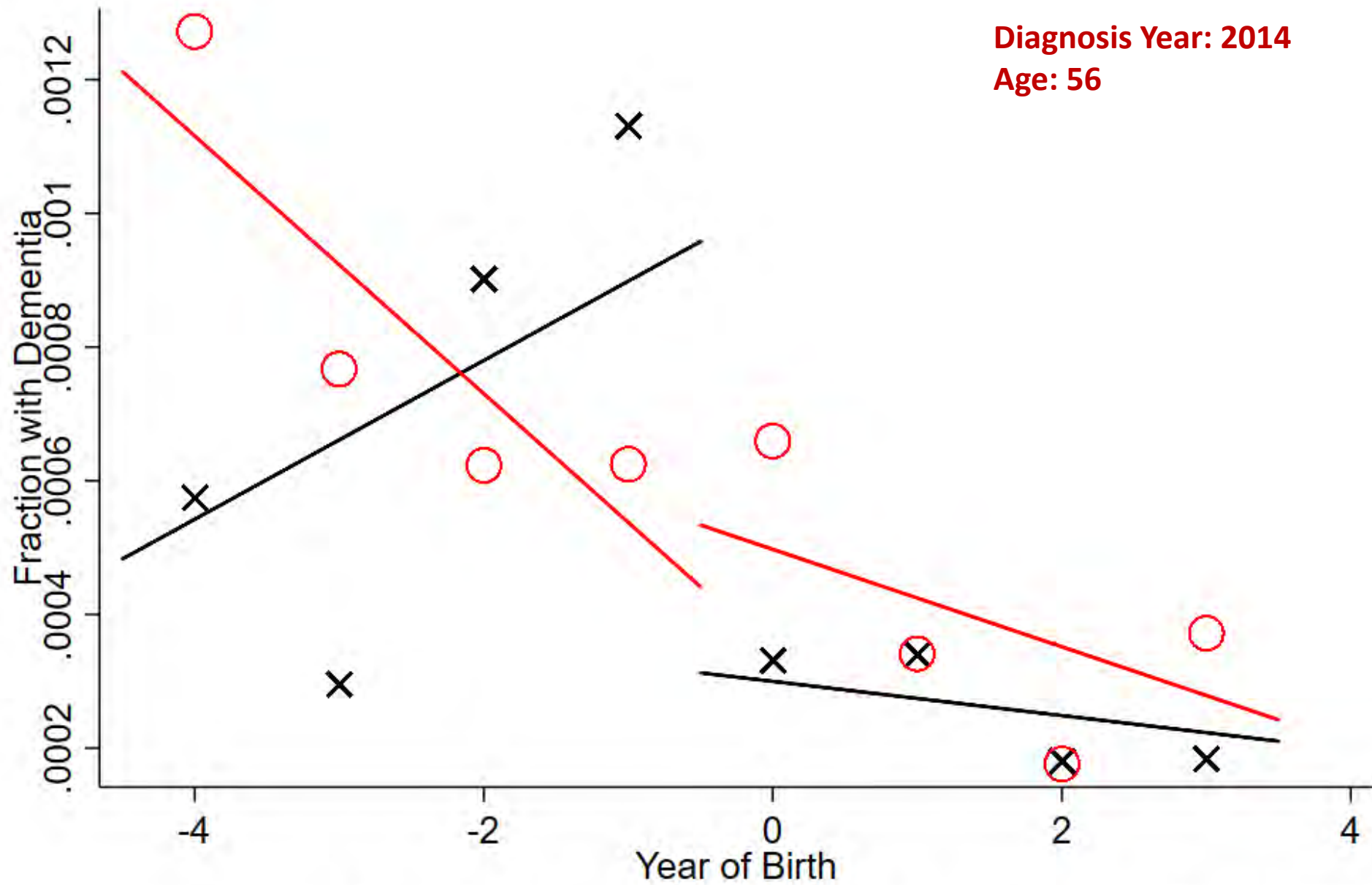


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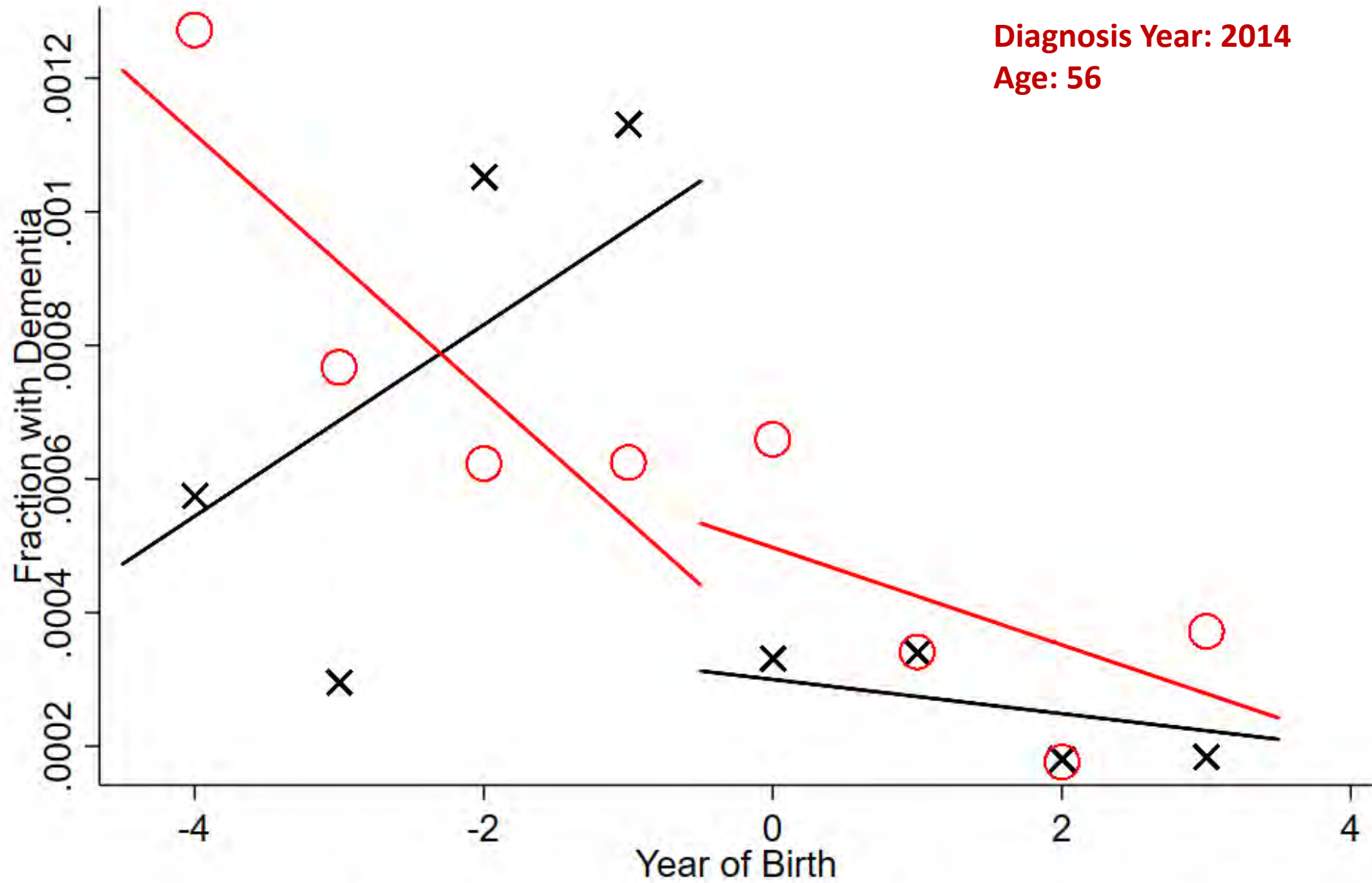
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Age: 56



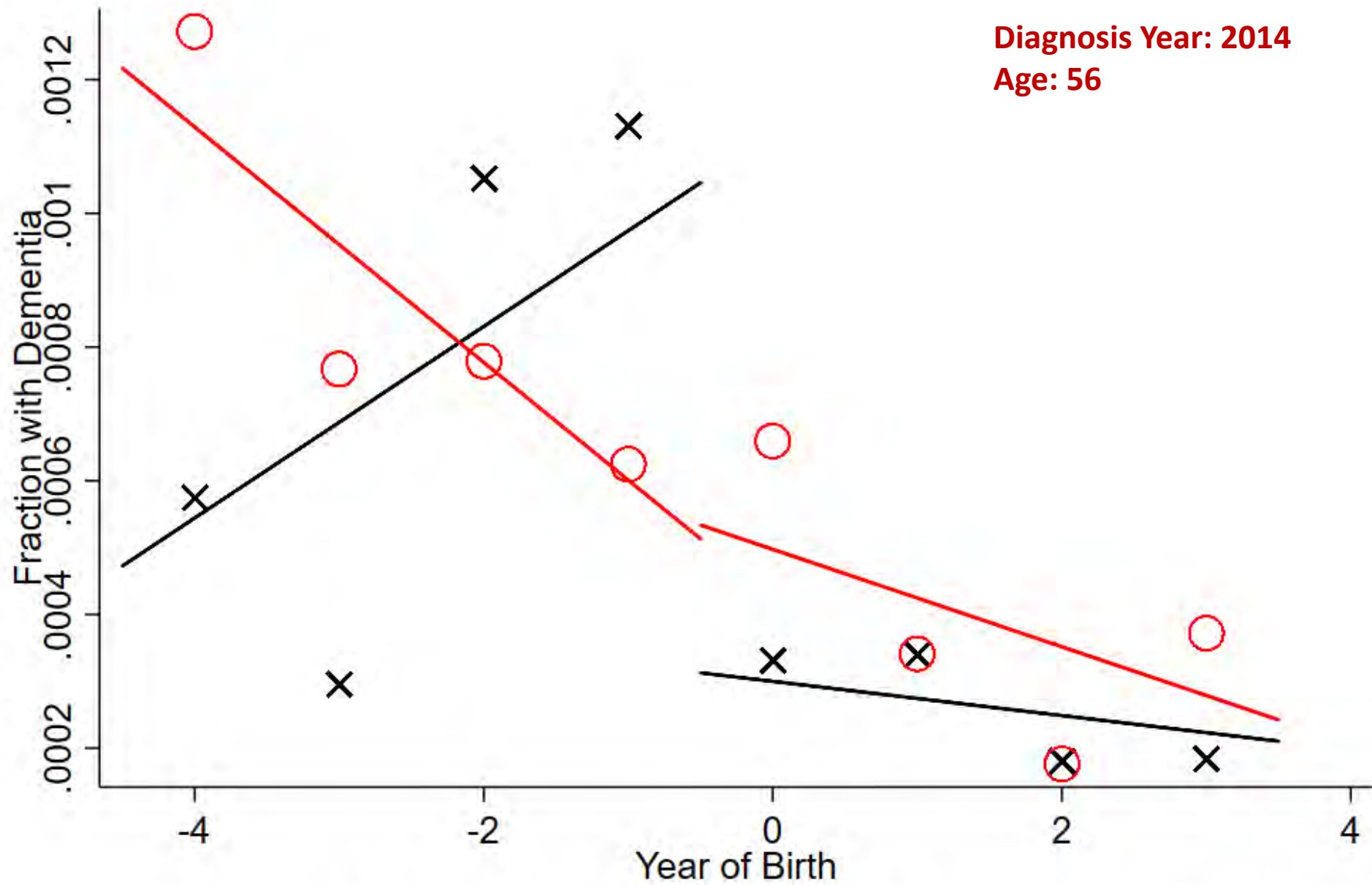
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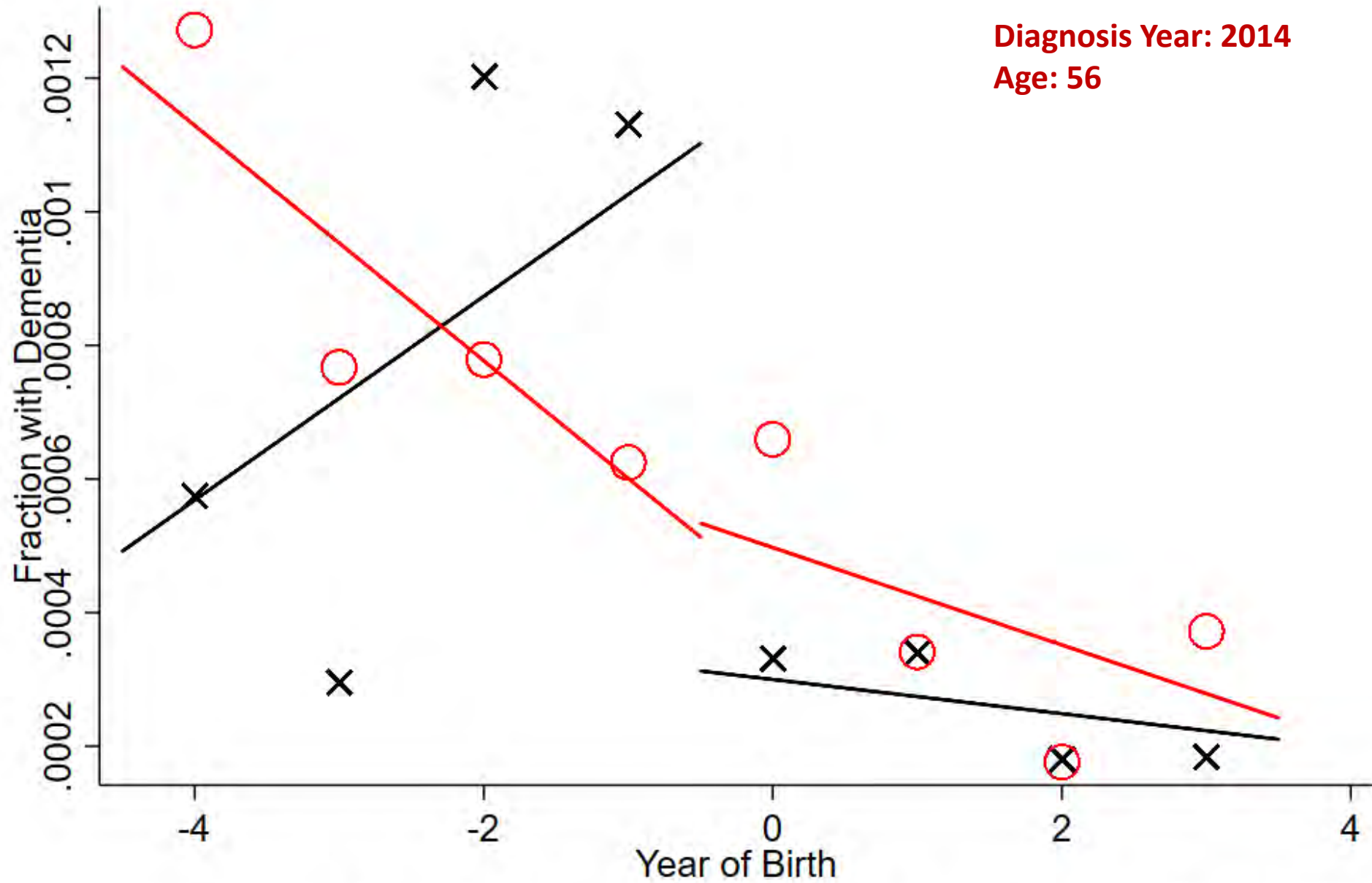
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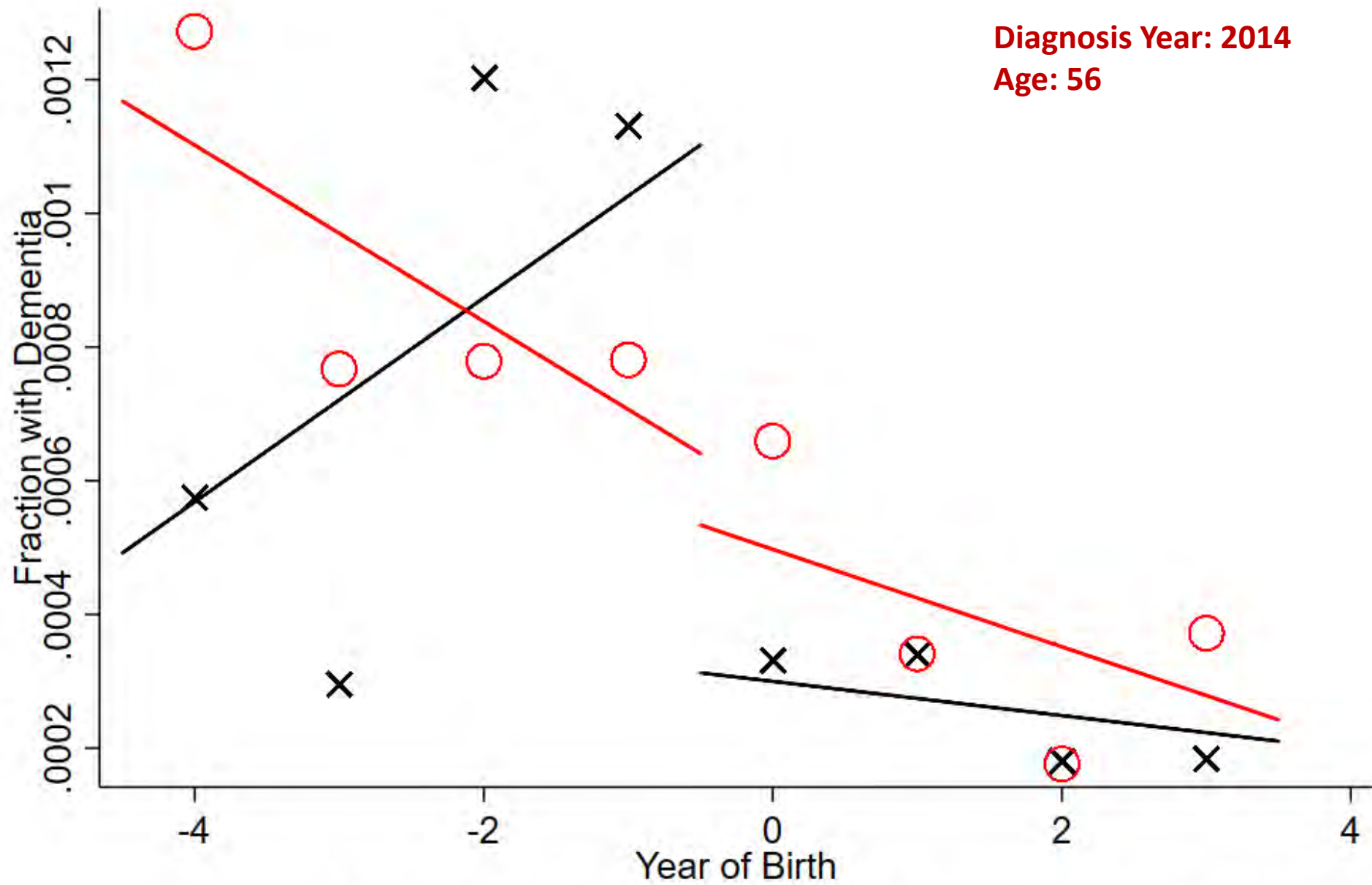
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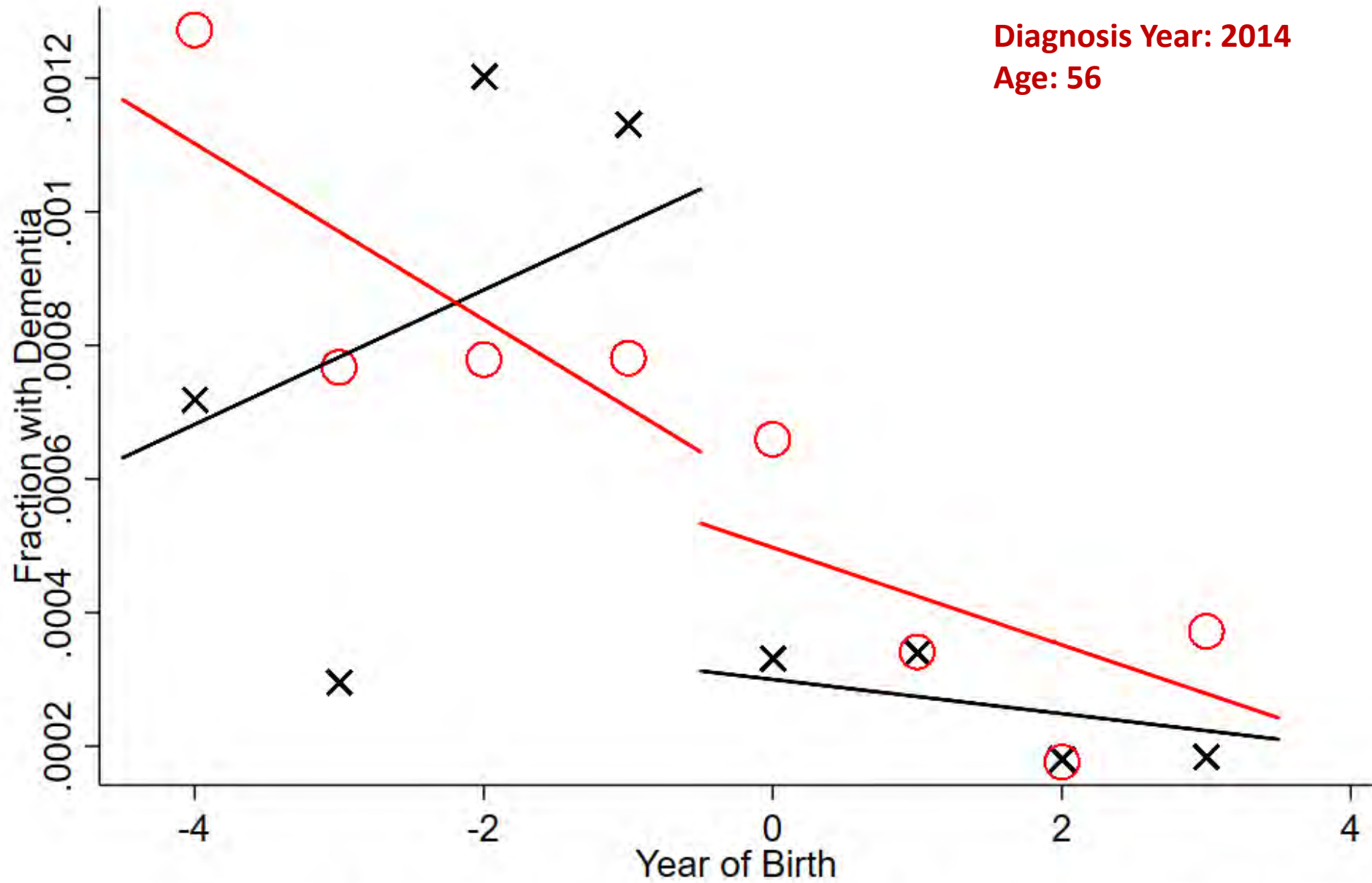
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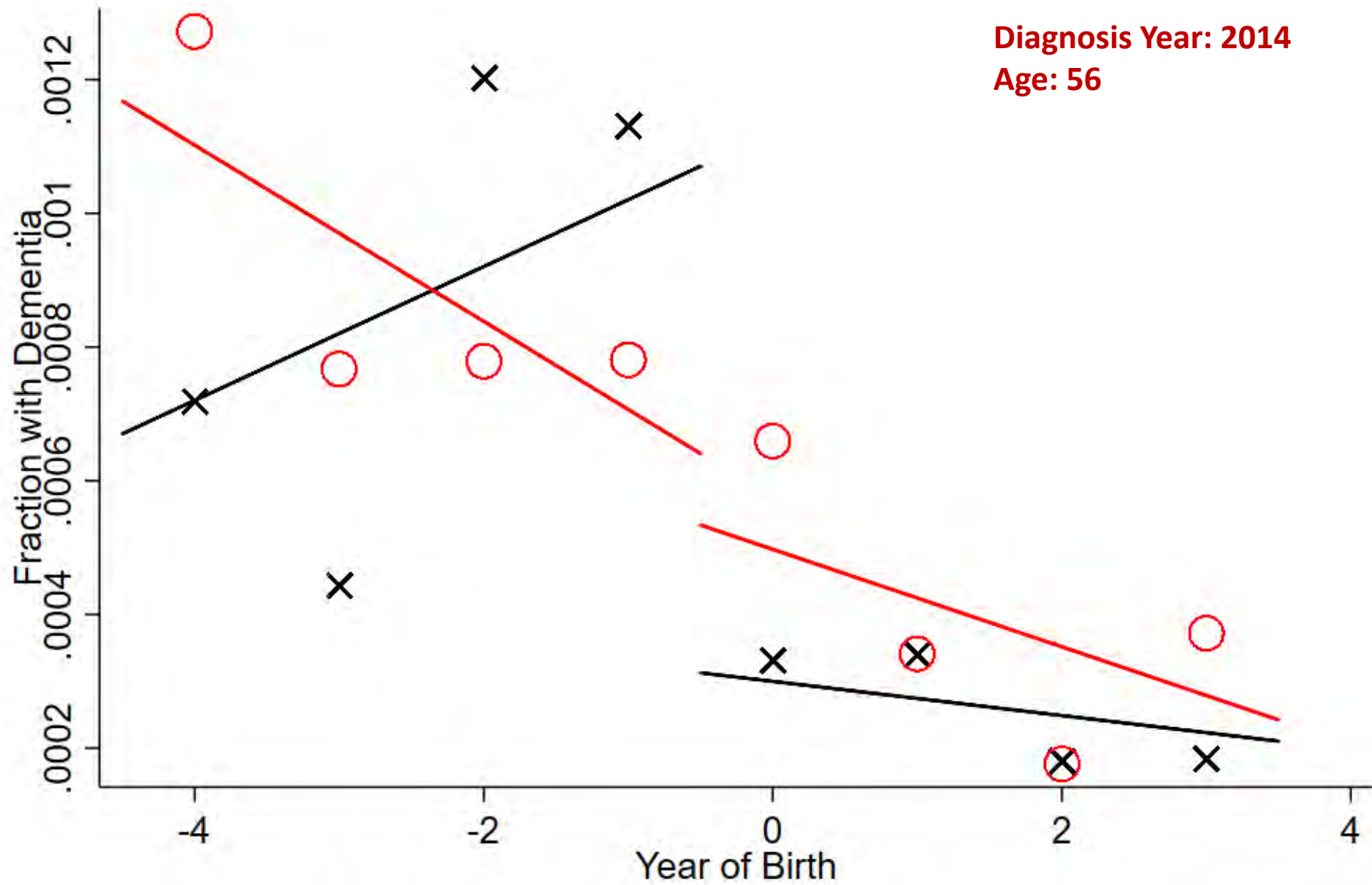
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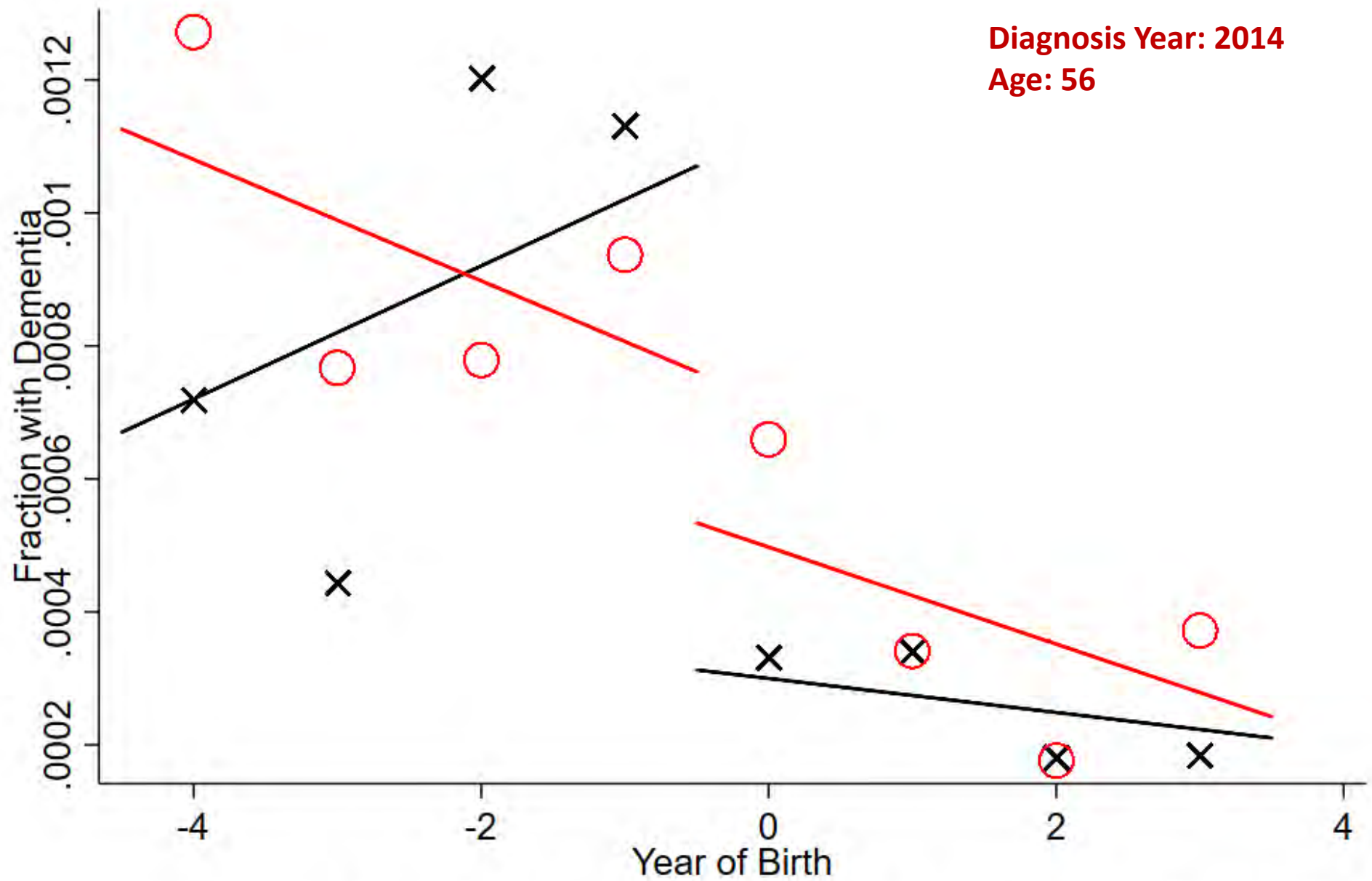


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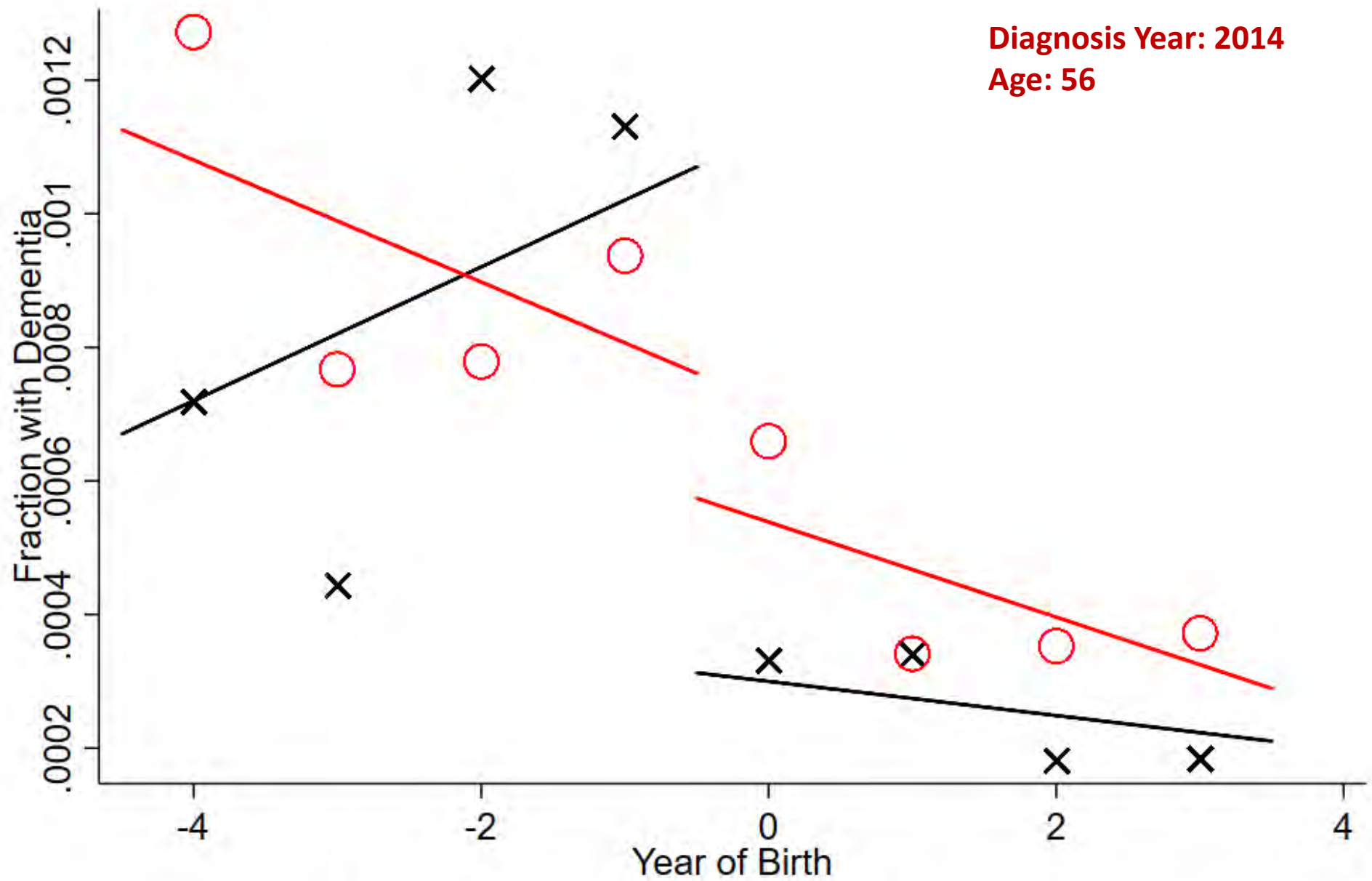
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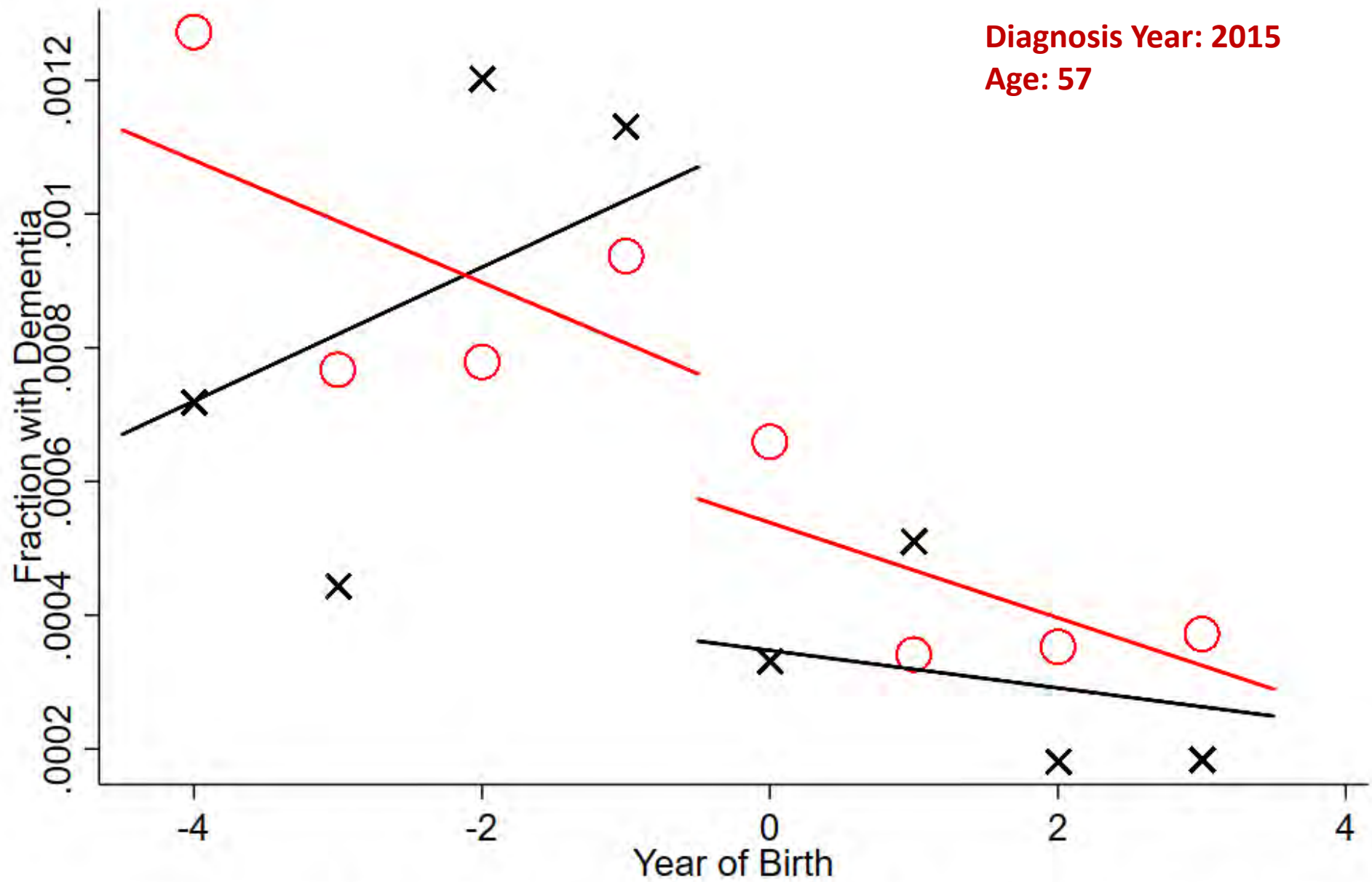
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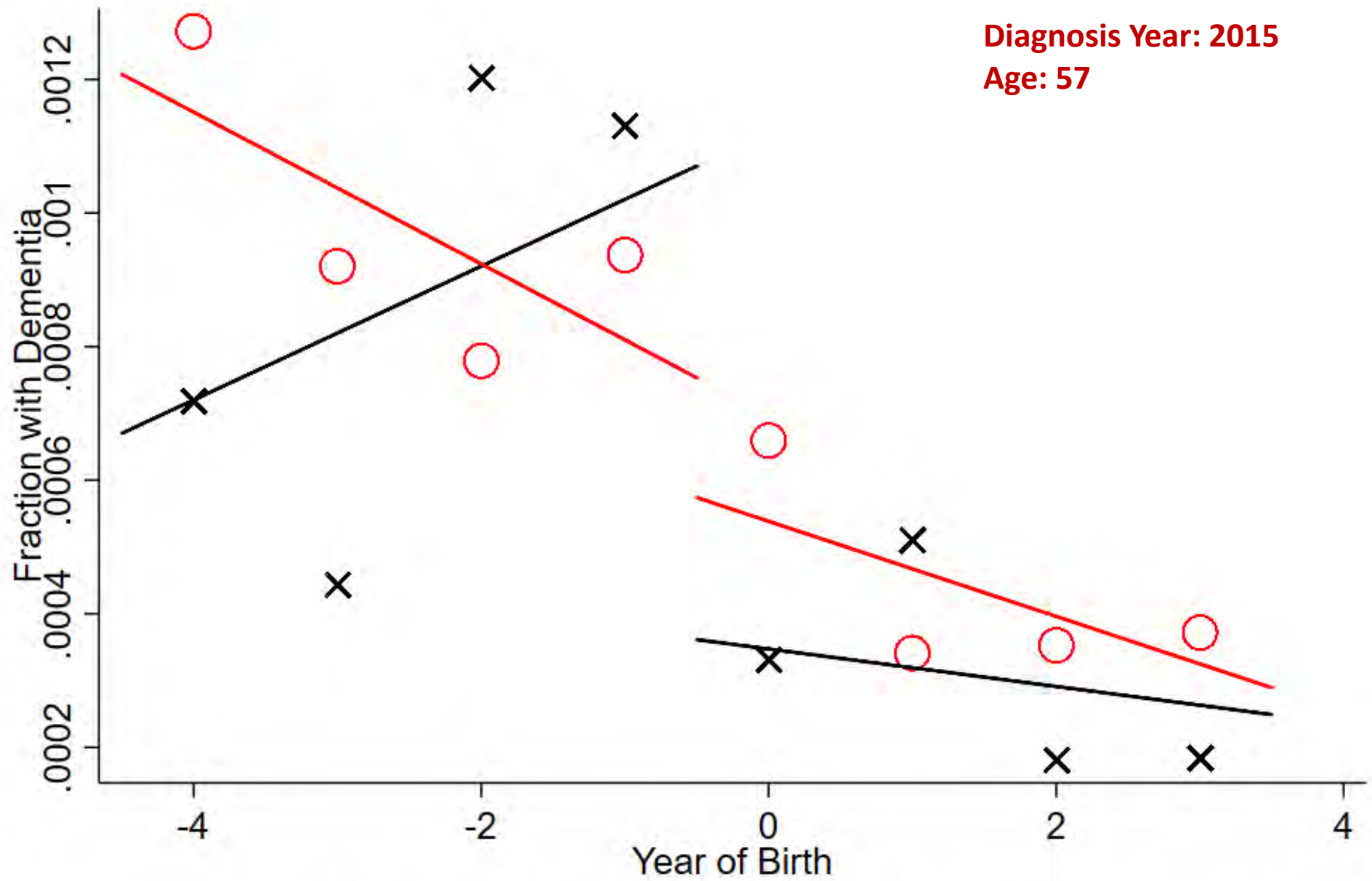
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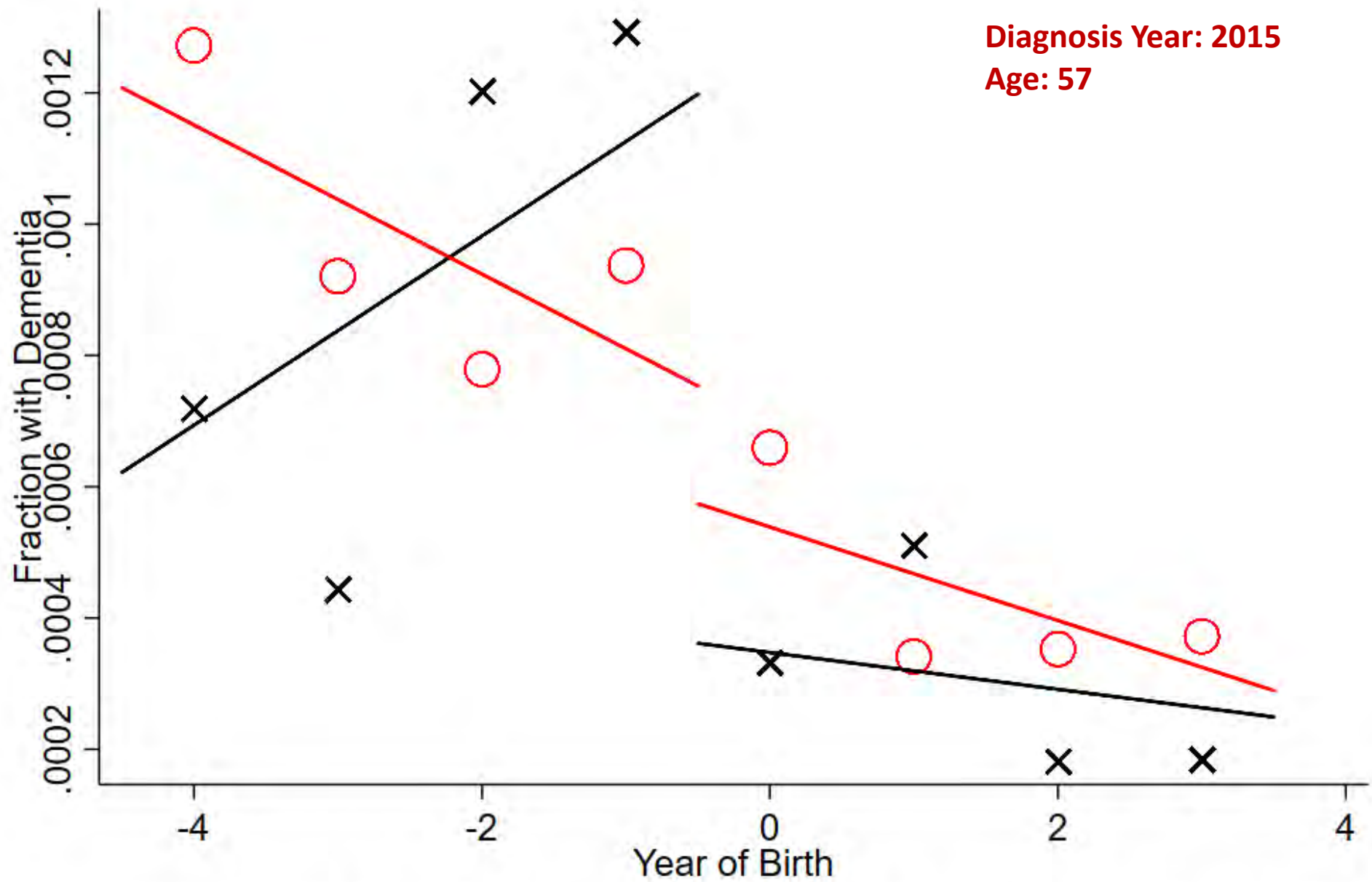
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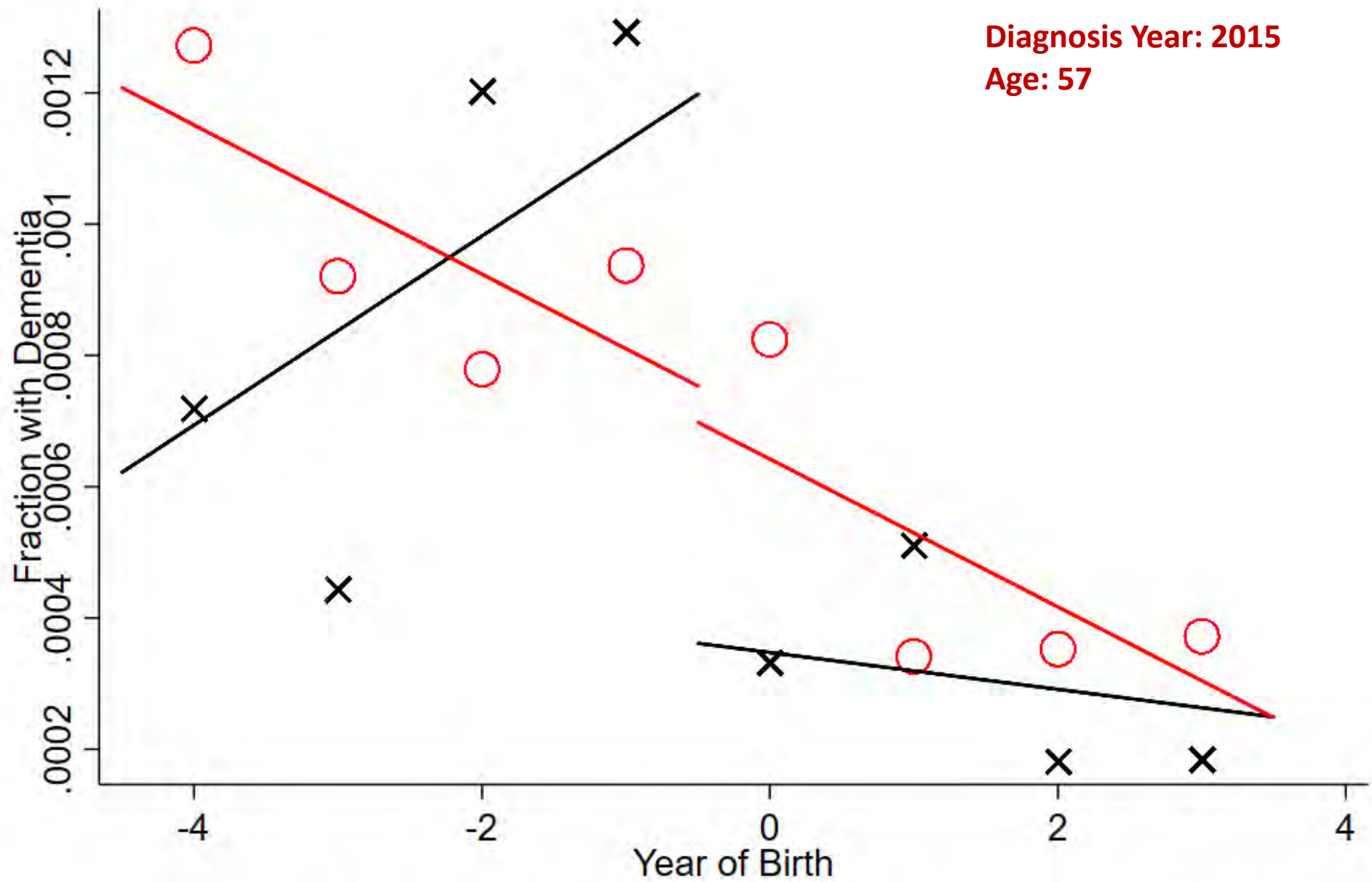
Diagnosis Year: 2015
Age: 57



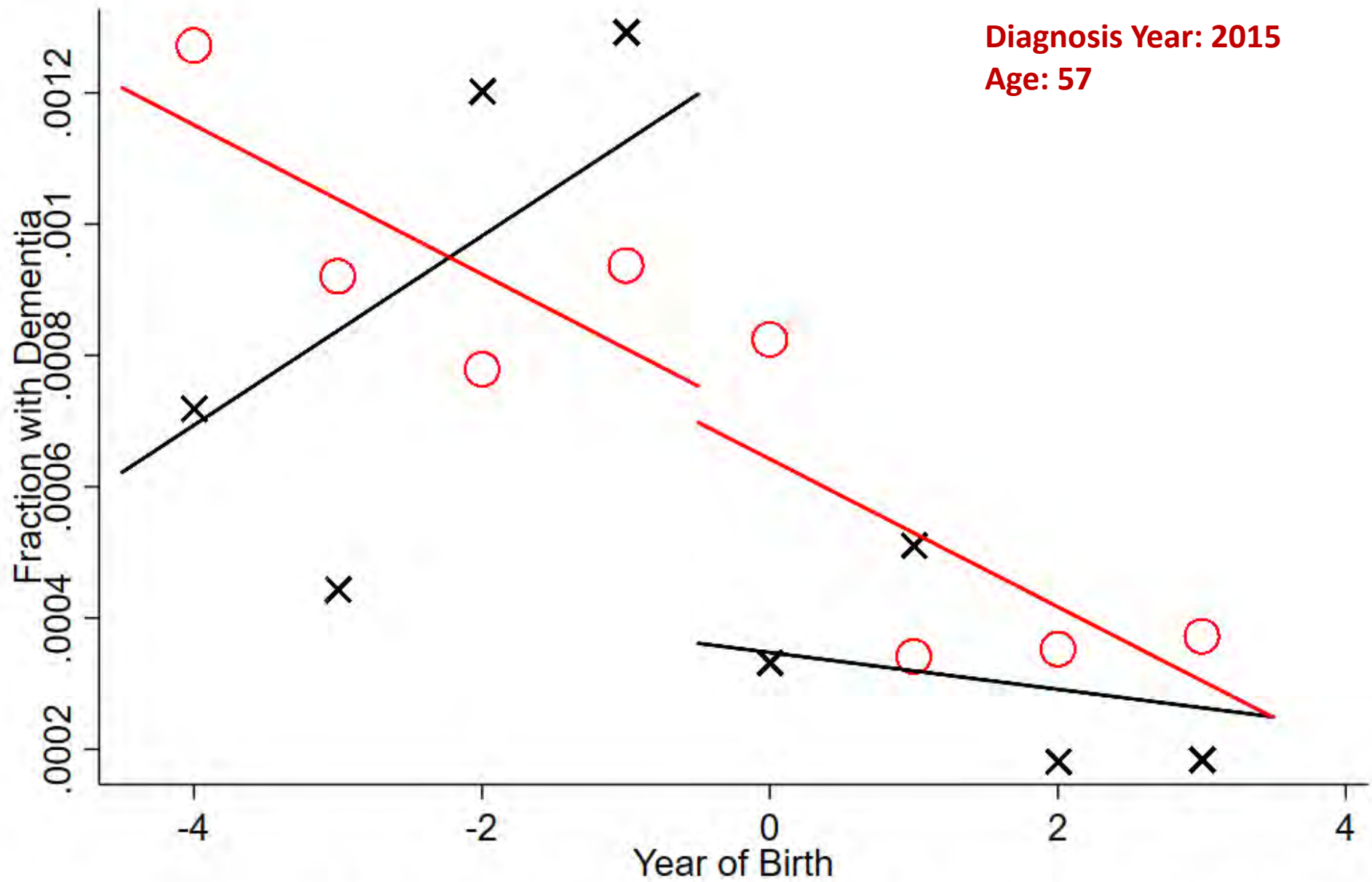
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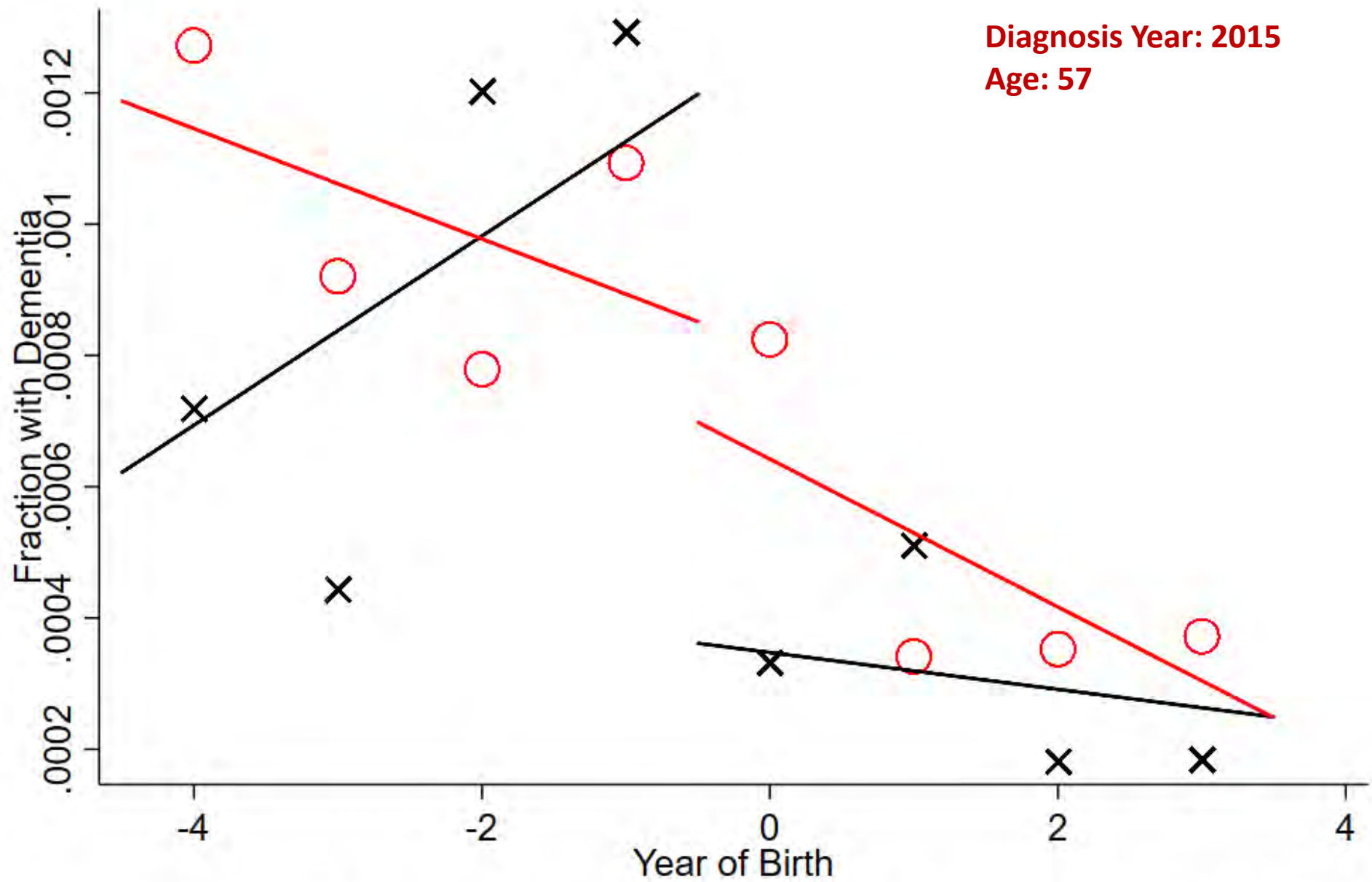
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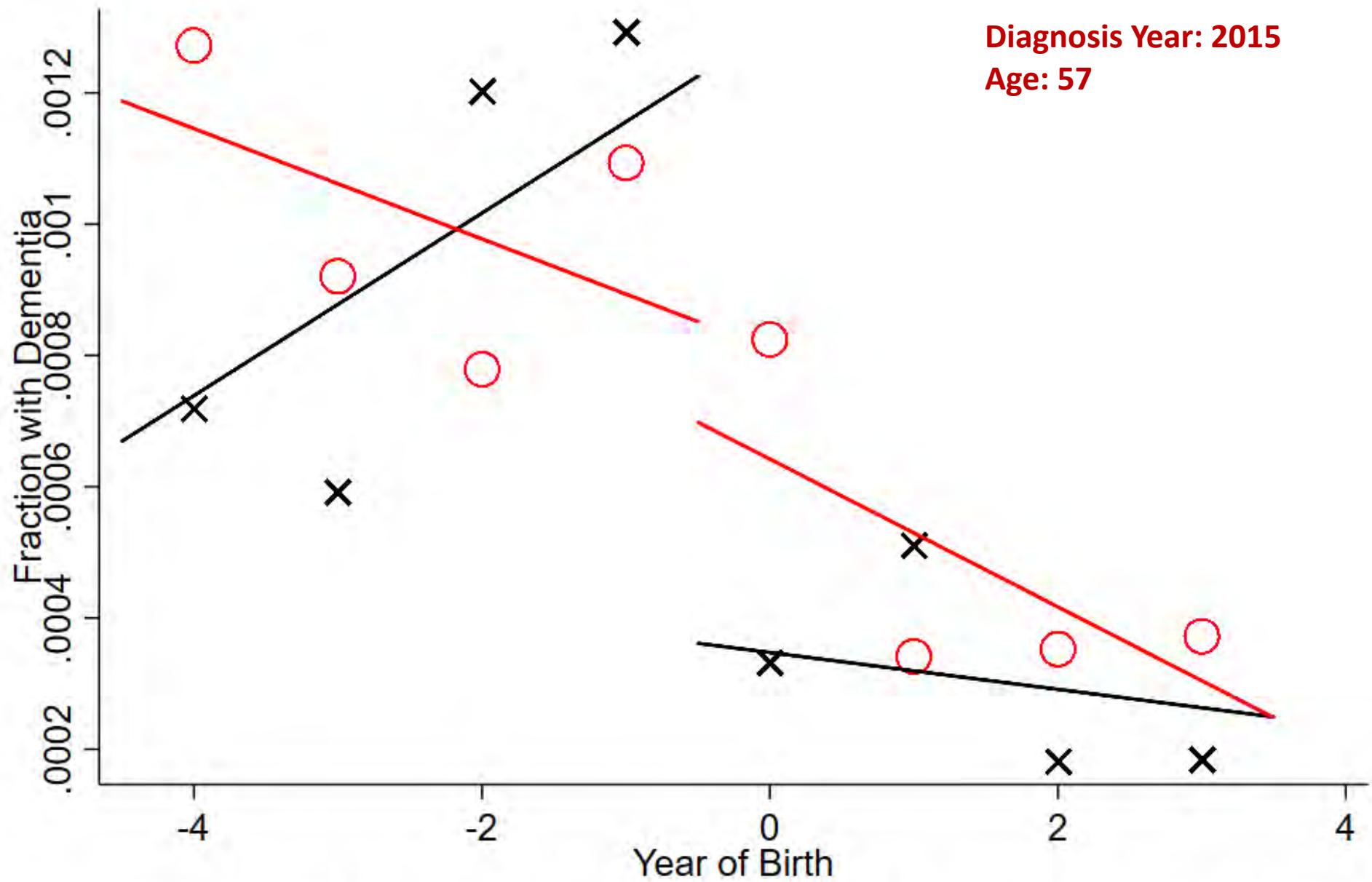


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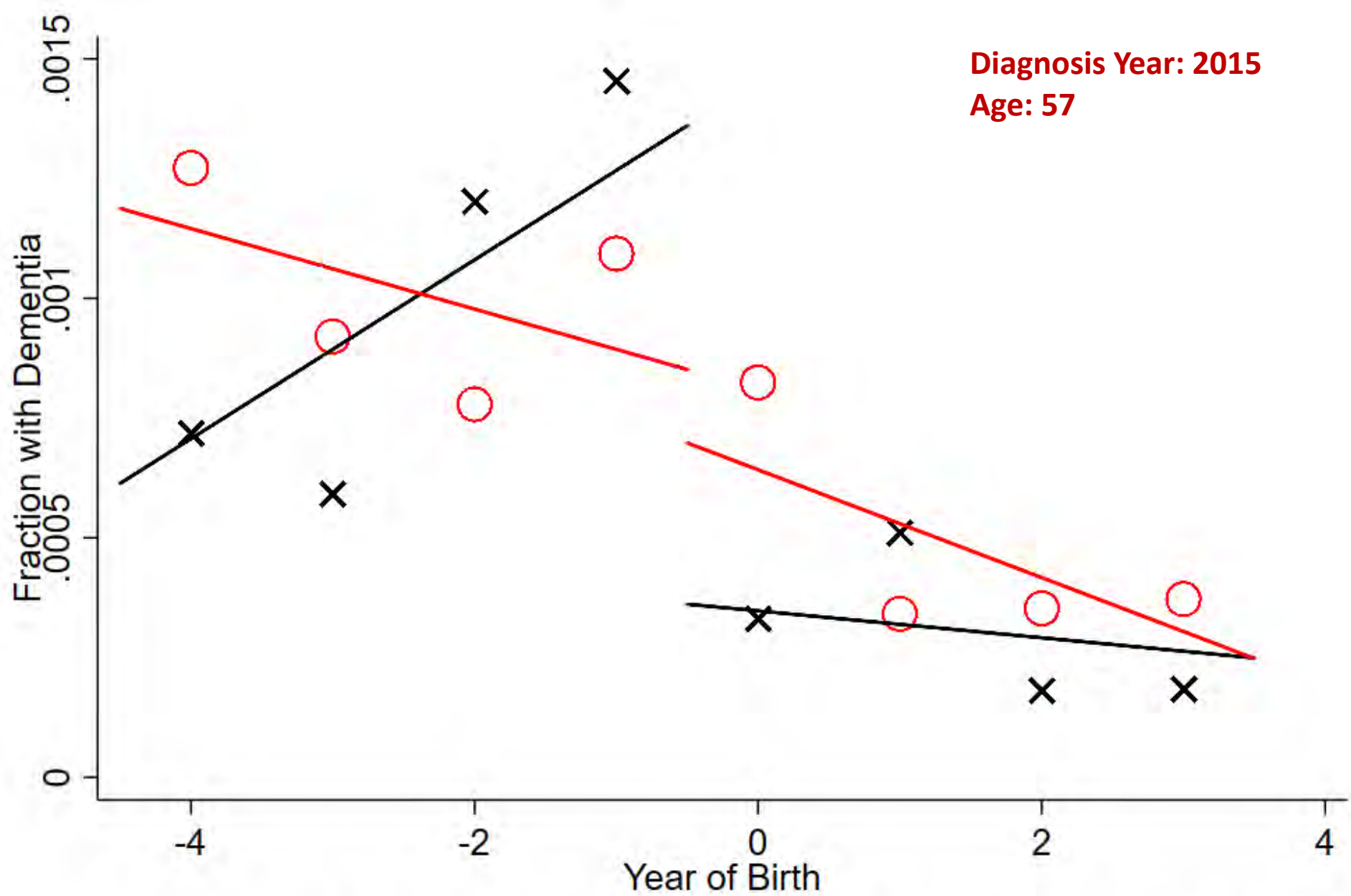


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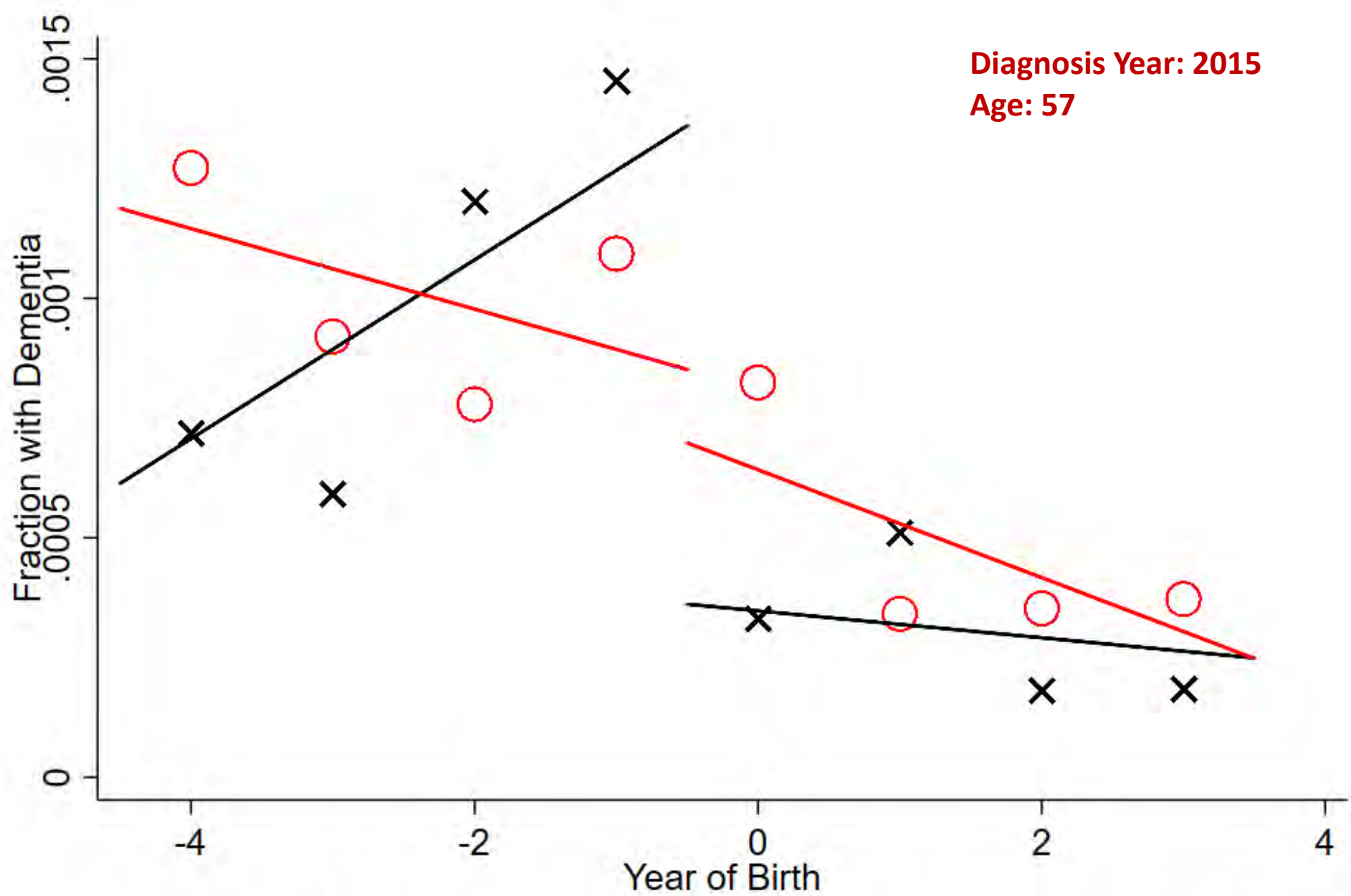




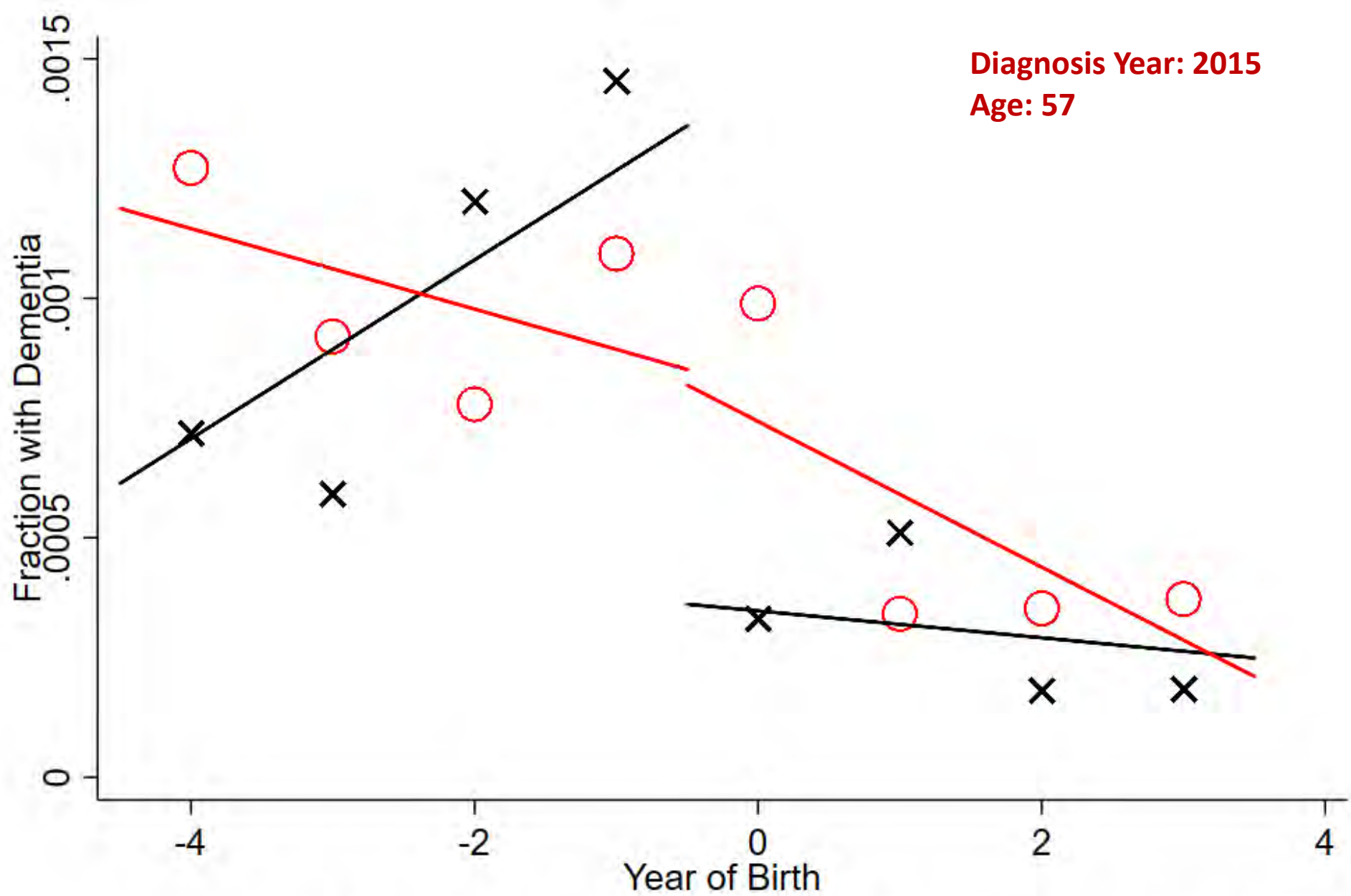
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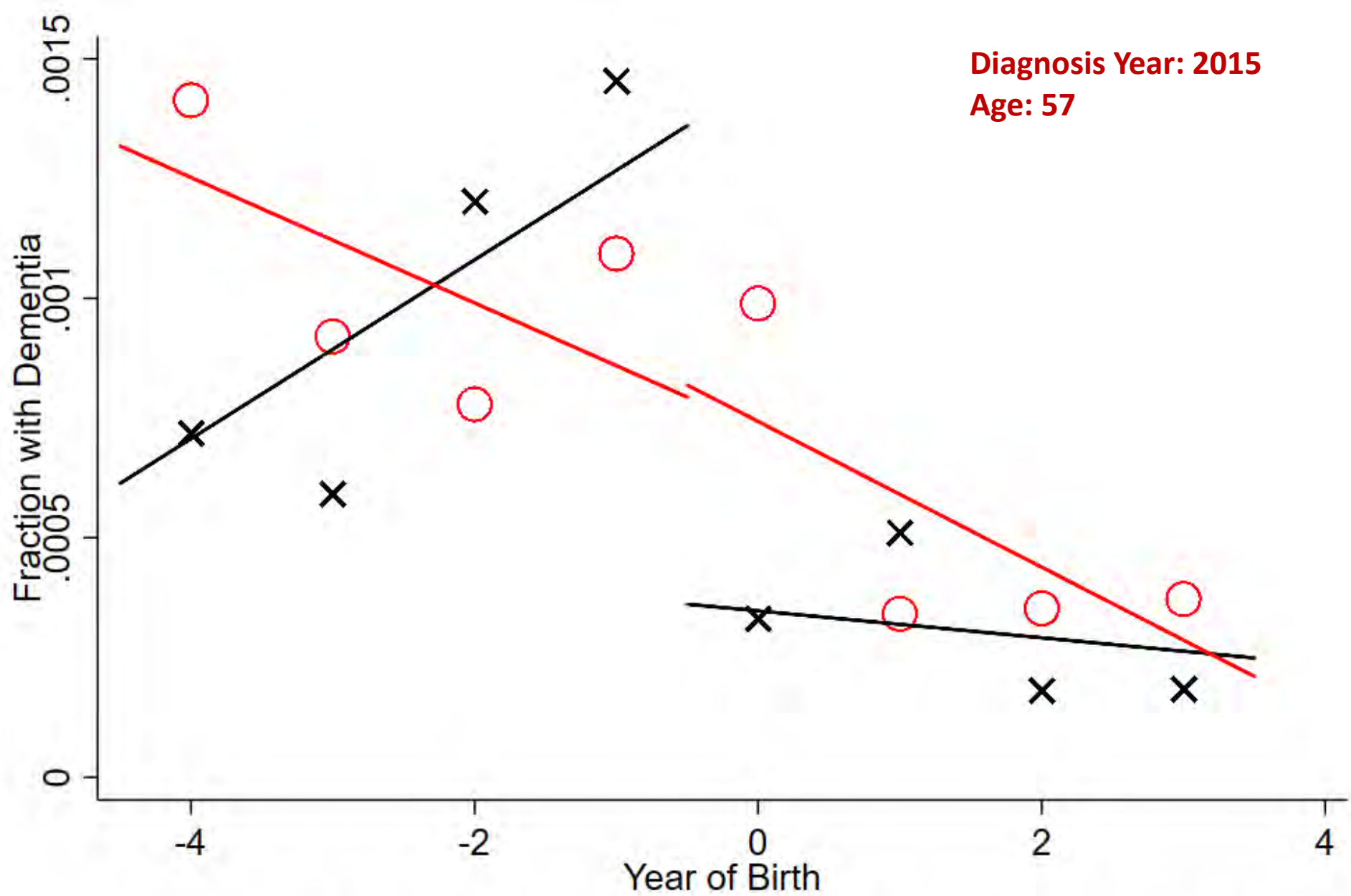
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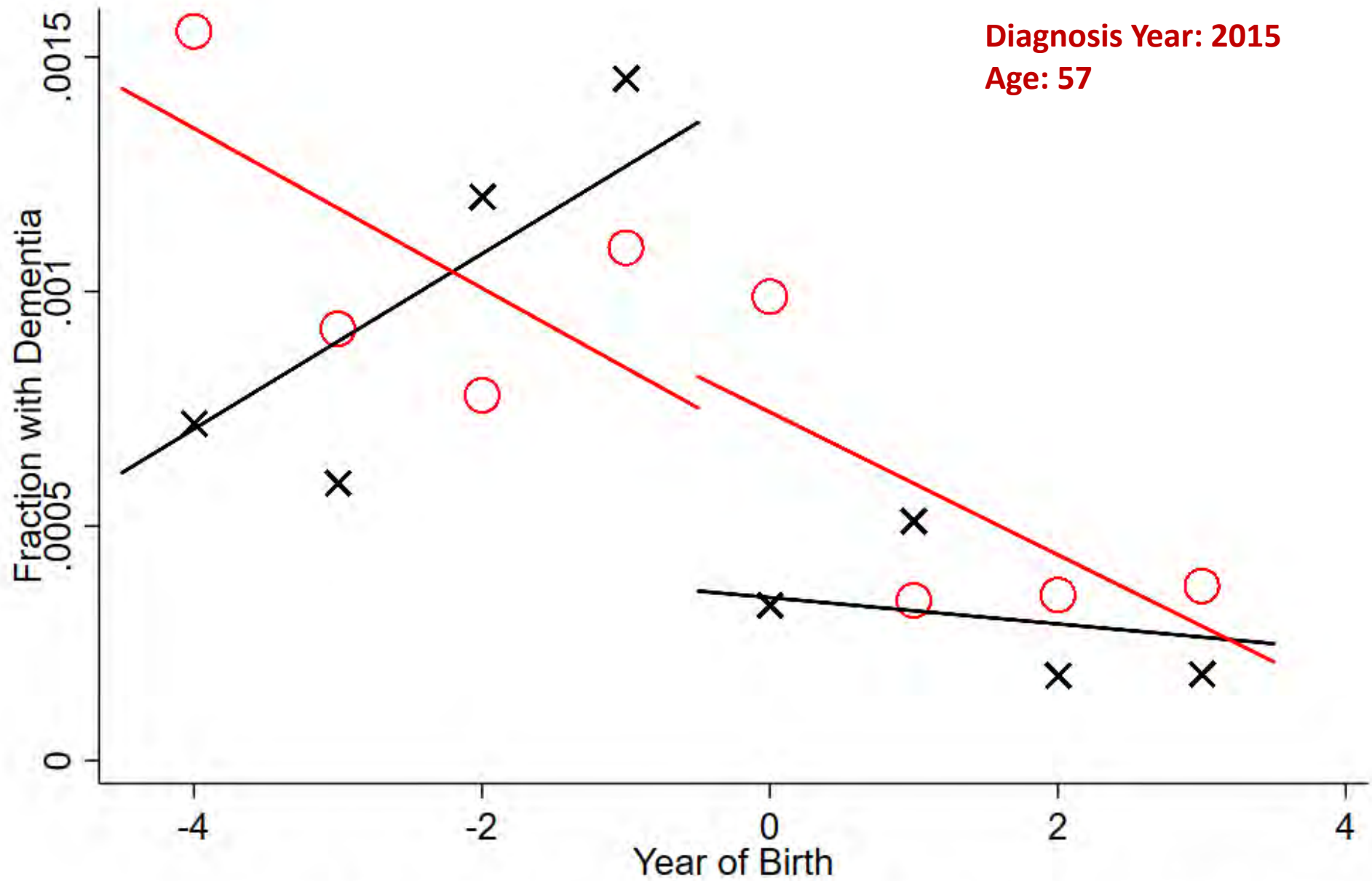
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

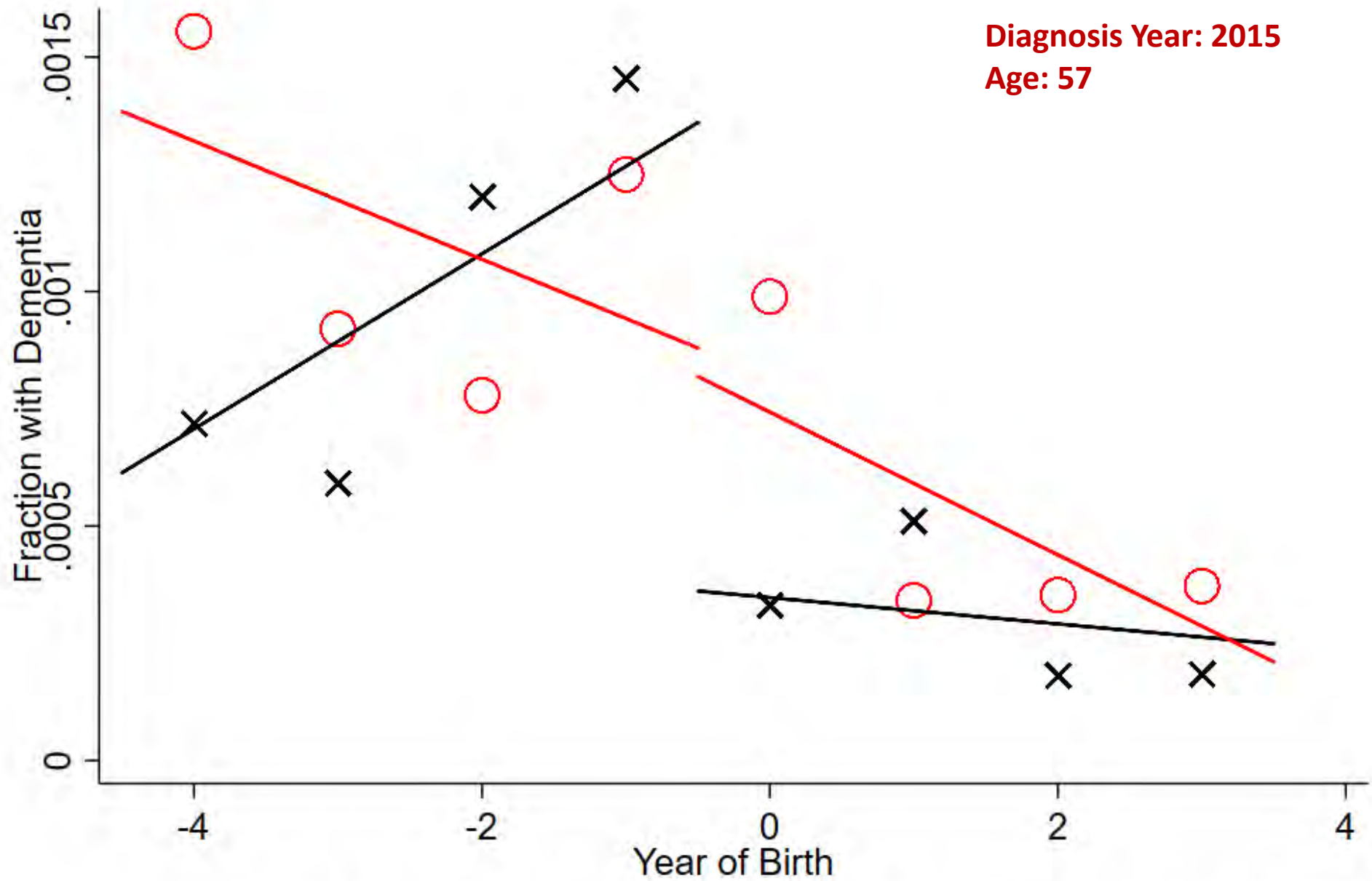


× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



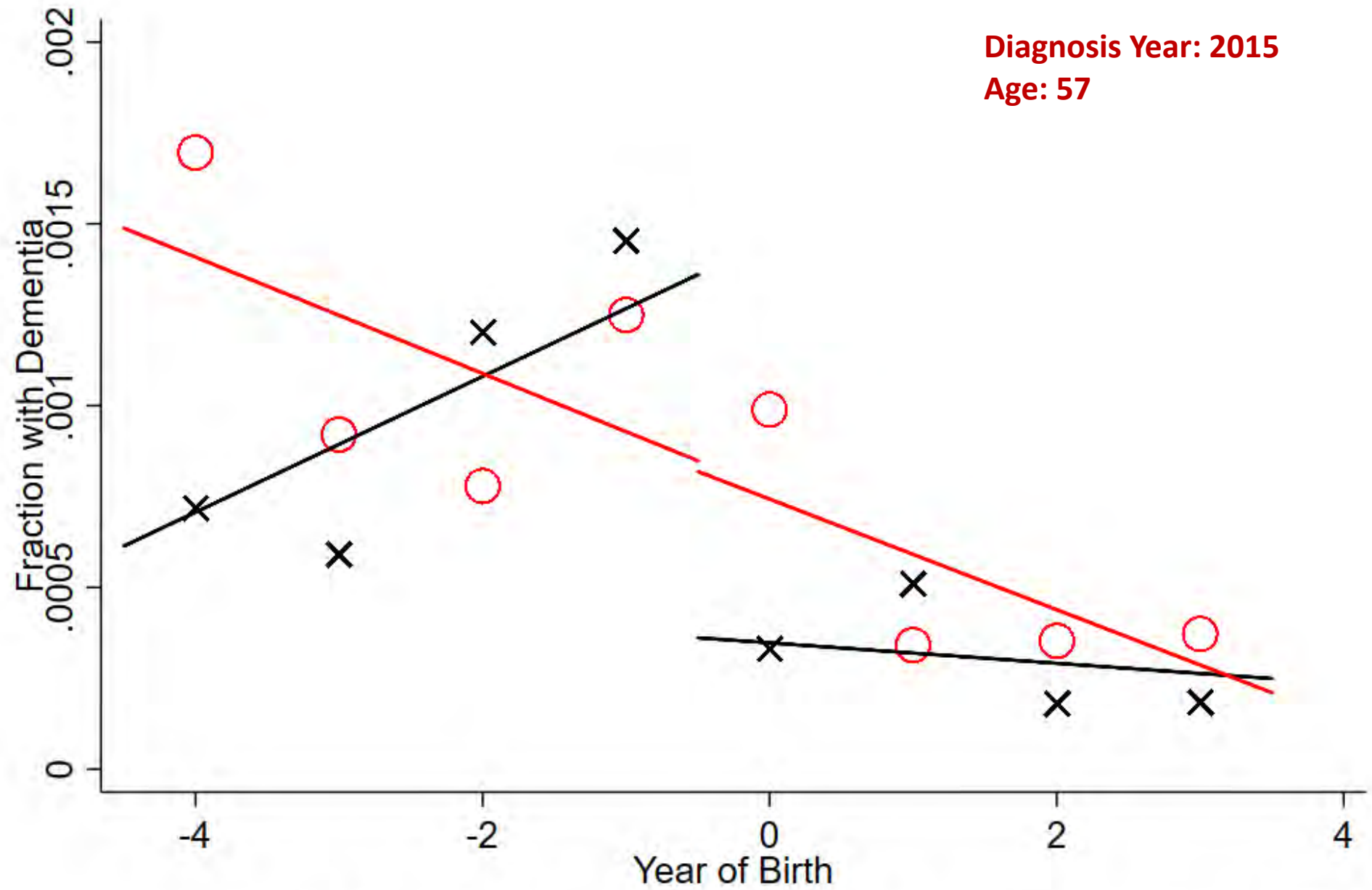
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk





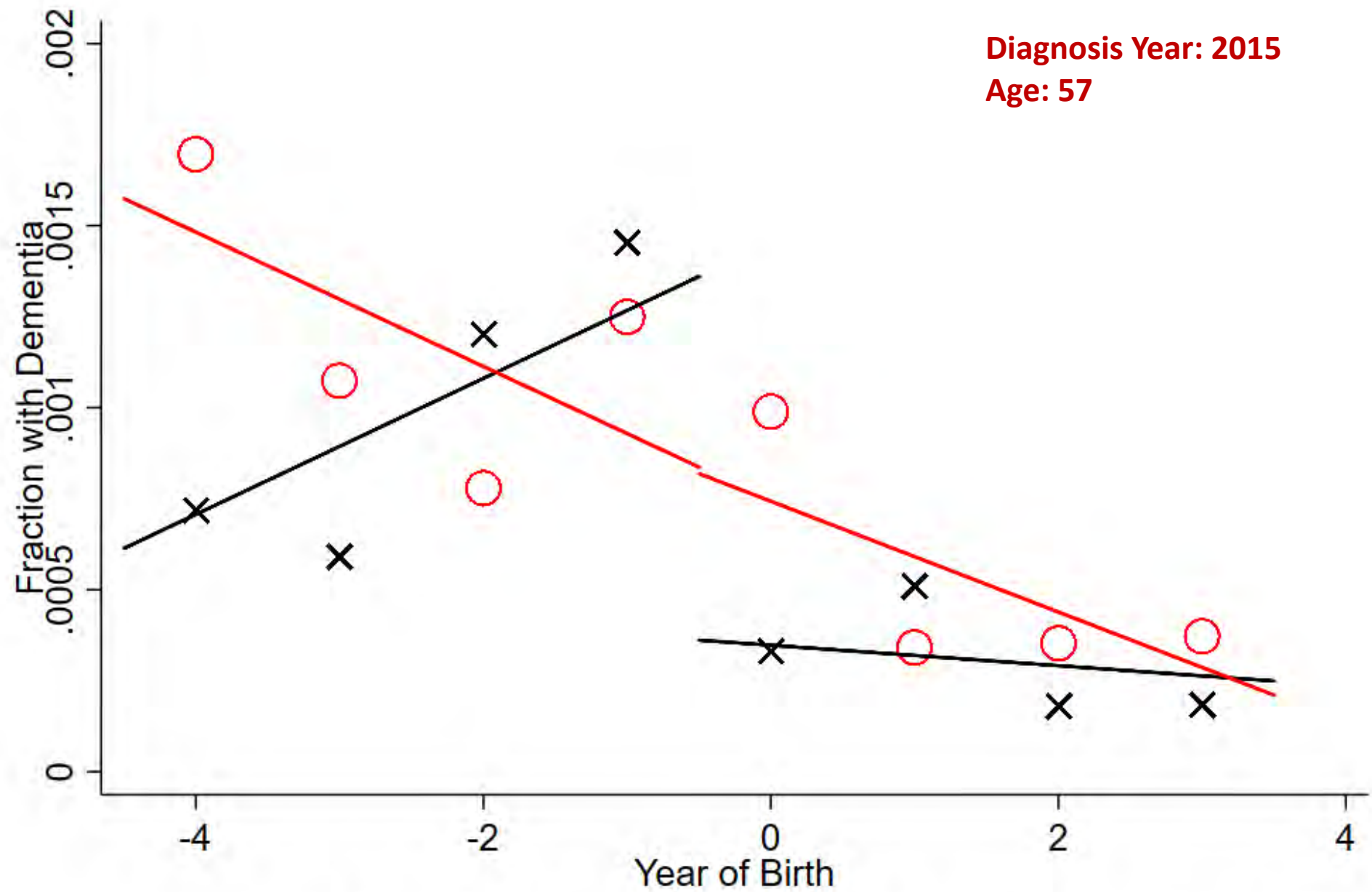
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

Diagnosis Year: 2015
Age: 57



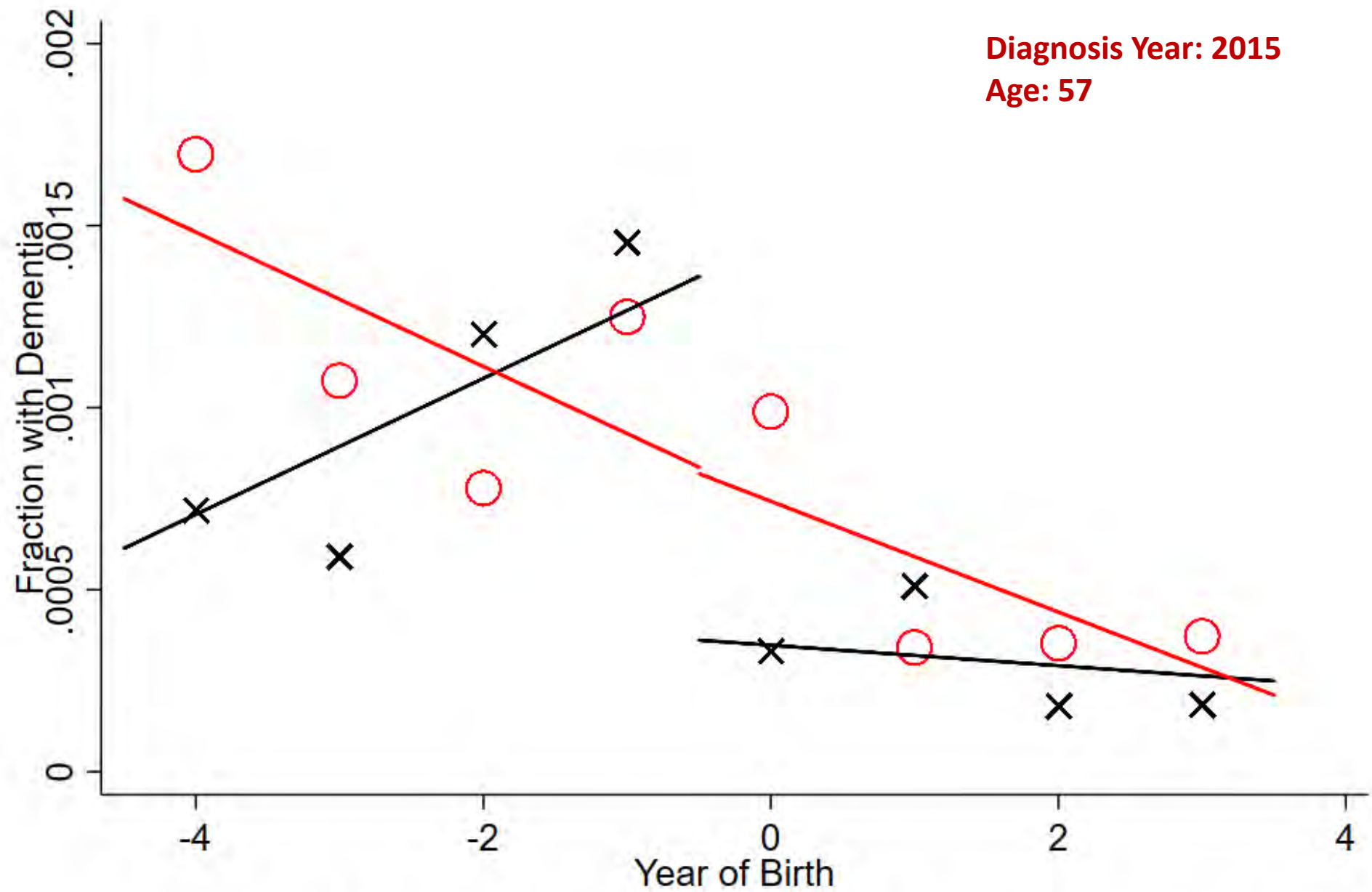
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

Diagnosis Year: 2015
Age: 57



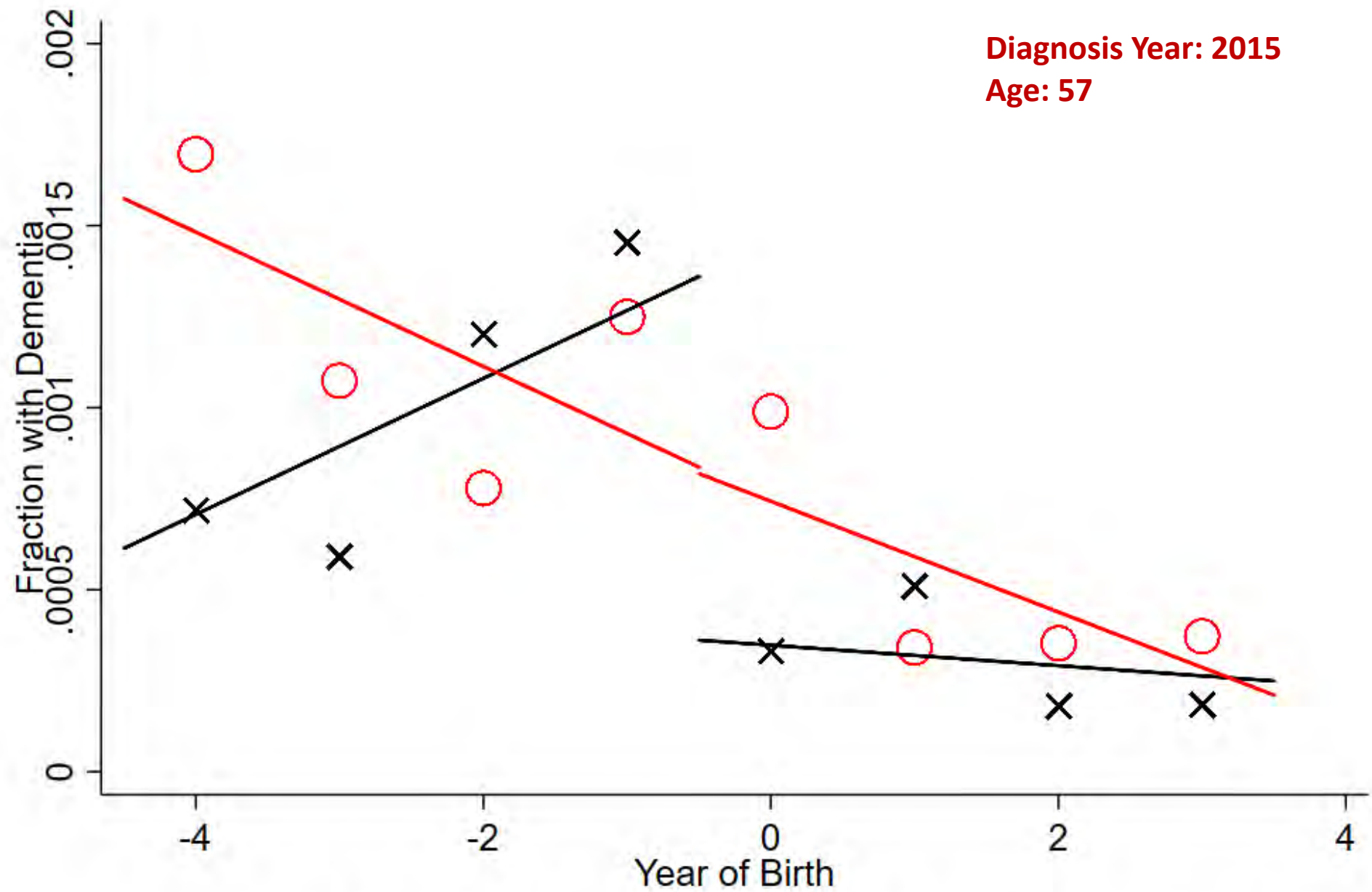
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

Diagnosis Year: 2015
Age: 57



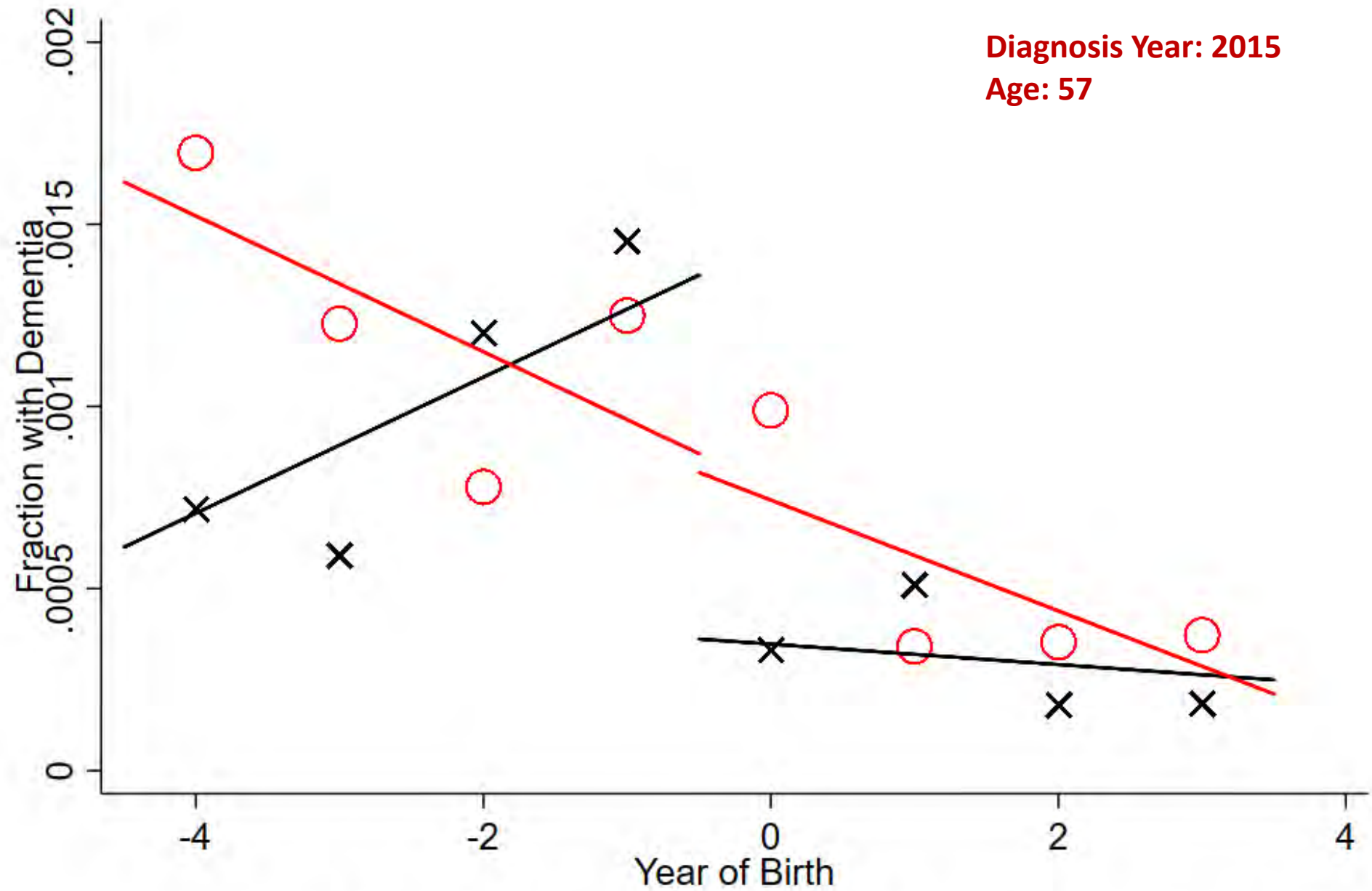
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

Diagnosis Year: 2015
Age: 57



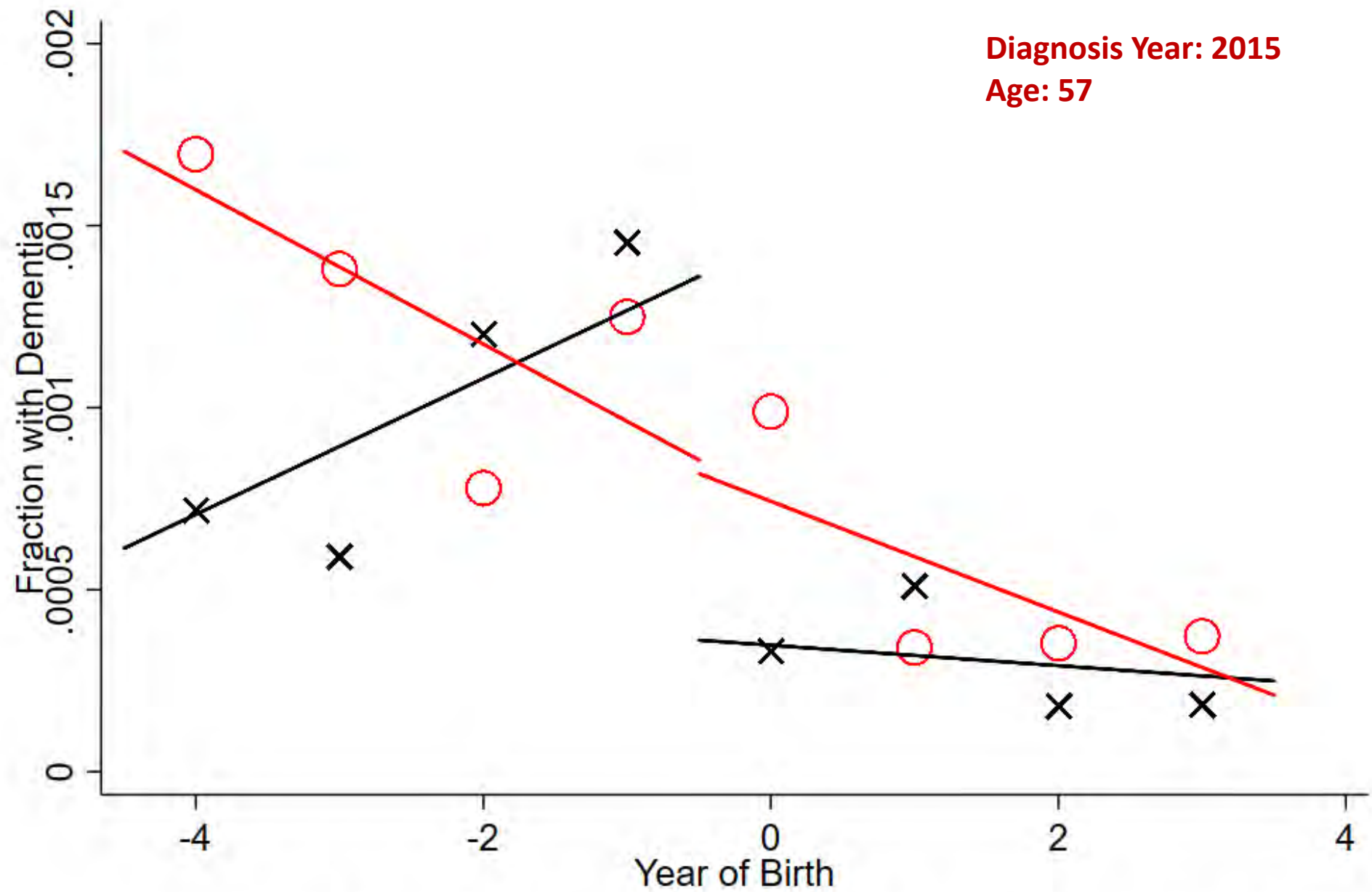
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

Diagnosis Year: 2015
Age: 57

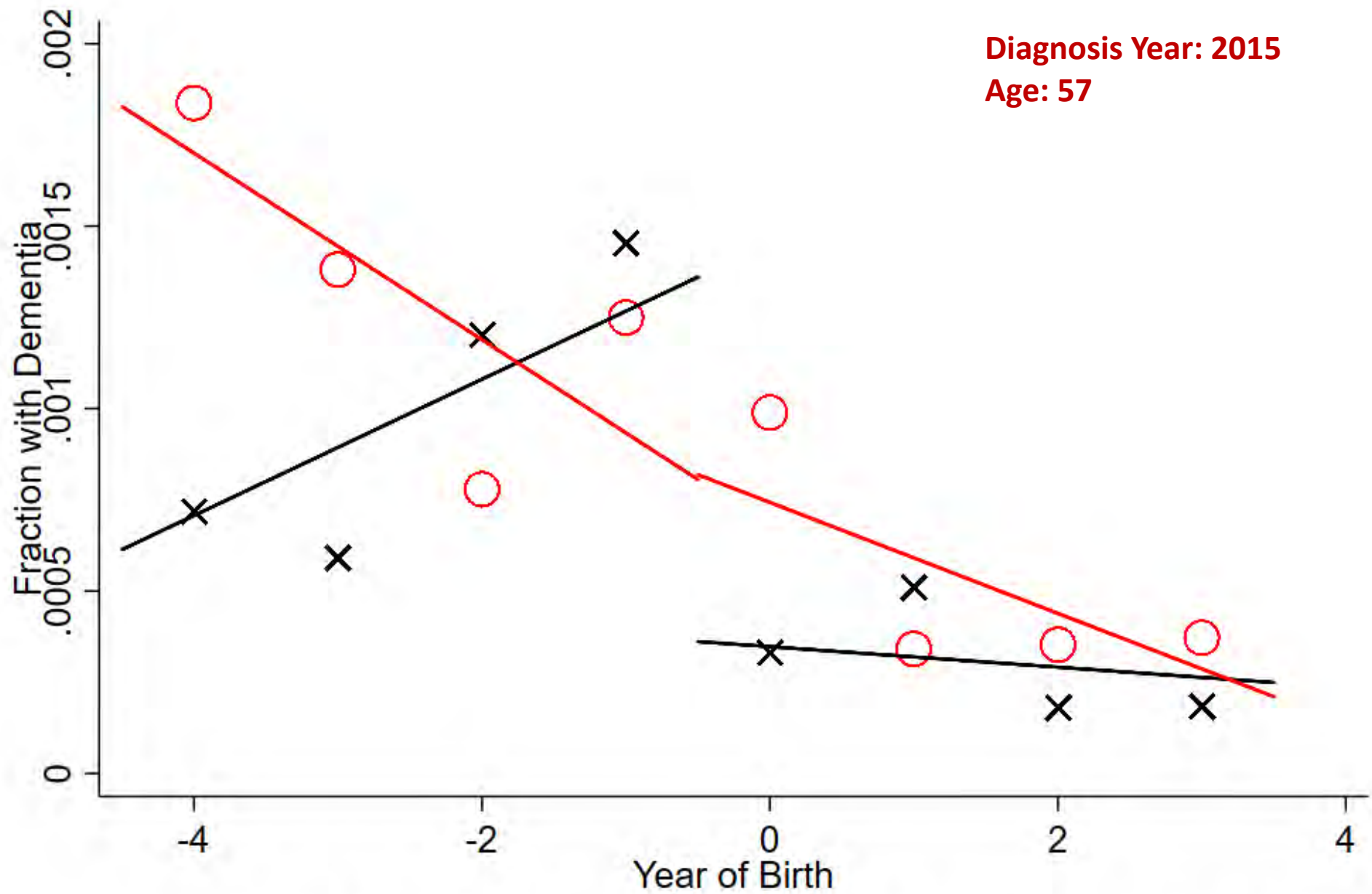


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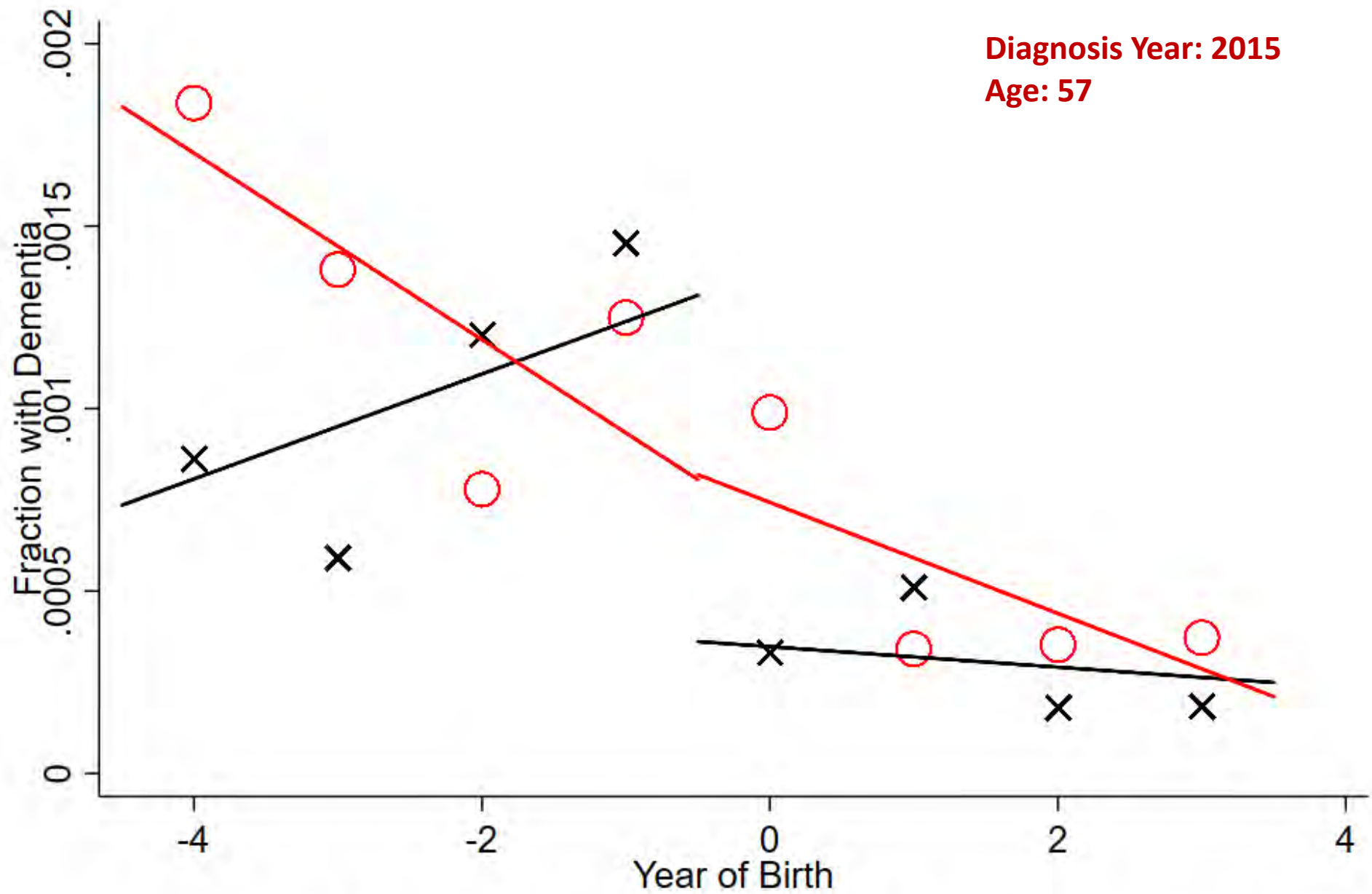
Diagnosis Year: 2015
Age: 57



× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

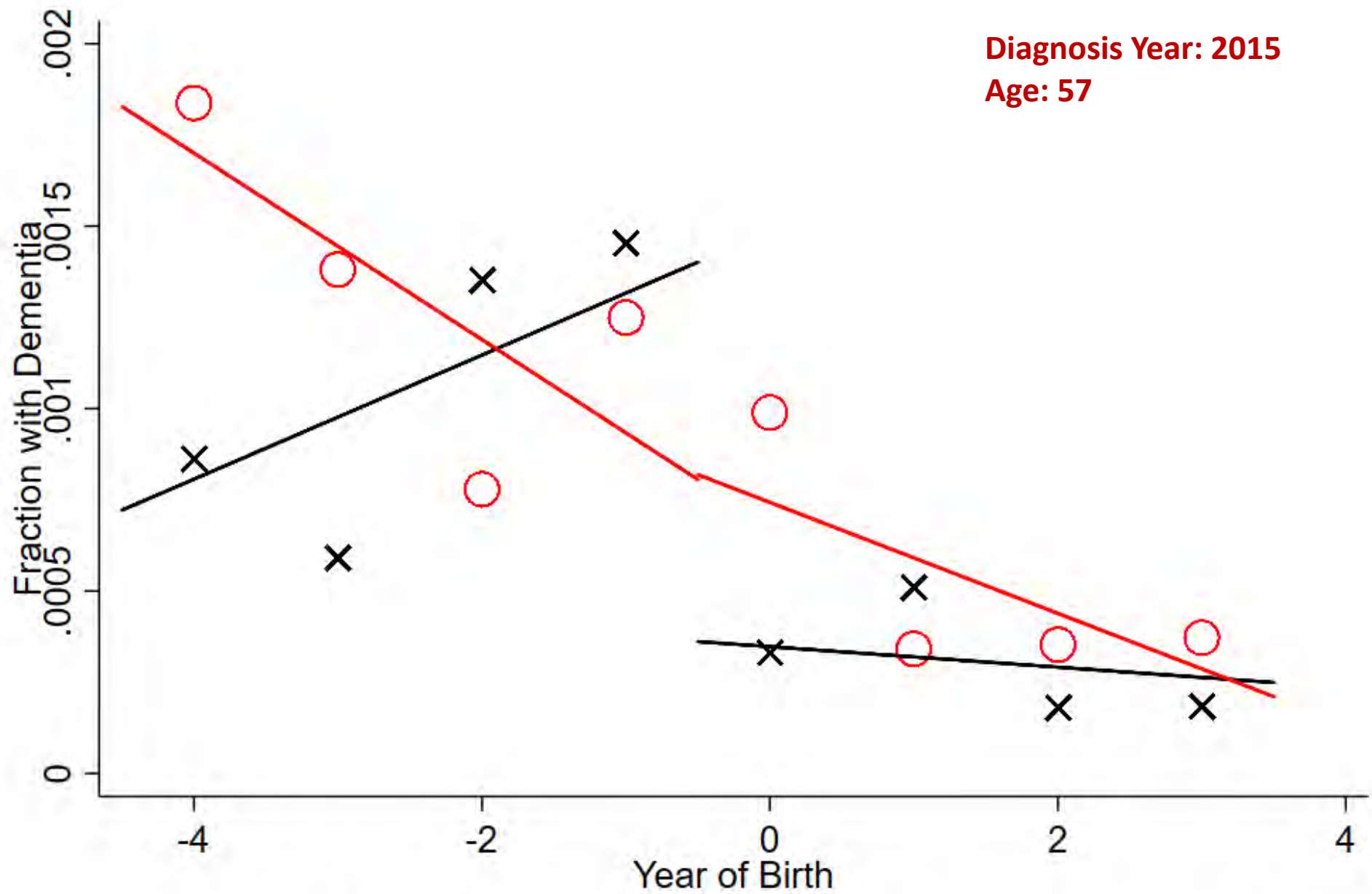


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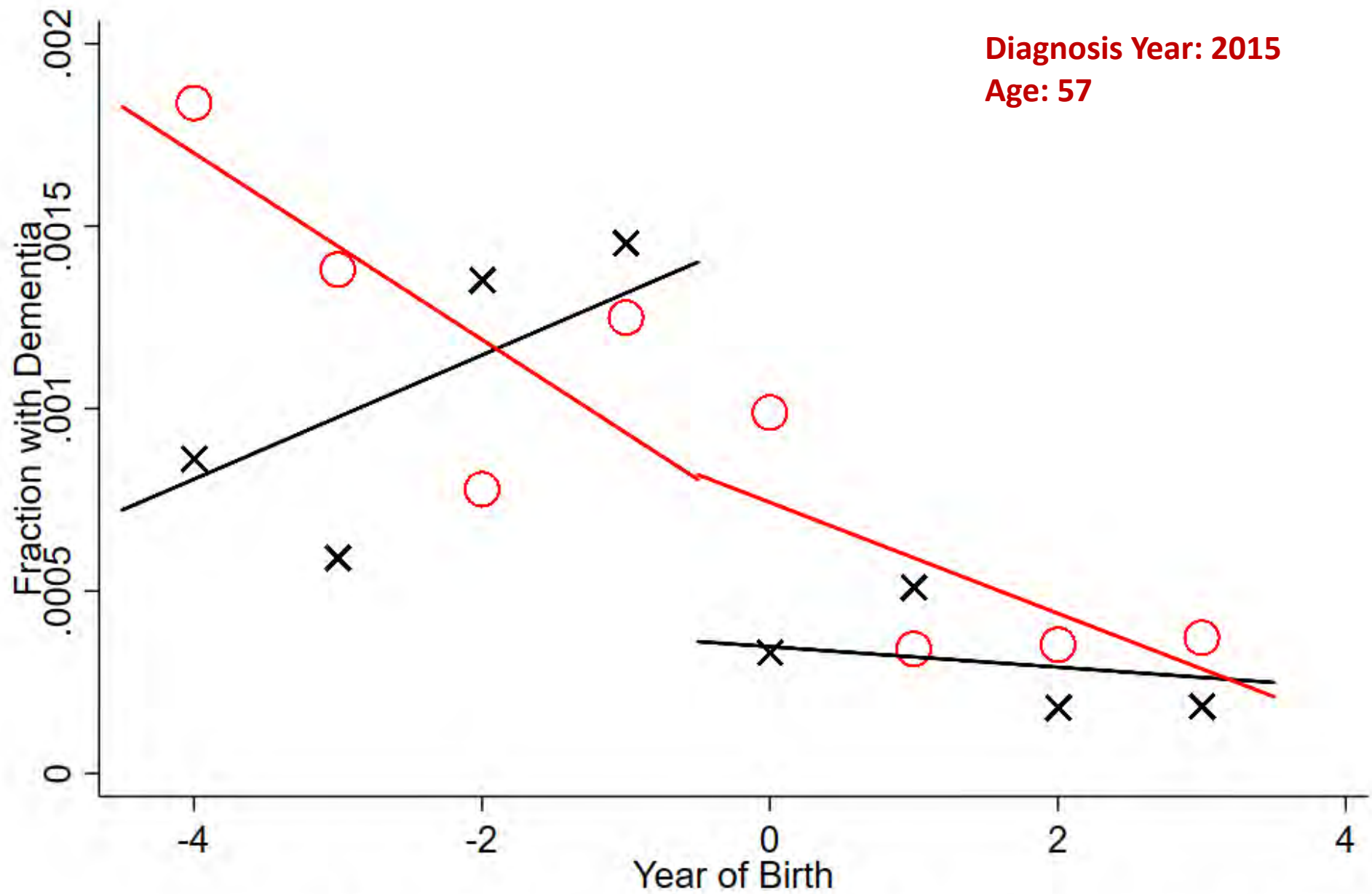
Diagnosis Year: 2015
Age: 57

x Bottom Half Composite Genetic Risk o Top Half Composite Genetic Risk



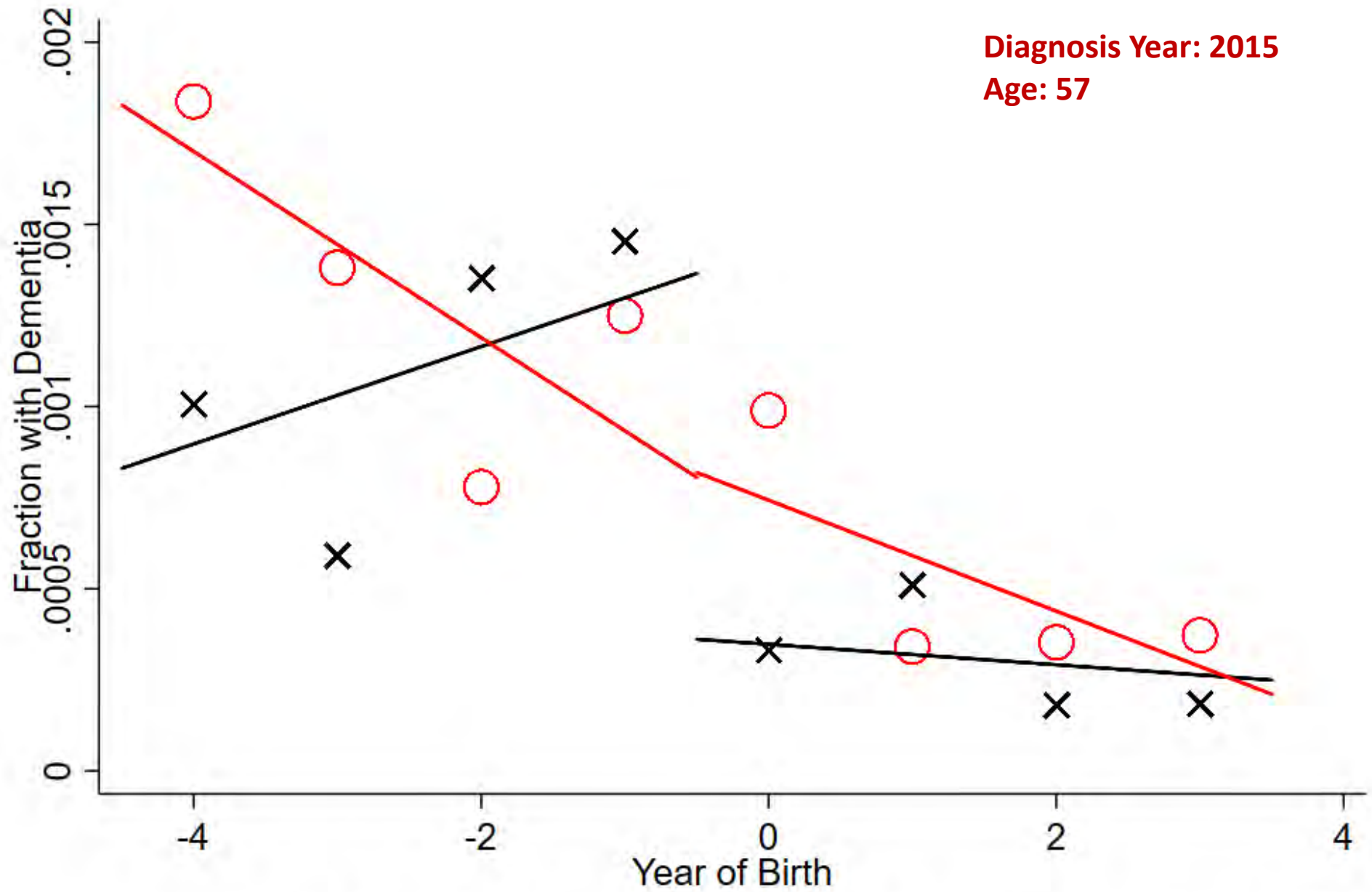
Diagnosis Year: 2015
Age: 57

x Bottom Half Composite Genetic Risk o Top Half Composite Genetic Risk



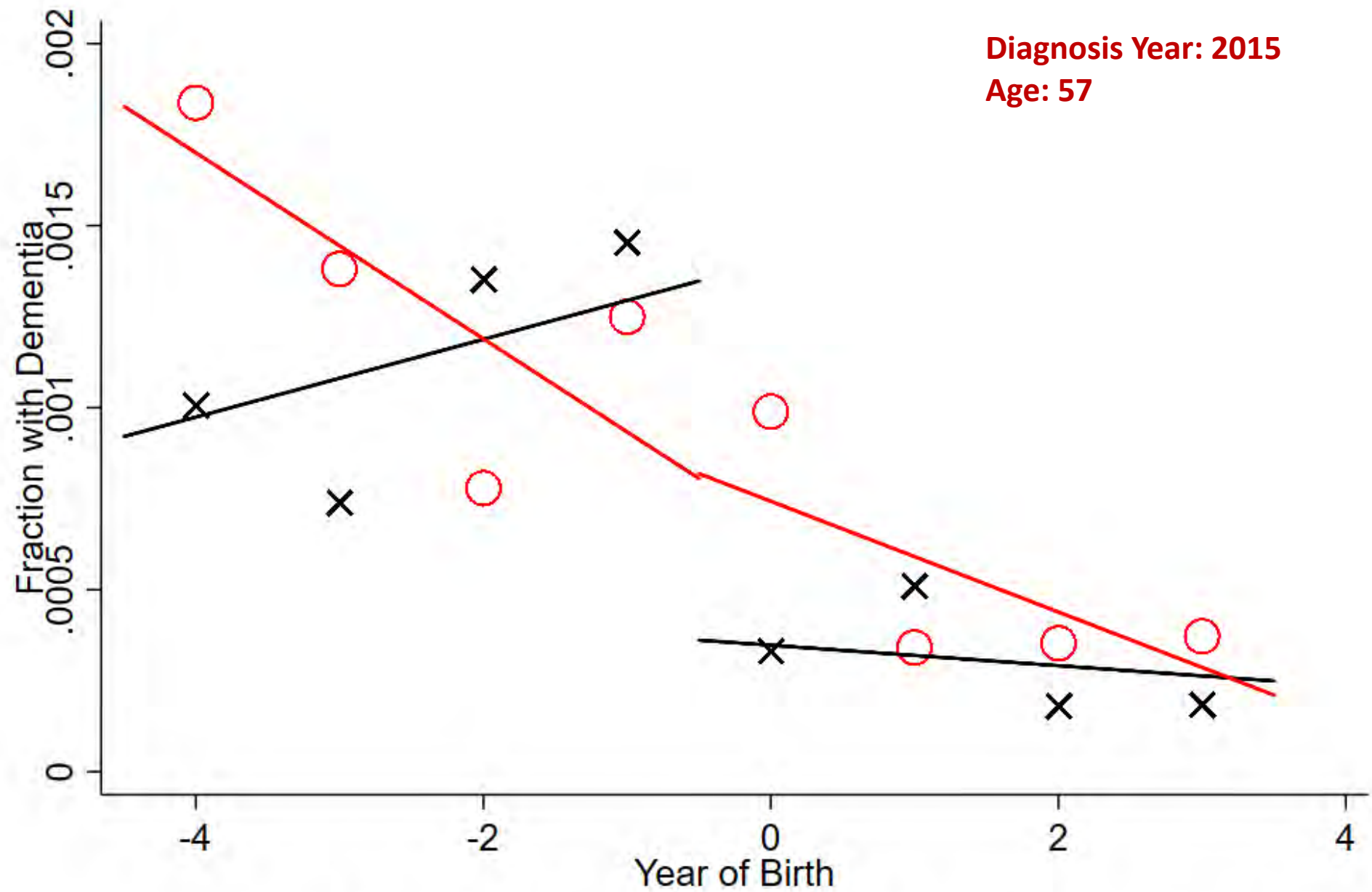
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Diagnosis Year: 2015
Age: 57

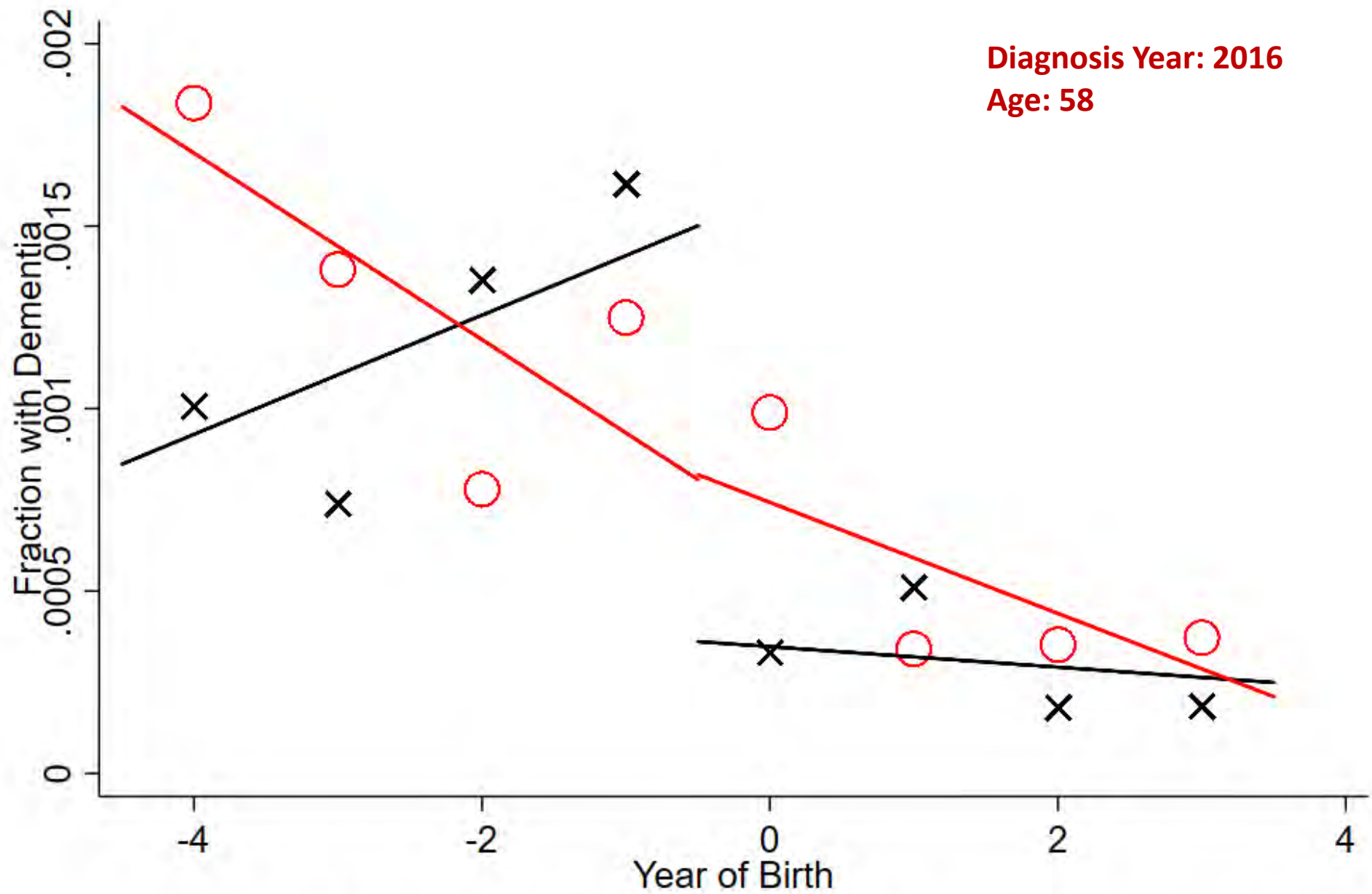


X Bottom Half Composite Genetic Risk O Top Half Composite Genetic Risk

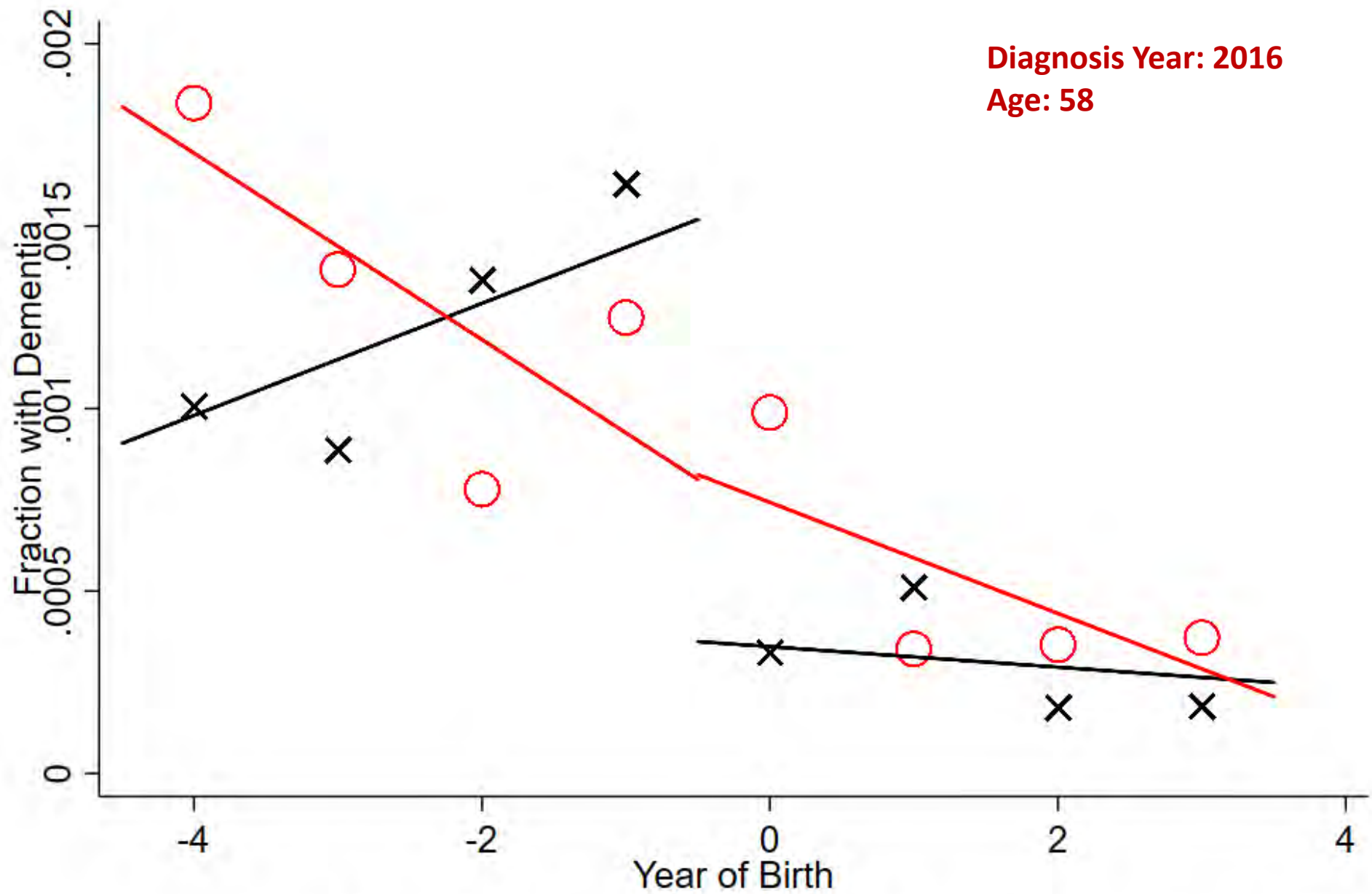
Diagnosis Year: 2015
Age: 57



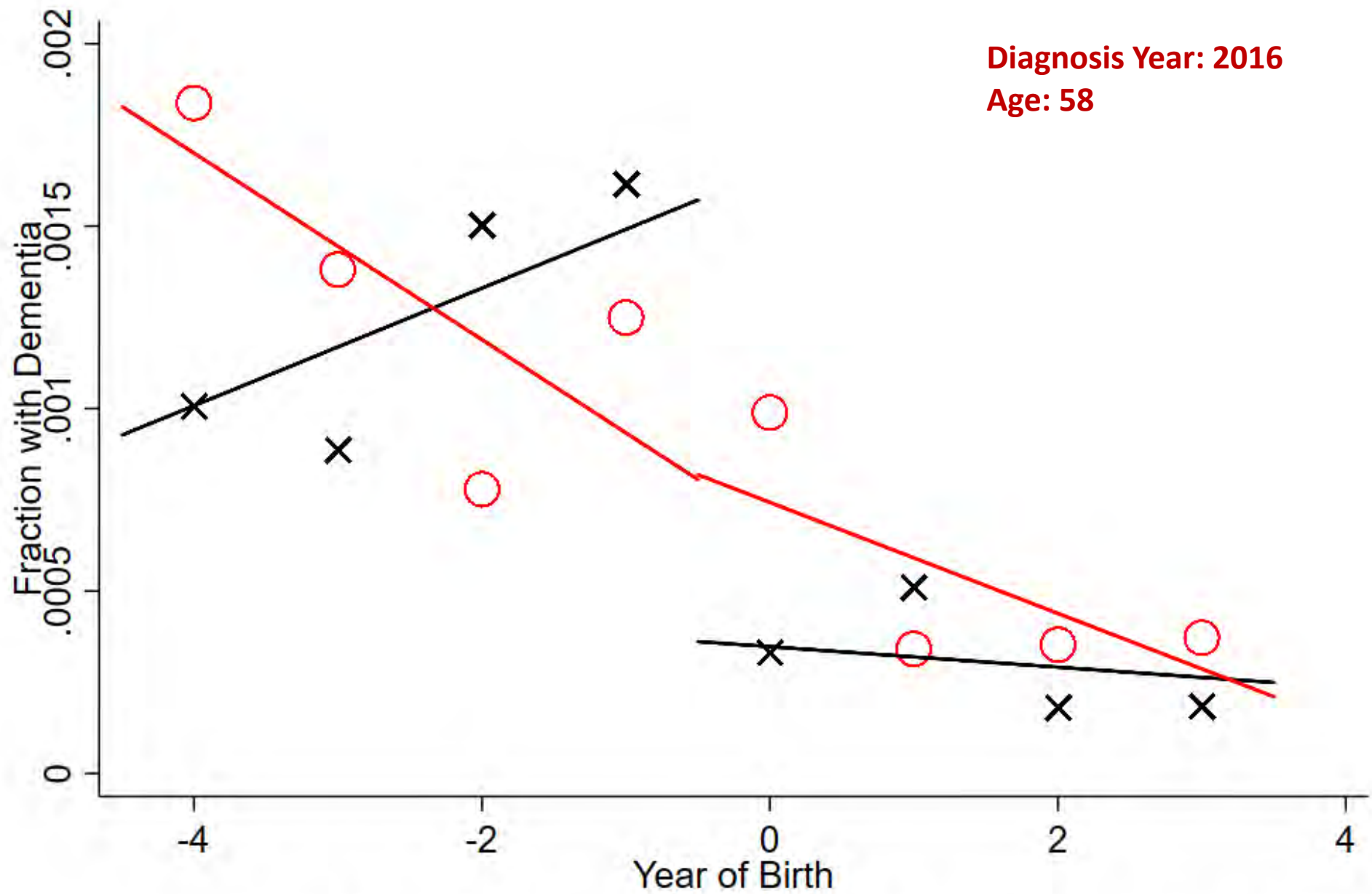
x Bottom Half Composite Genetic Risk o Top Half Composite Genetic Risk



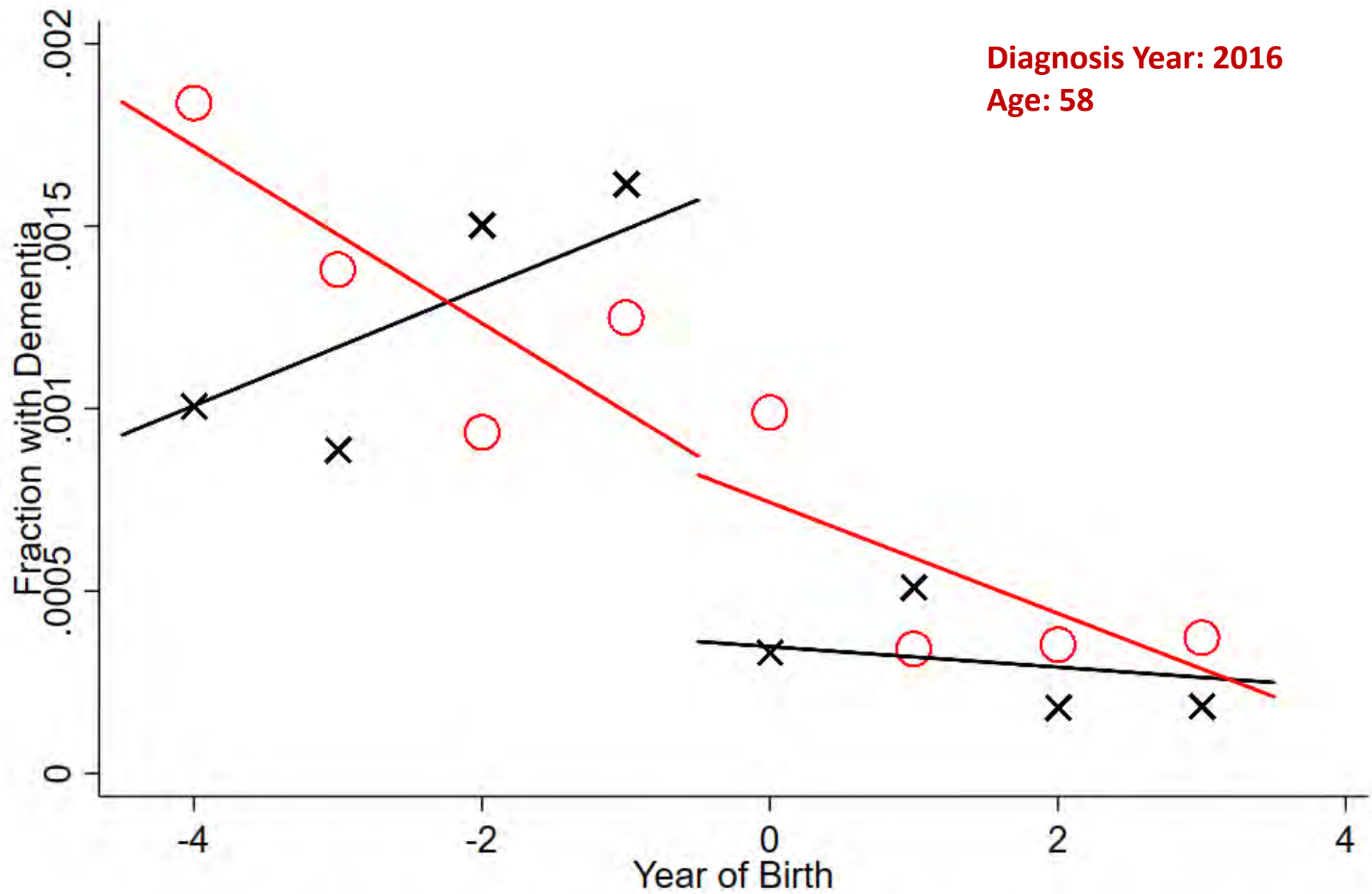
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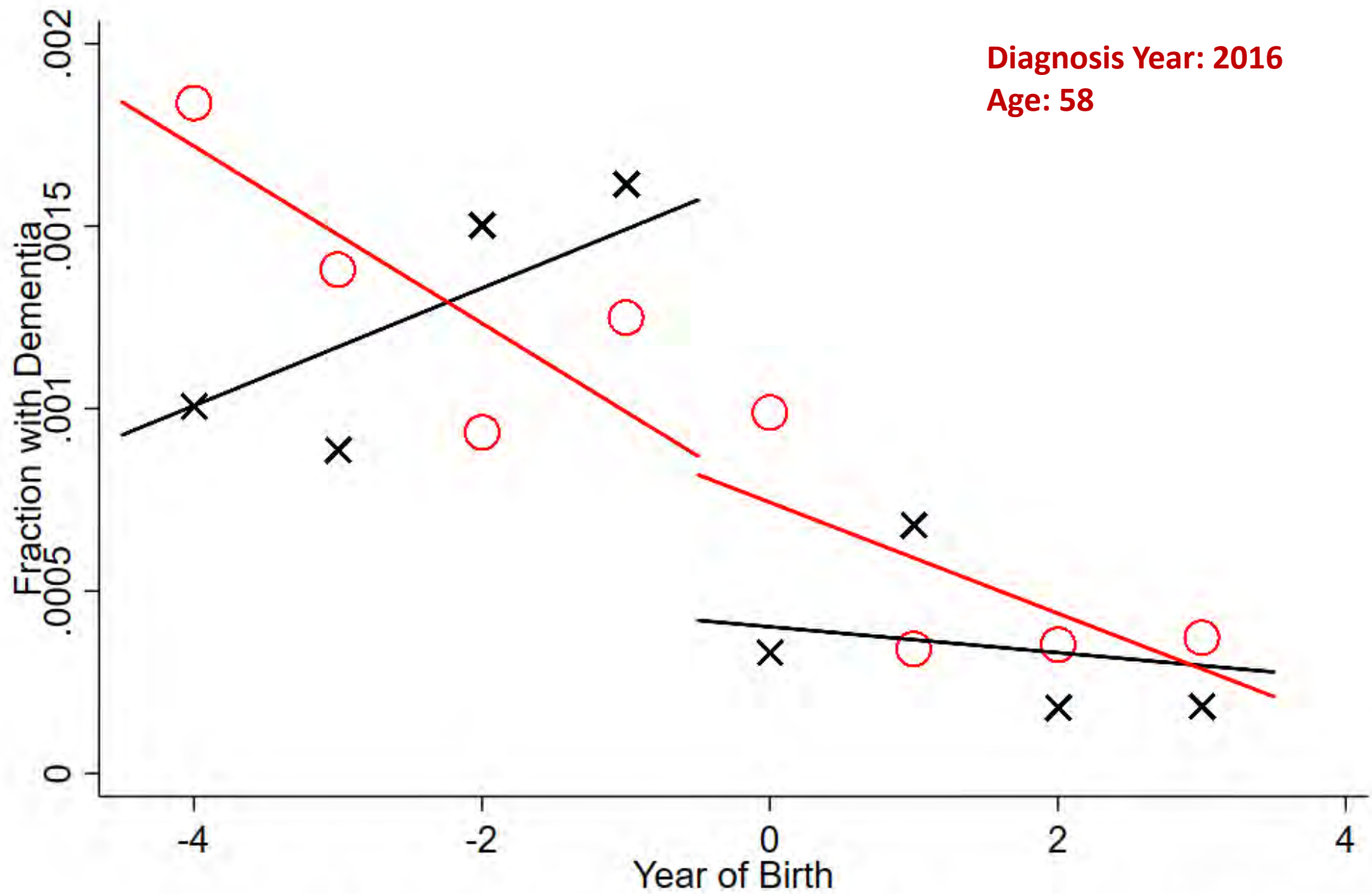
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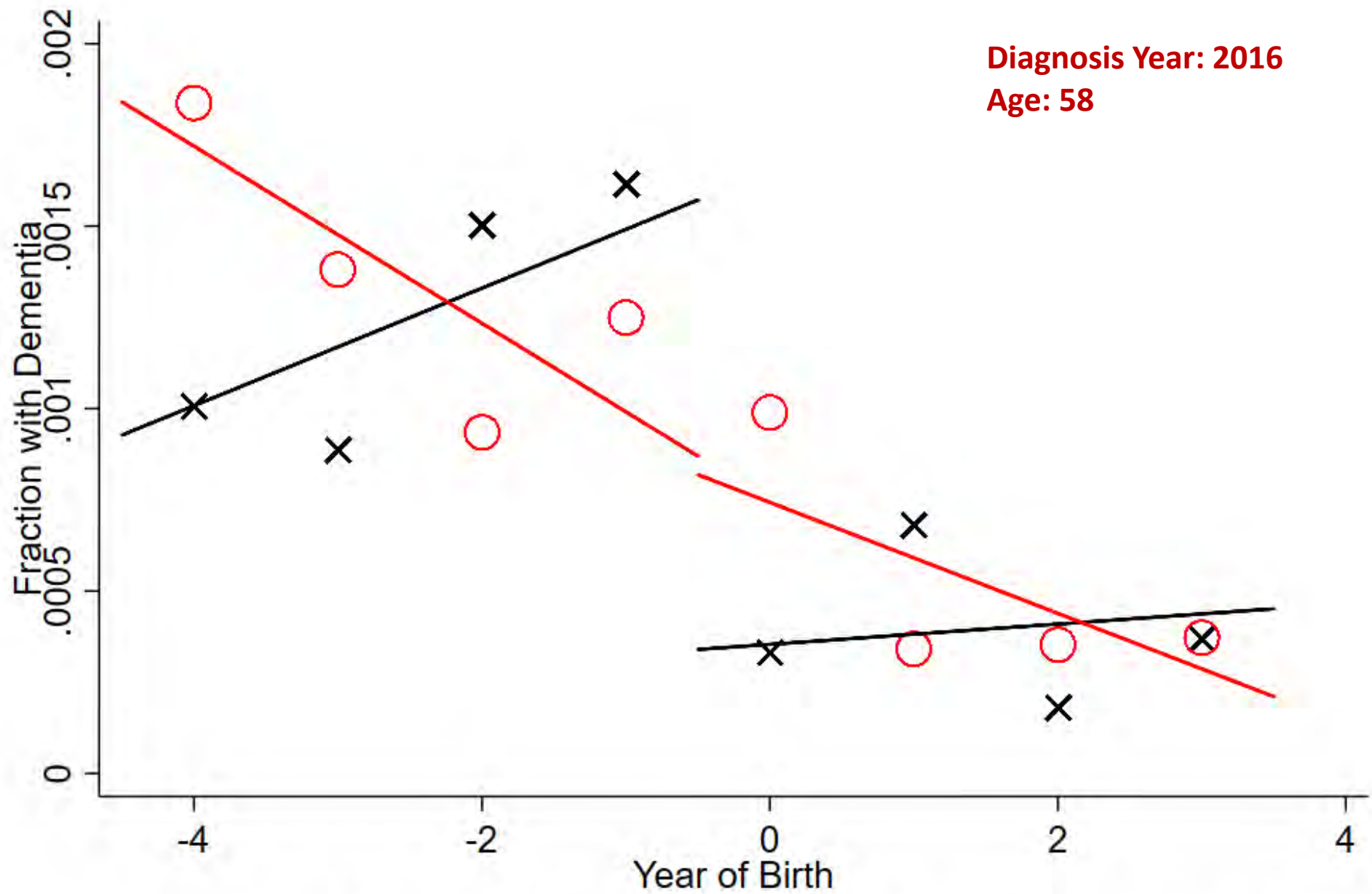
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



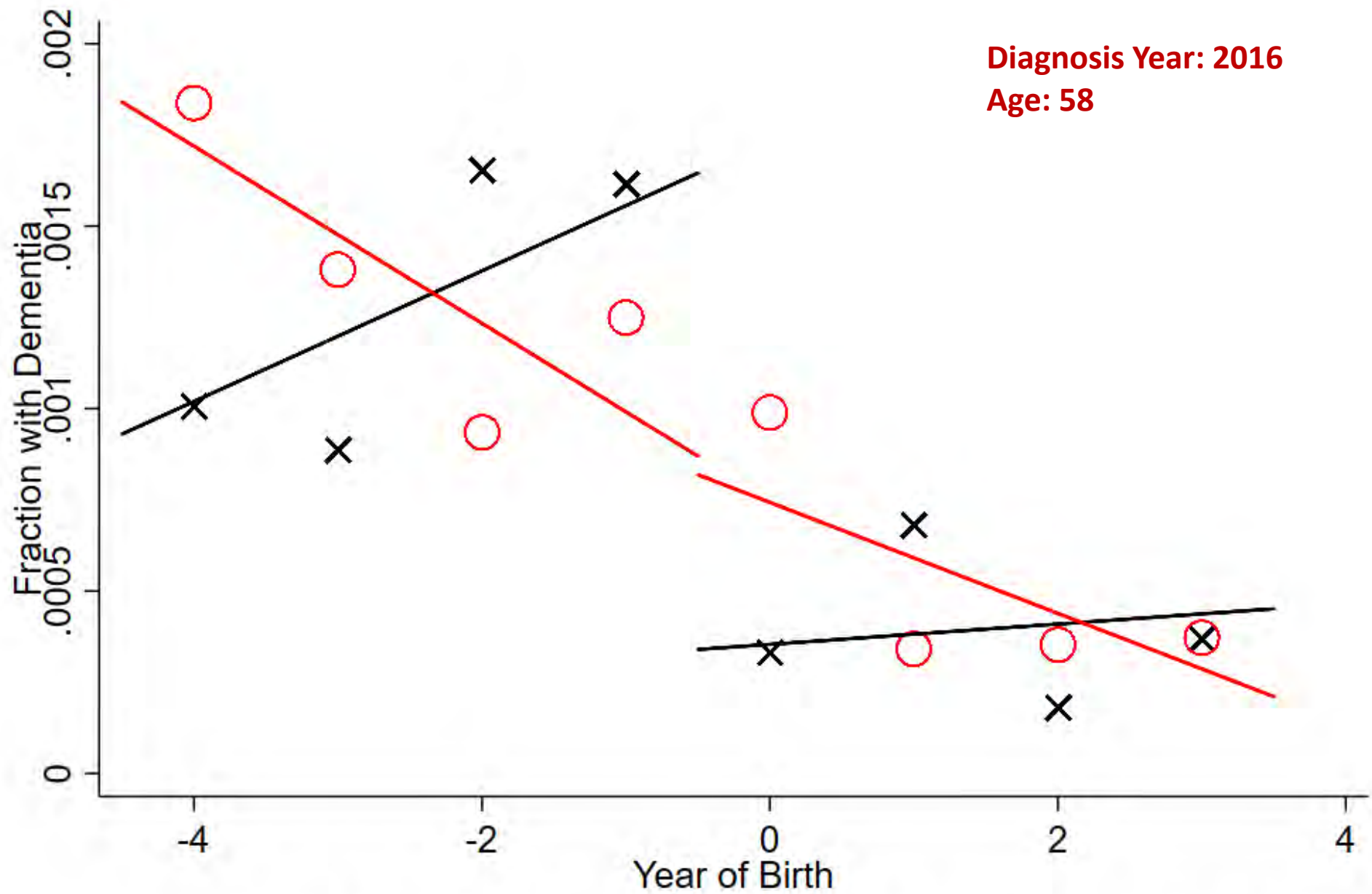
X Bottom Half Composite Genetic Risk O Top Half Composite Genetic Risk



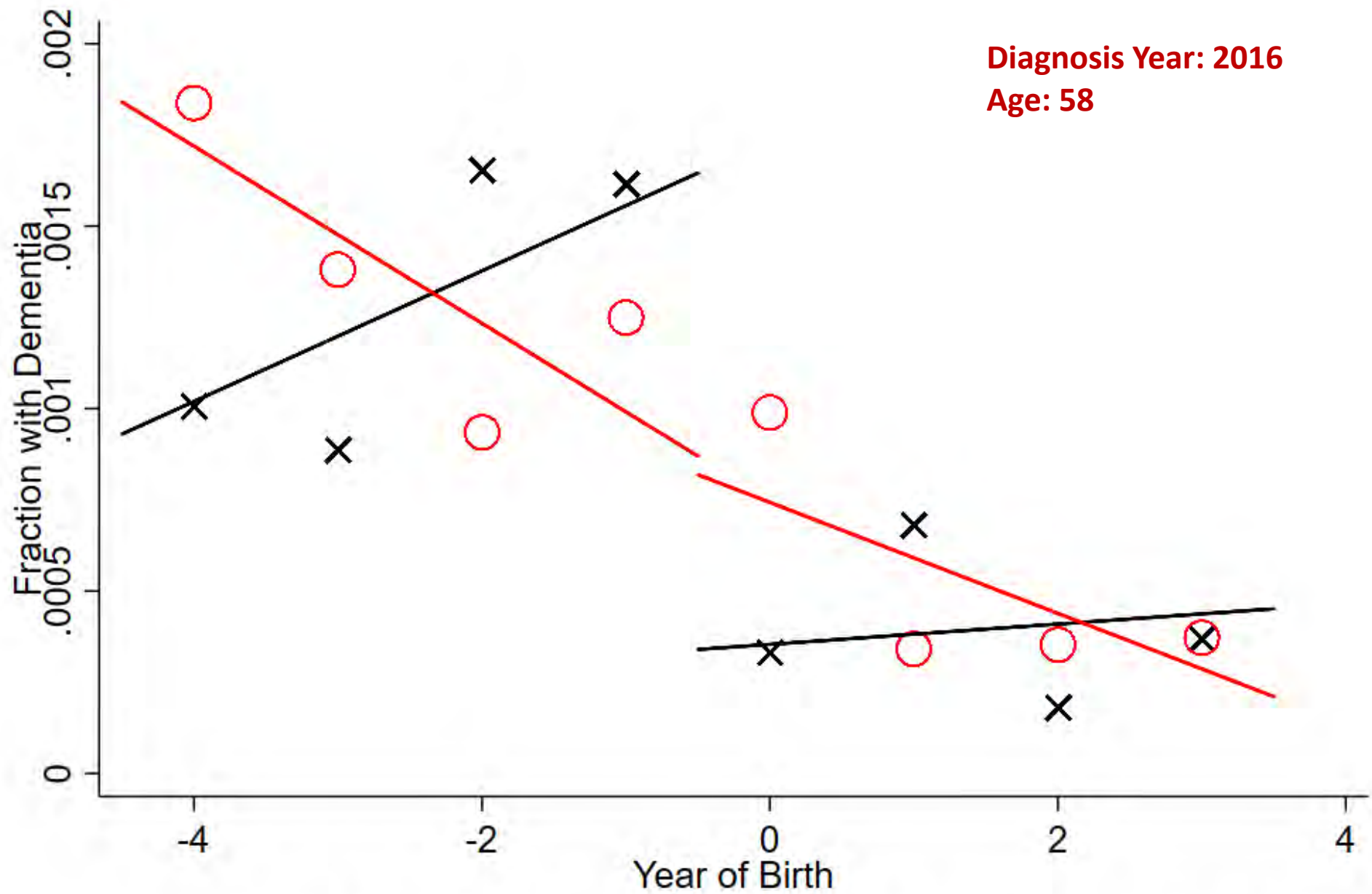
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



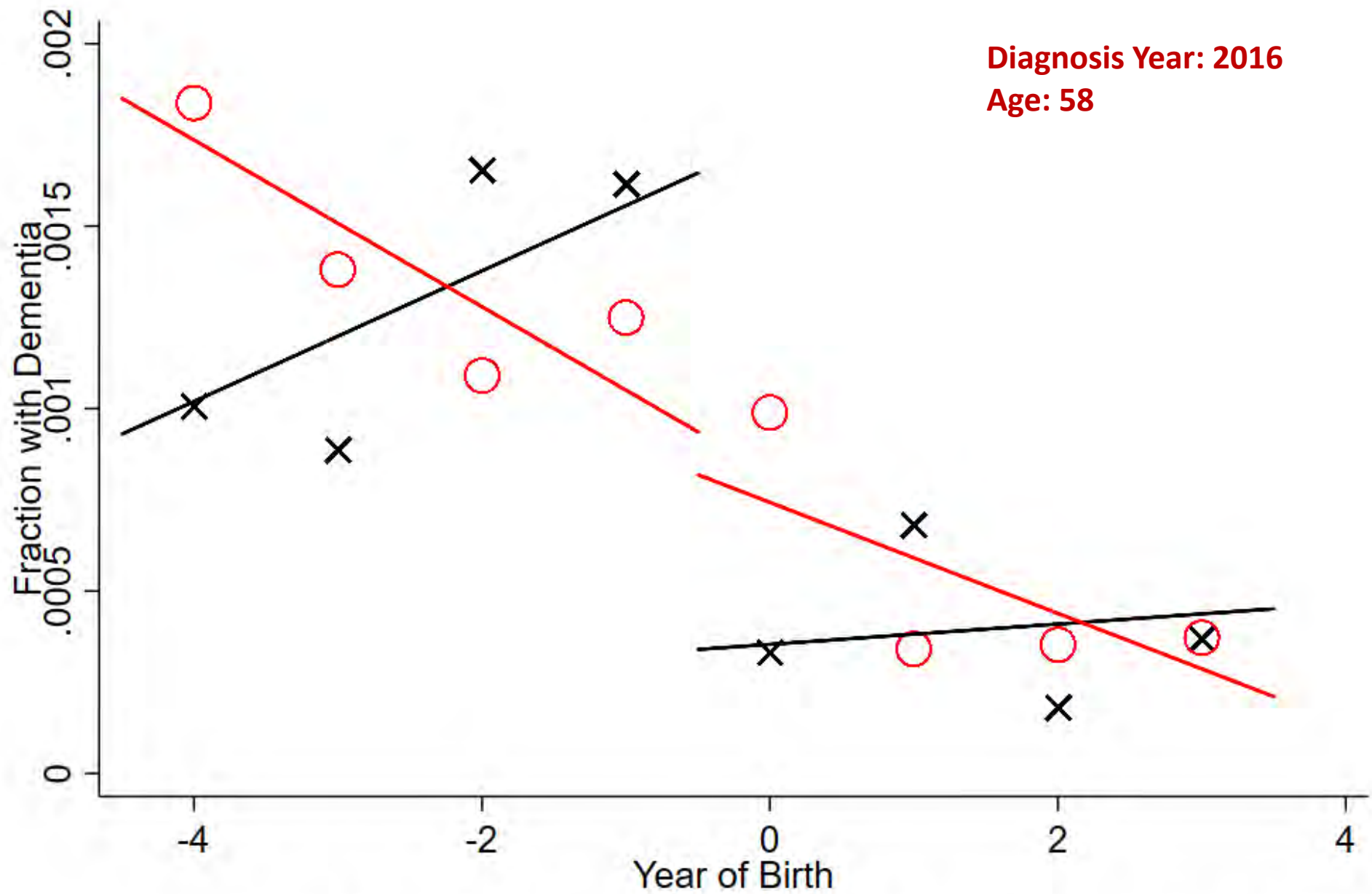
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

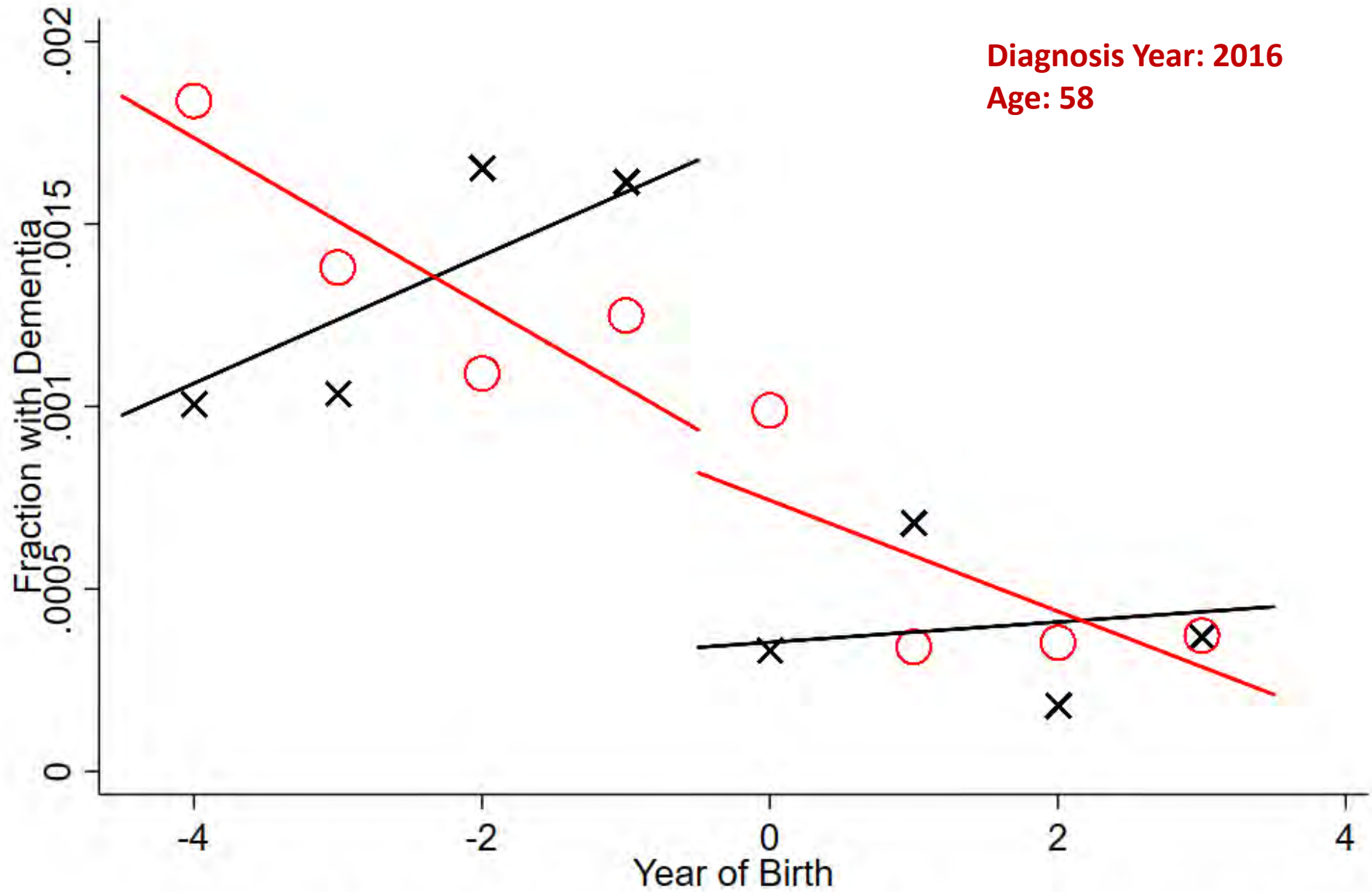


× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

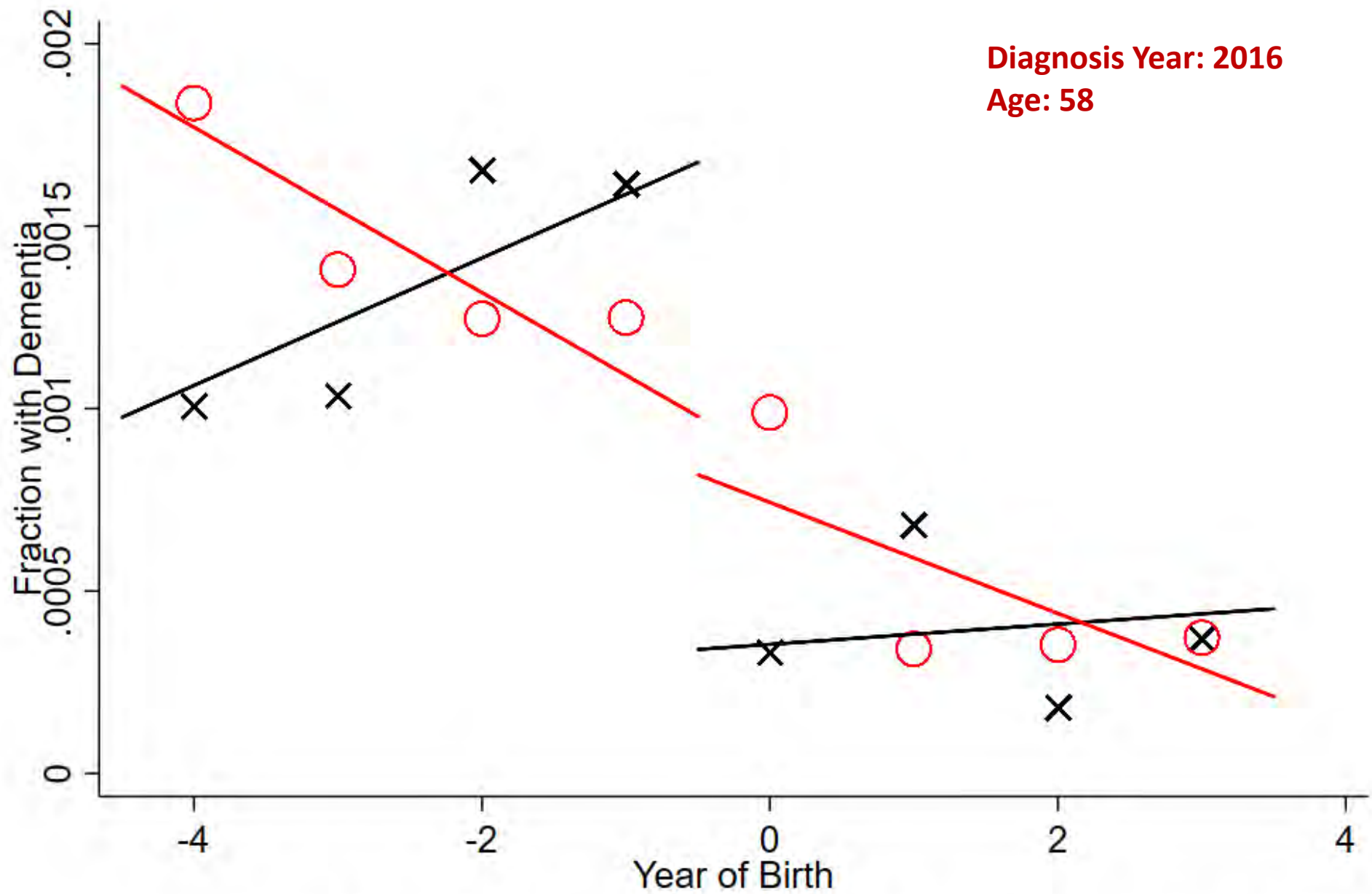


× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

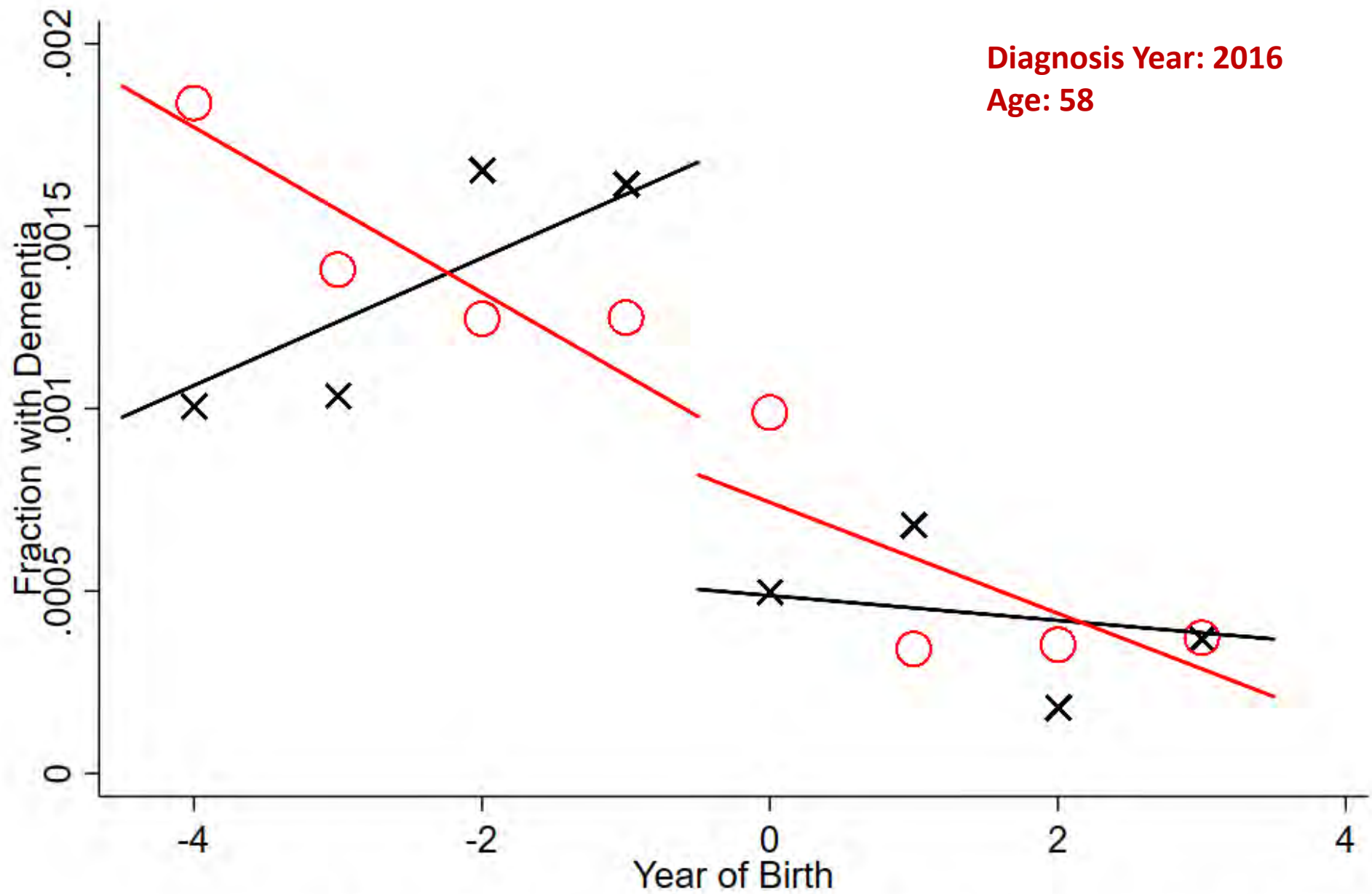
Diagnosis Year: 2016
Age: 58



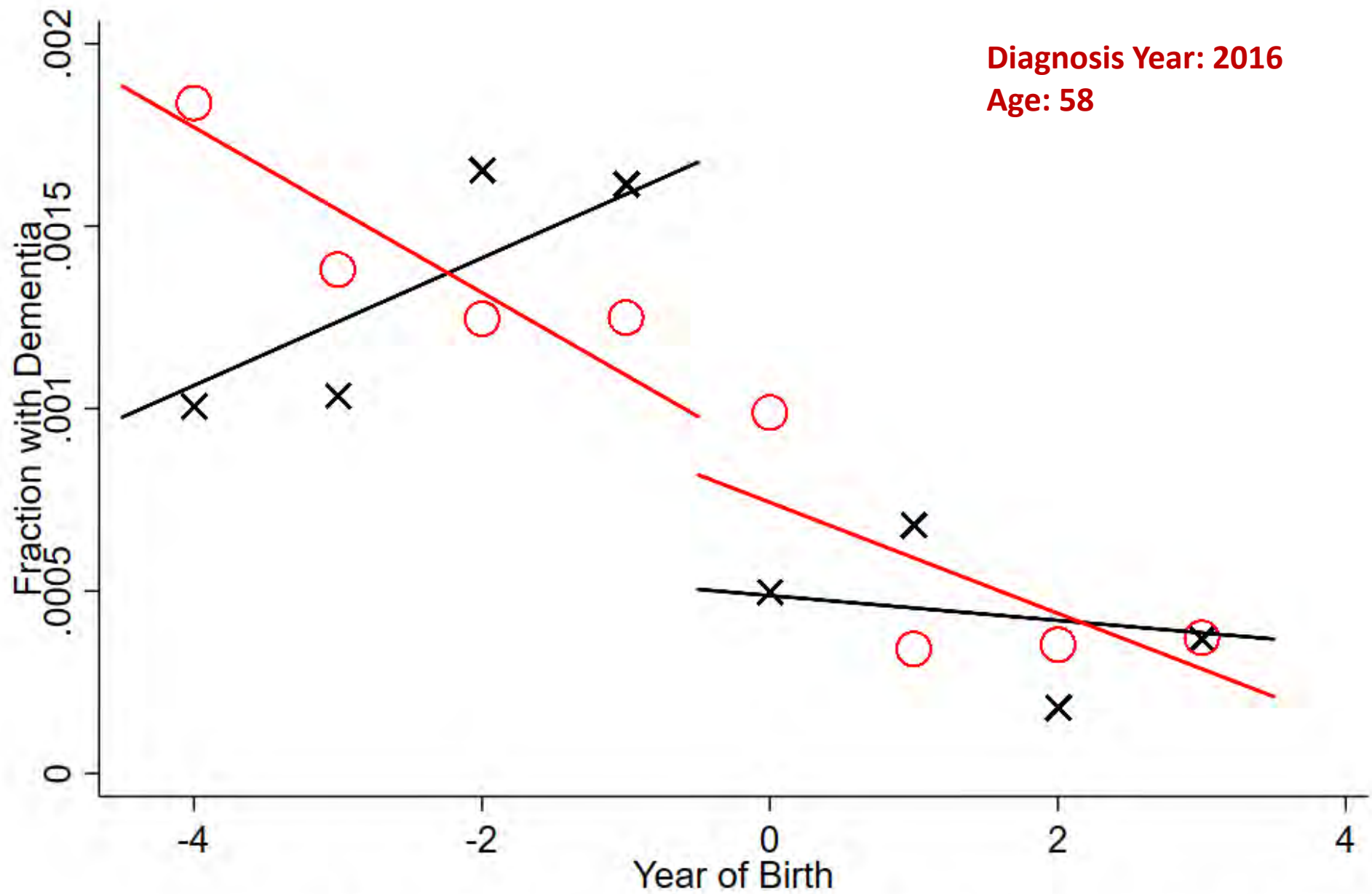
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



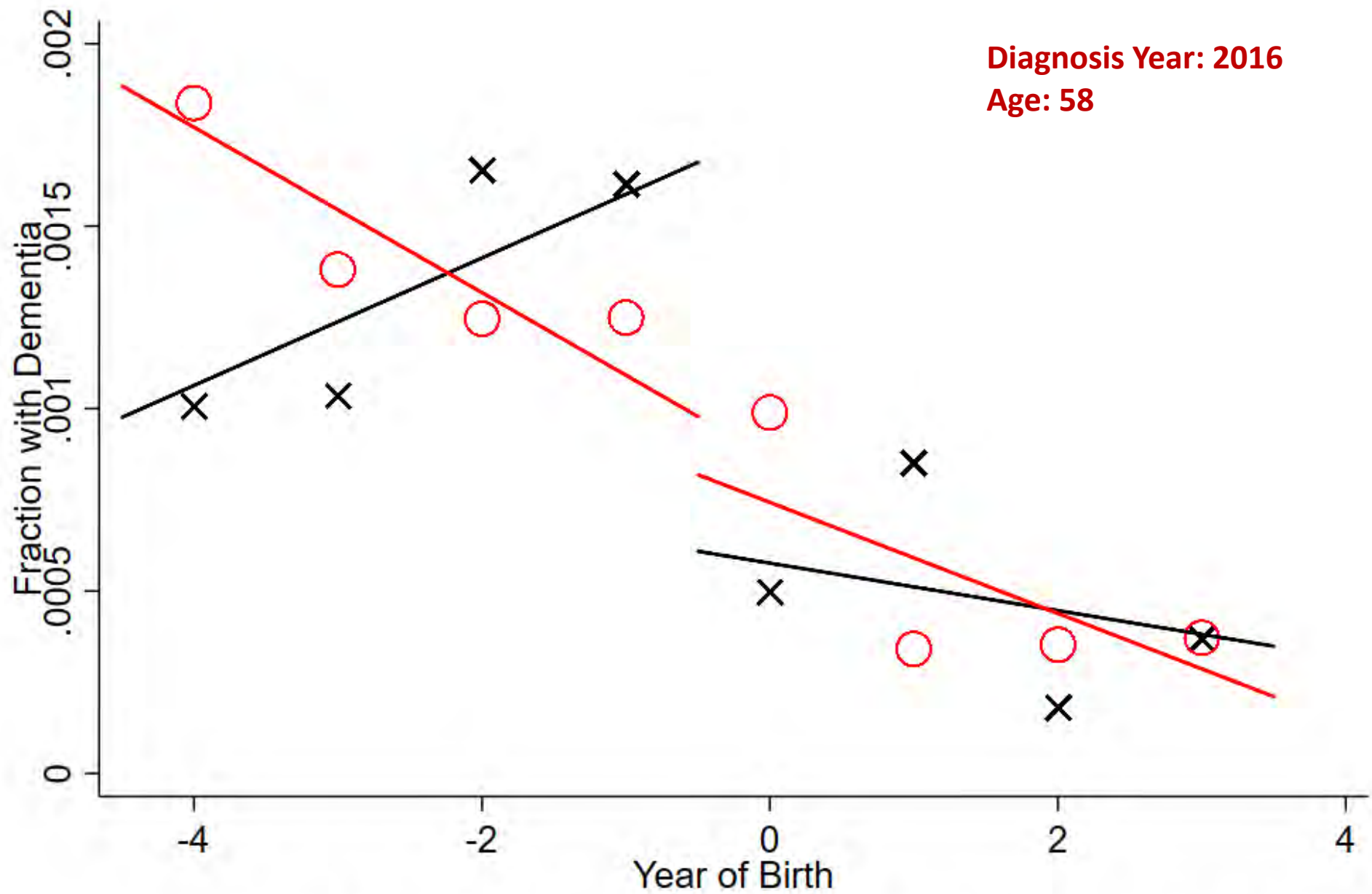
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



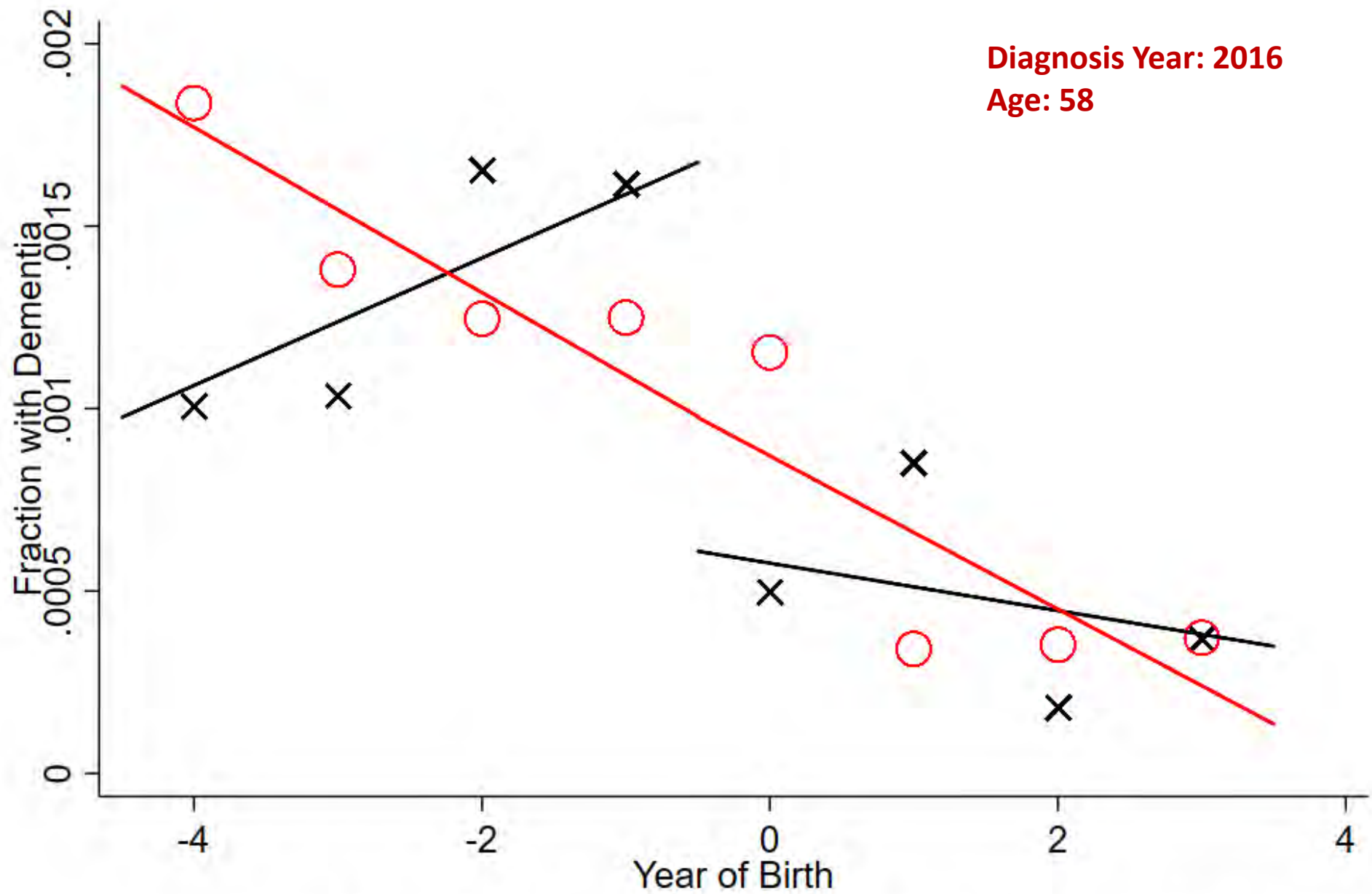
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



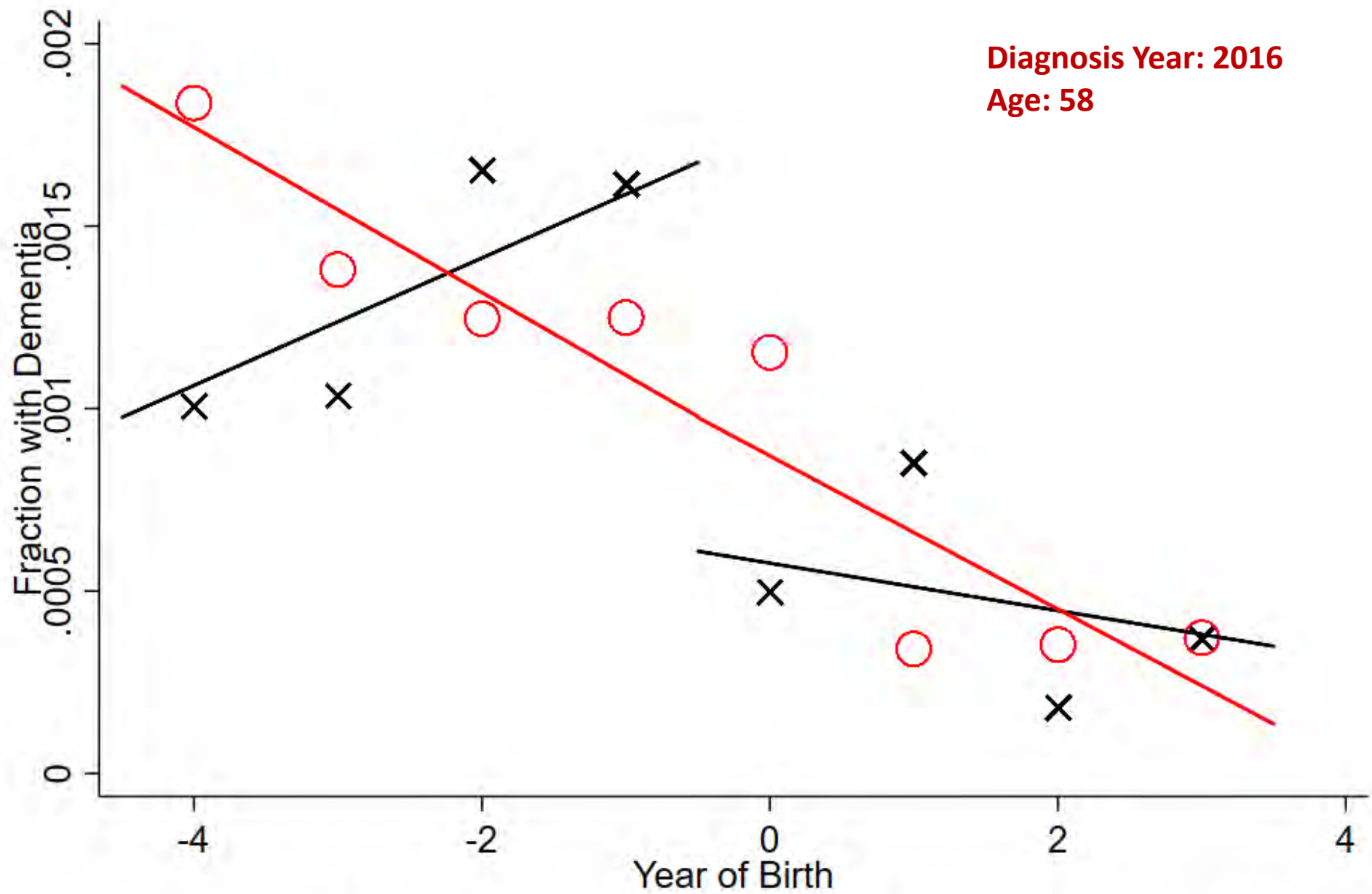
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



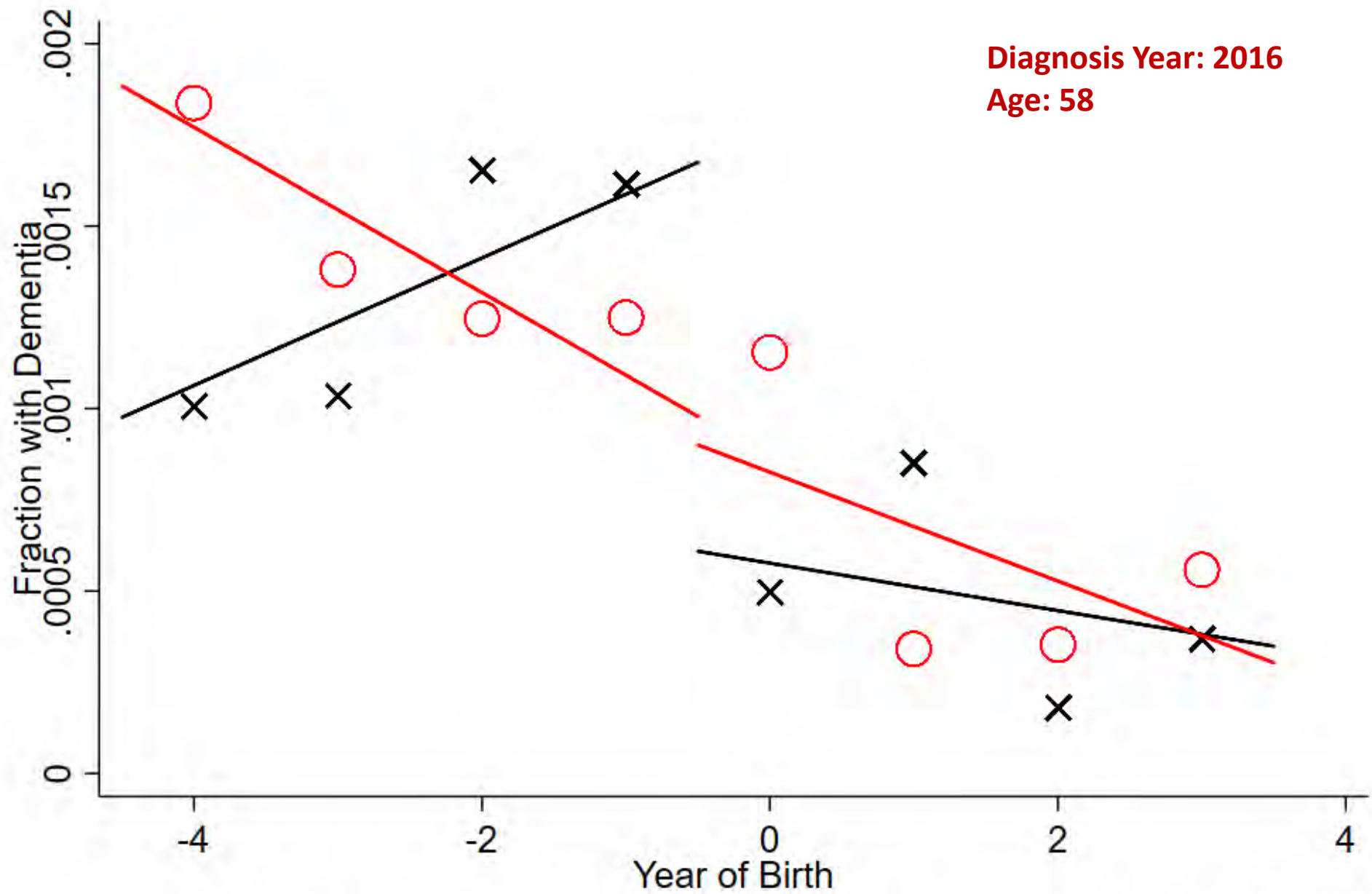
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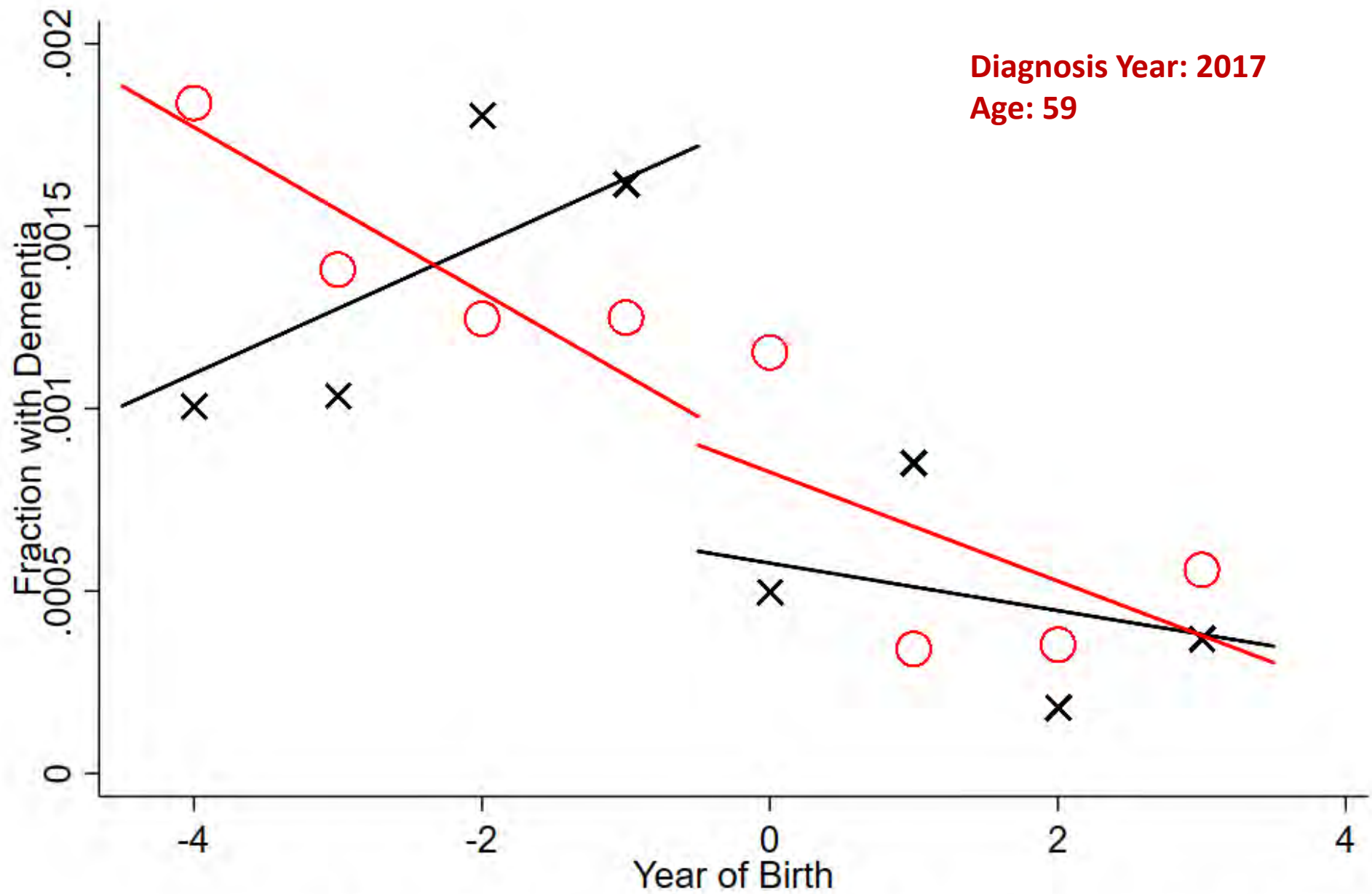
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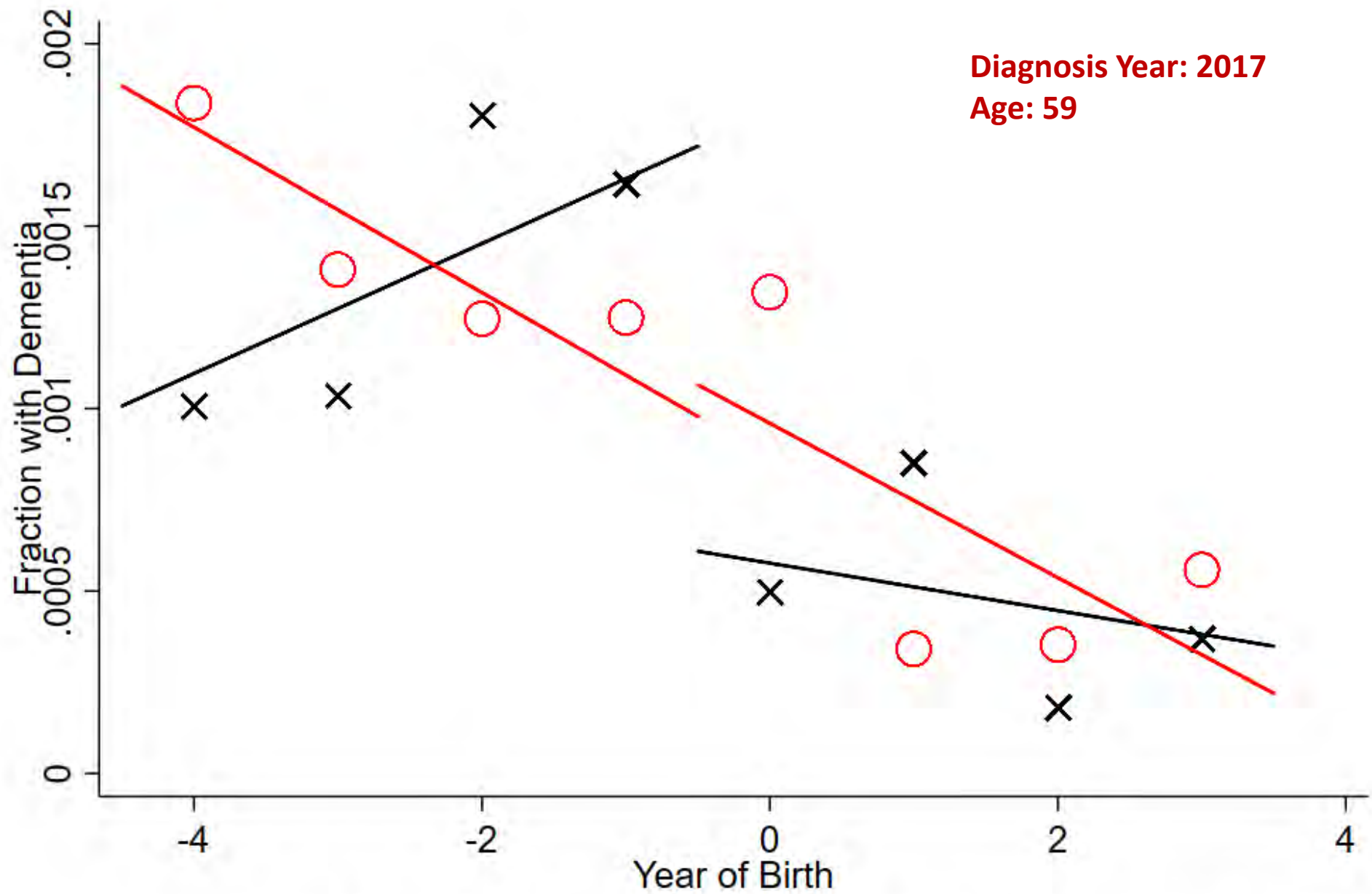


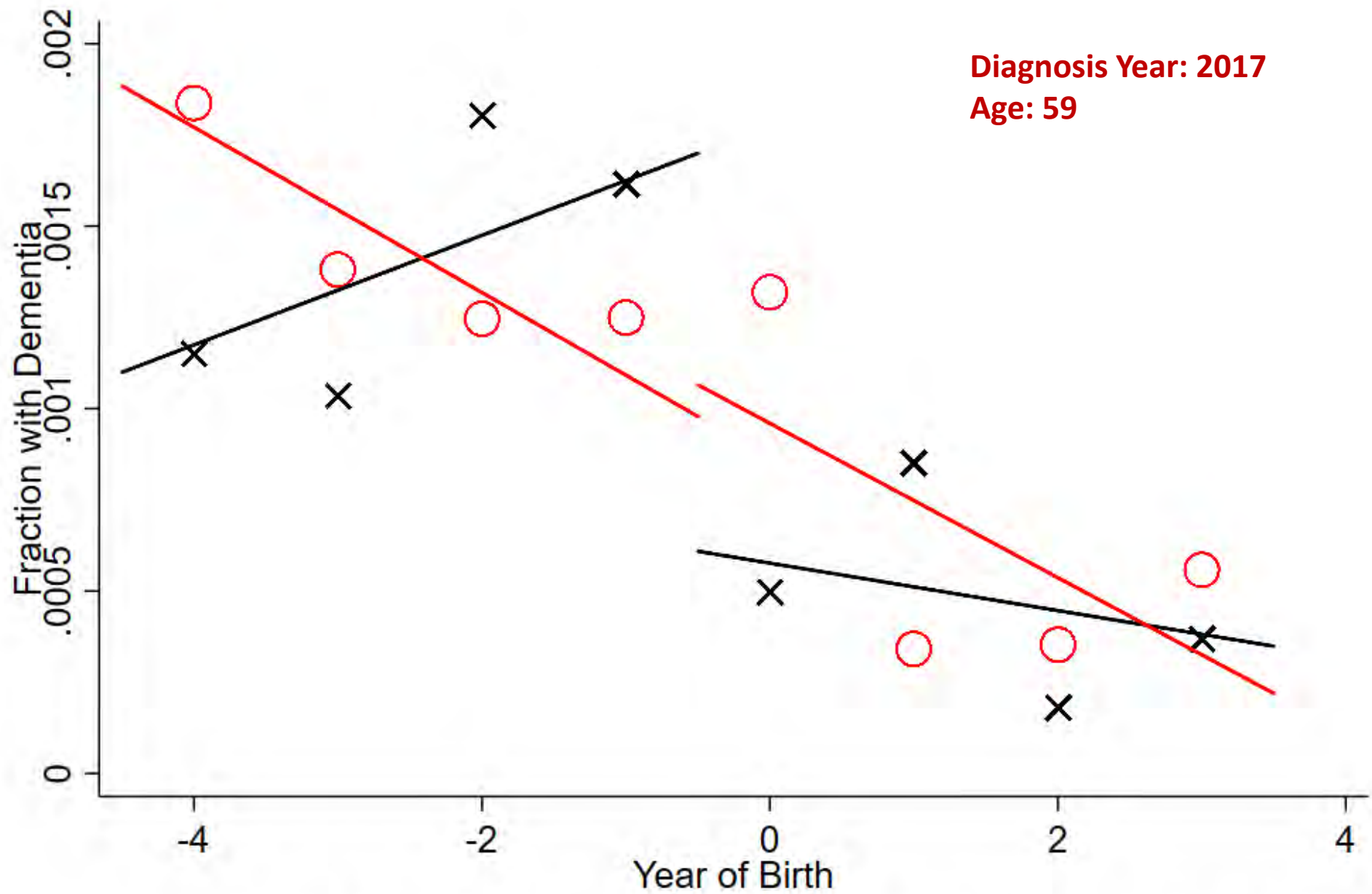
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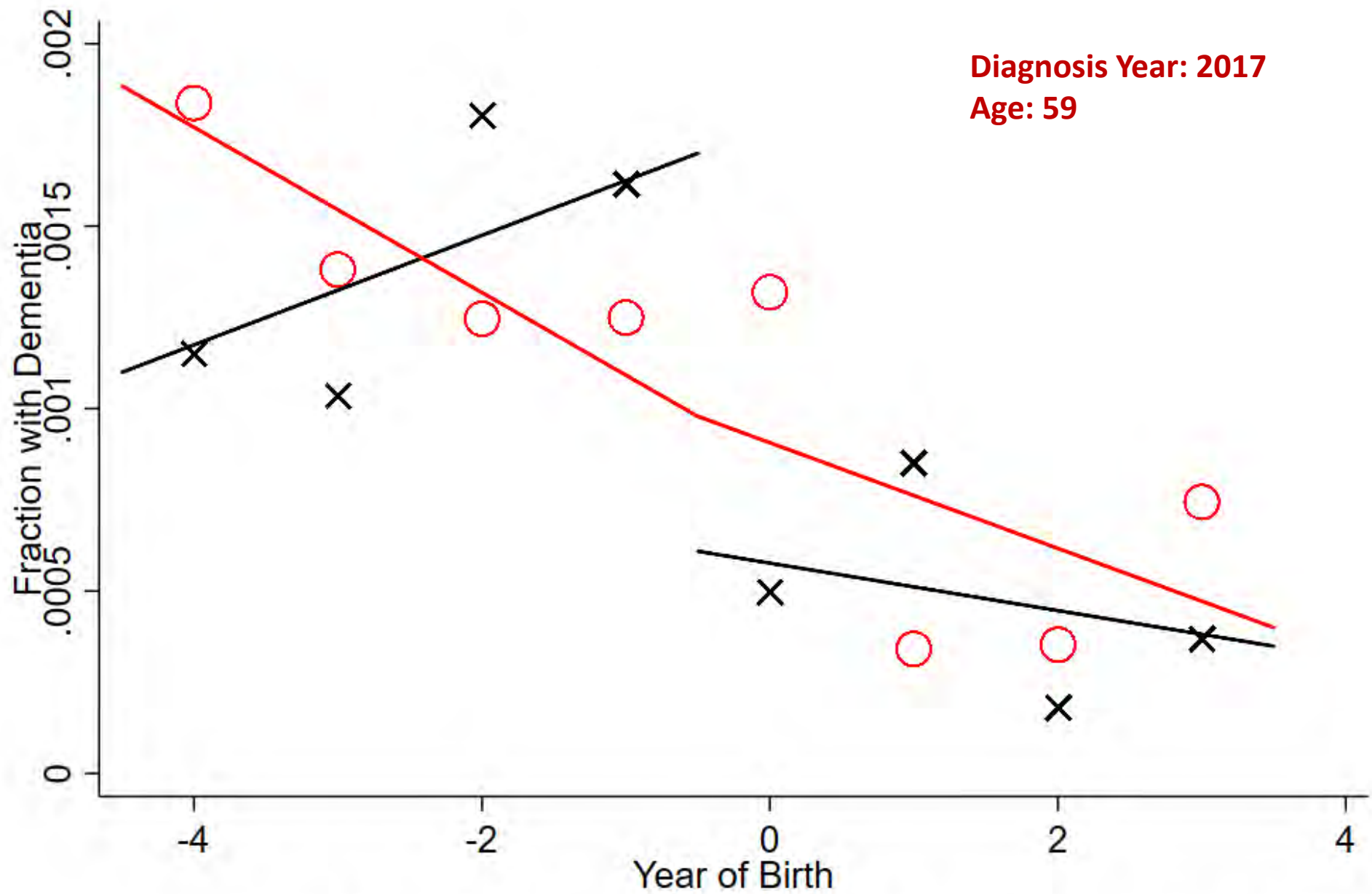


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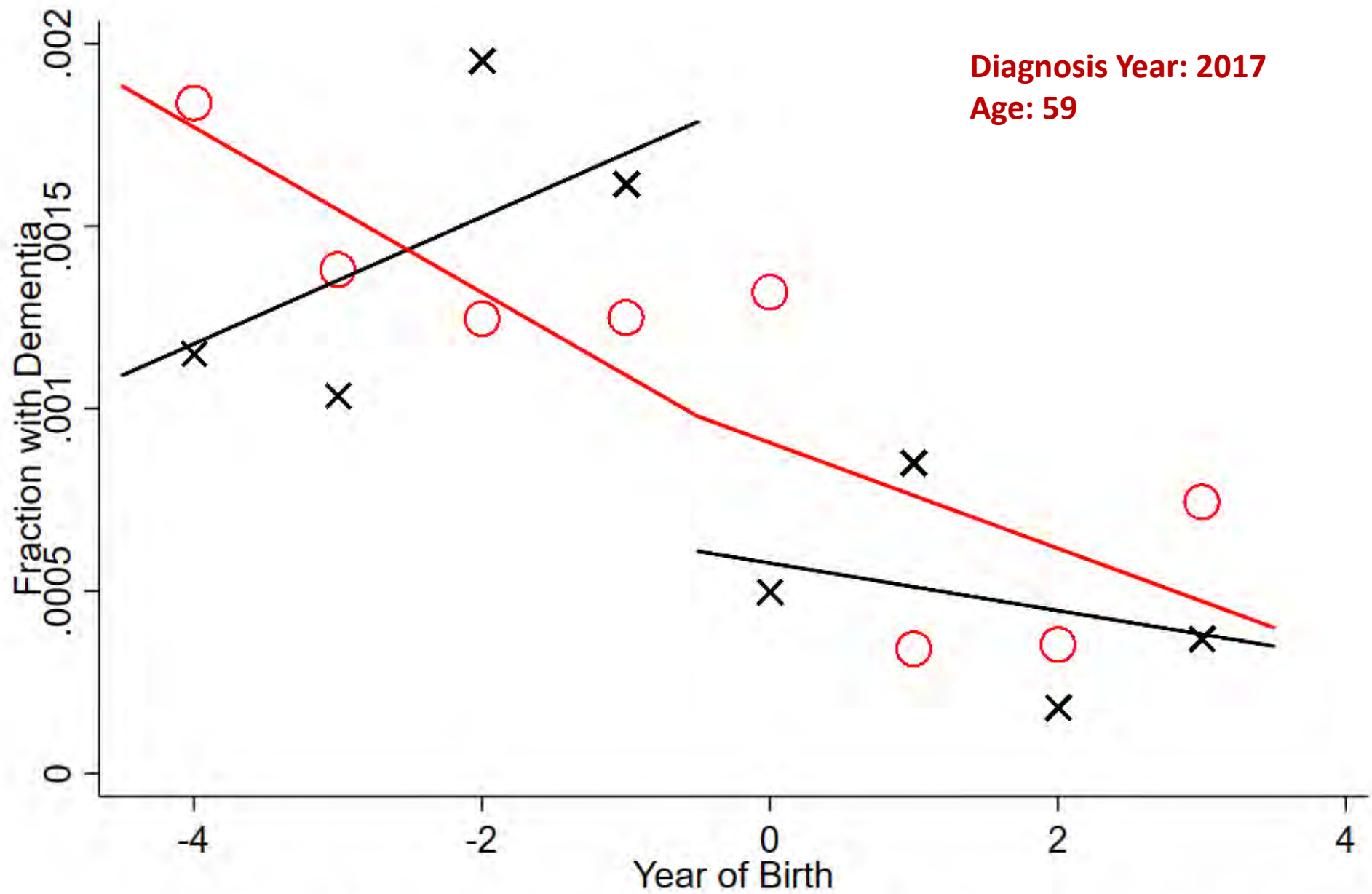




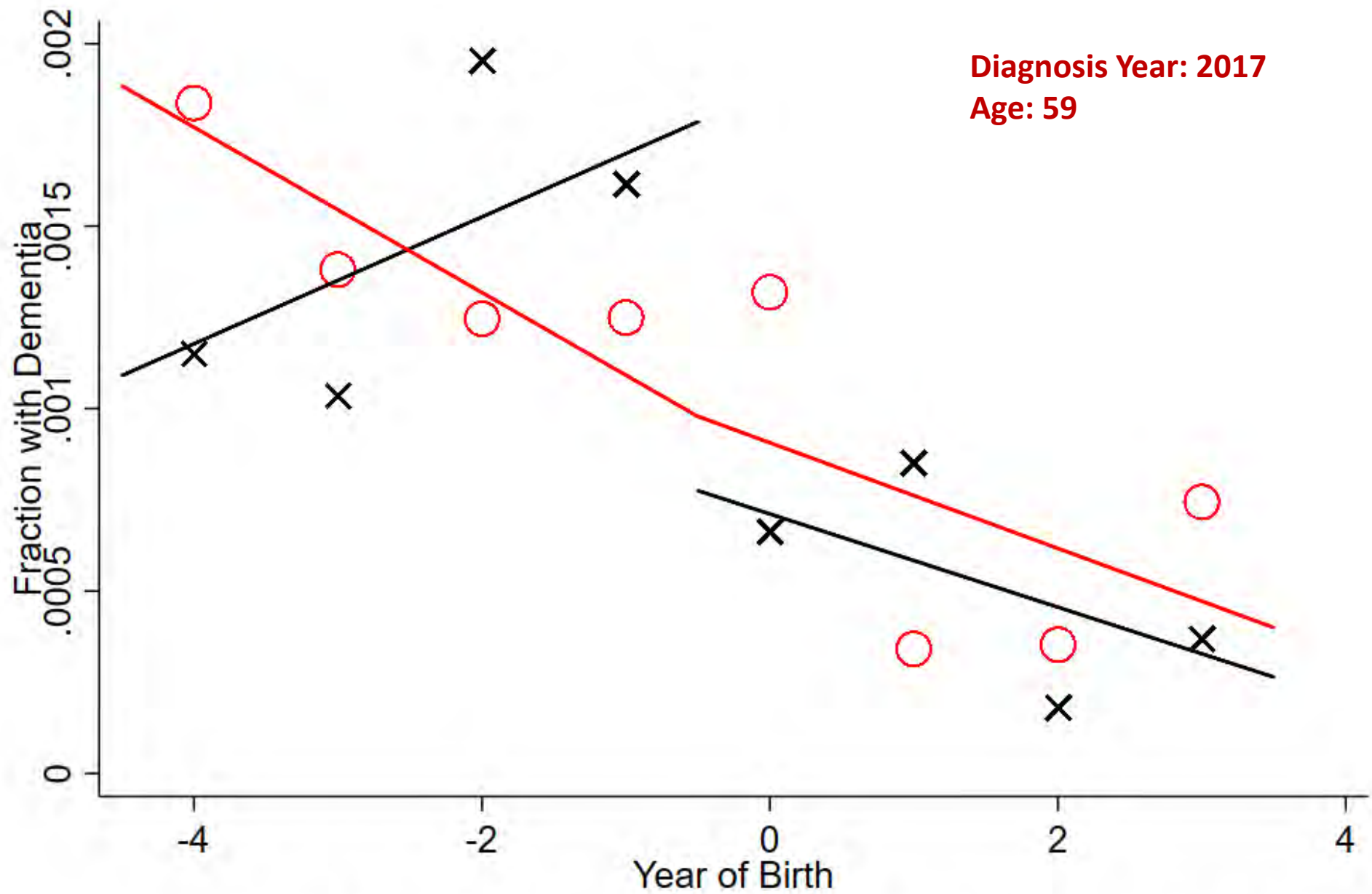




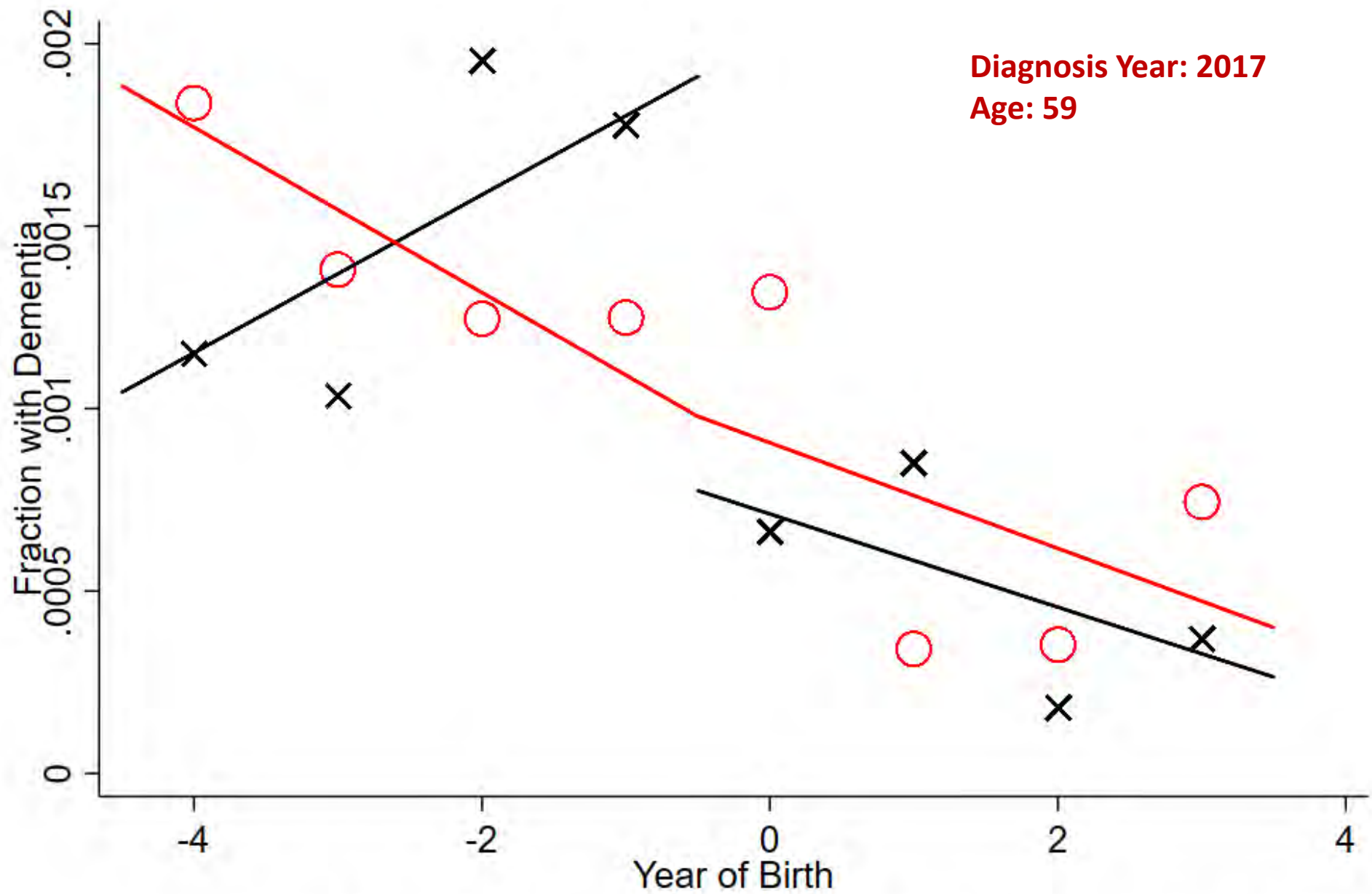
x Bottom Half Composite Genetic Risk o Top Half Composite Genetic Risk



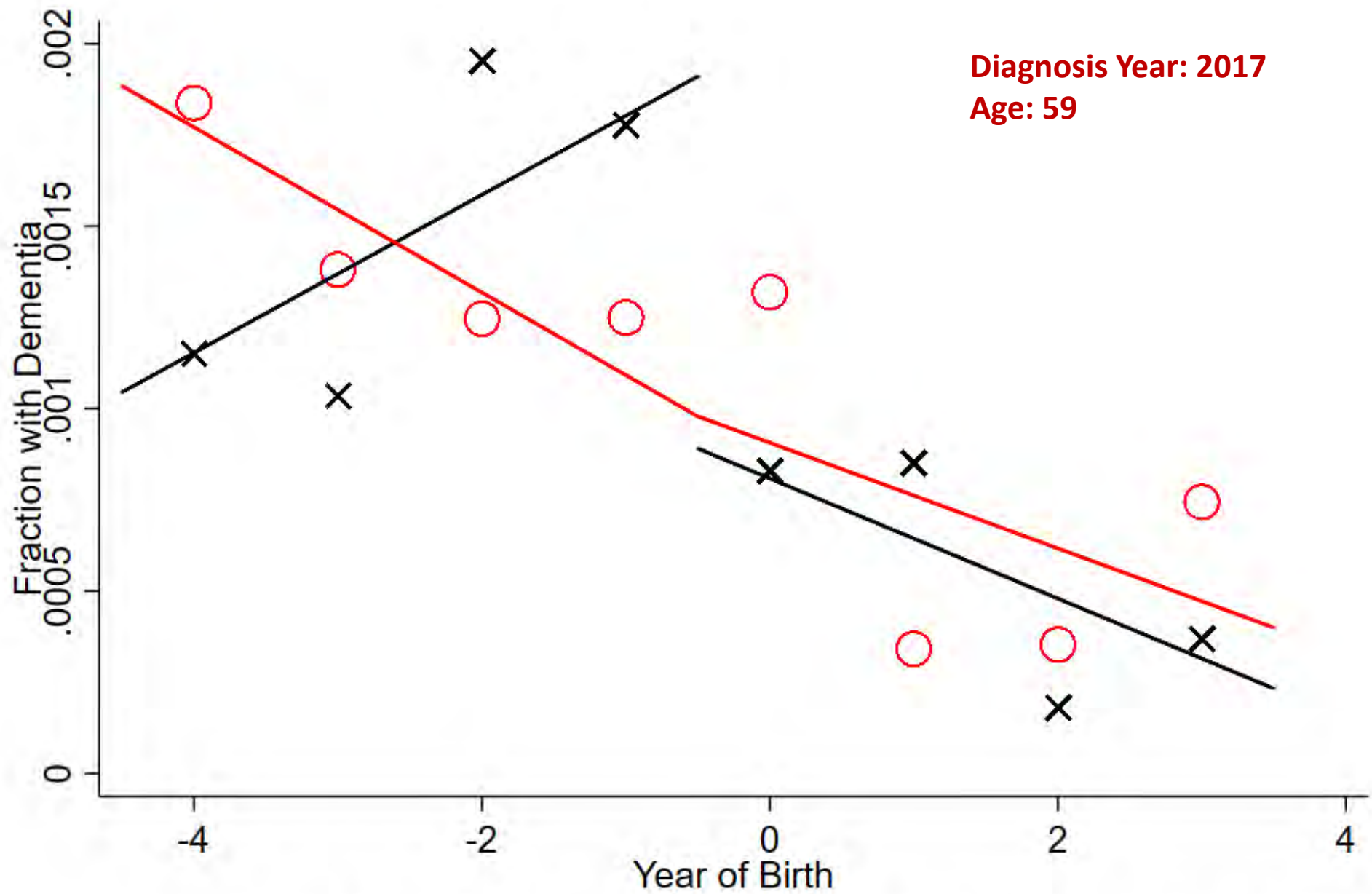
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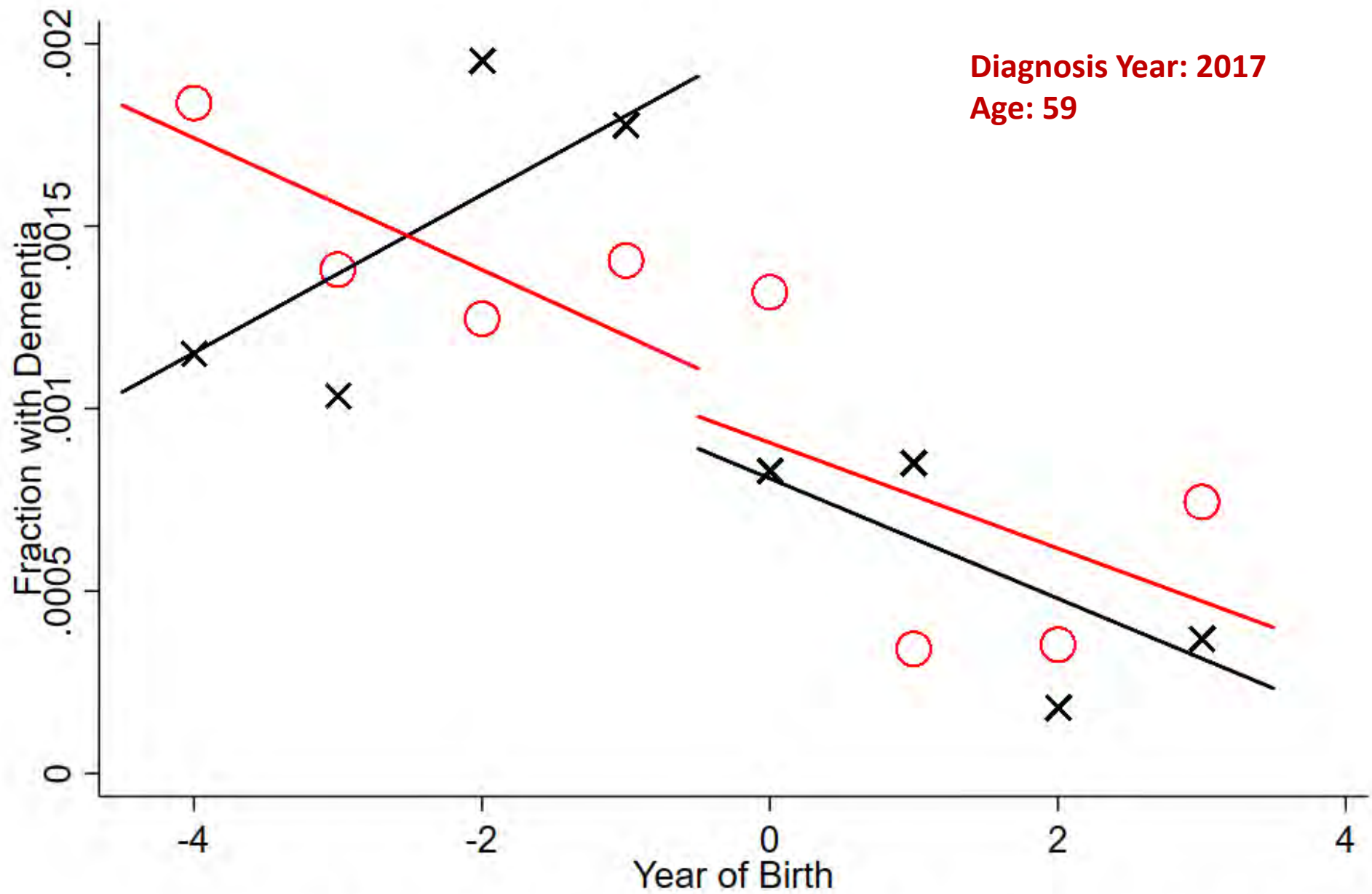
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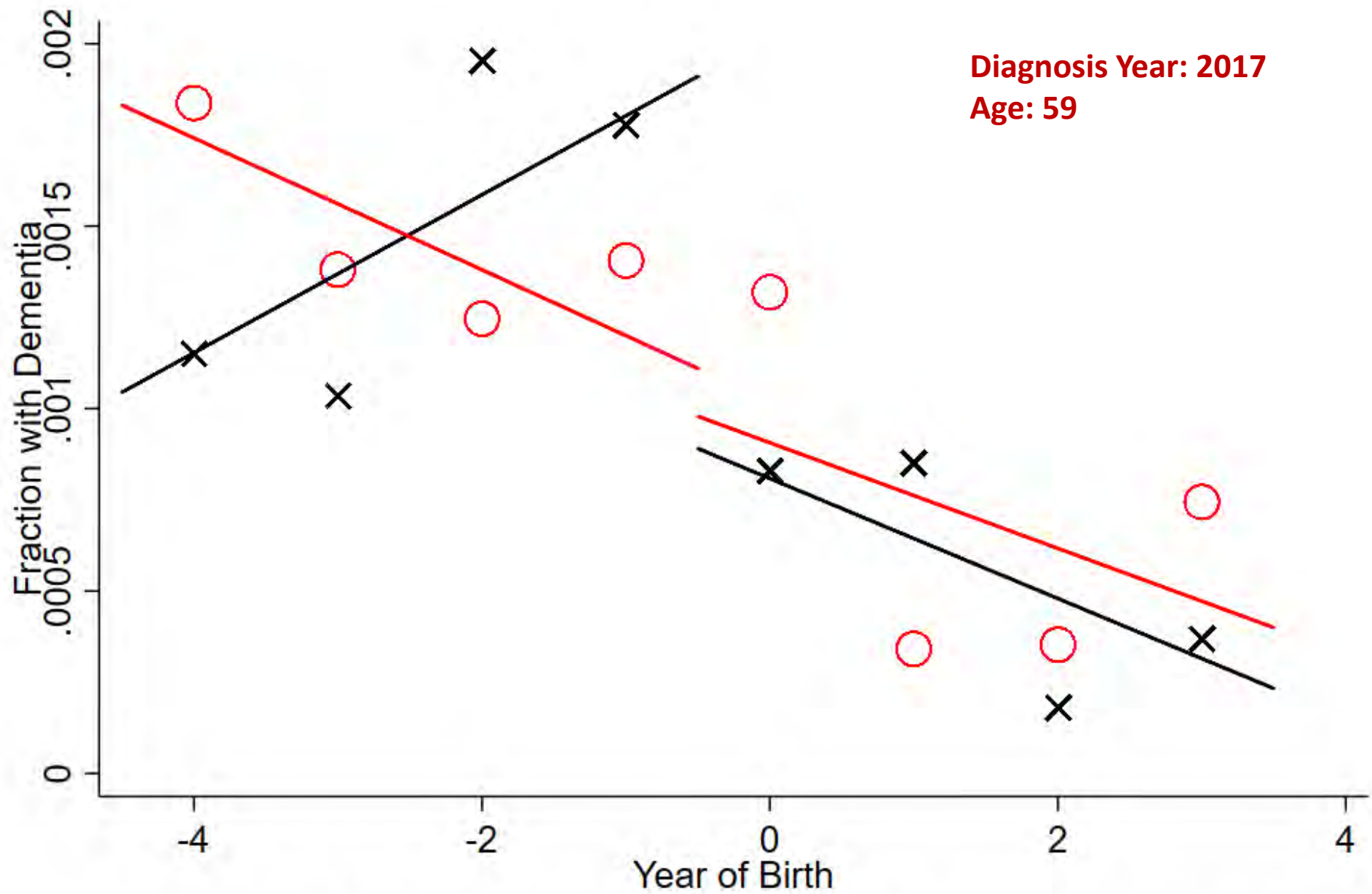


× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

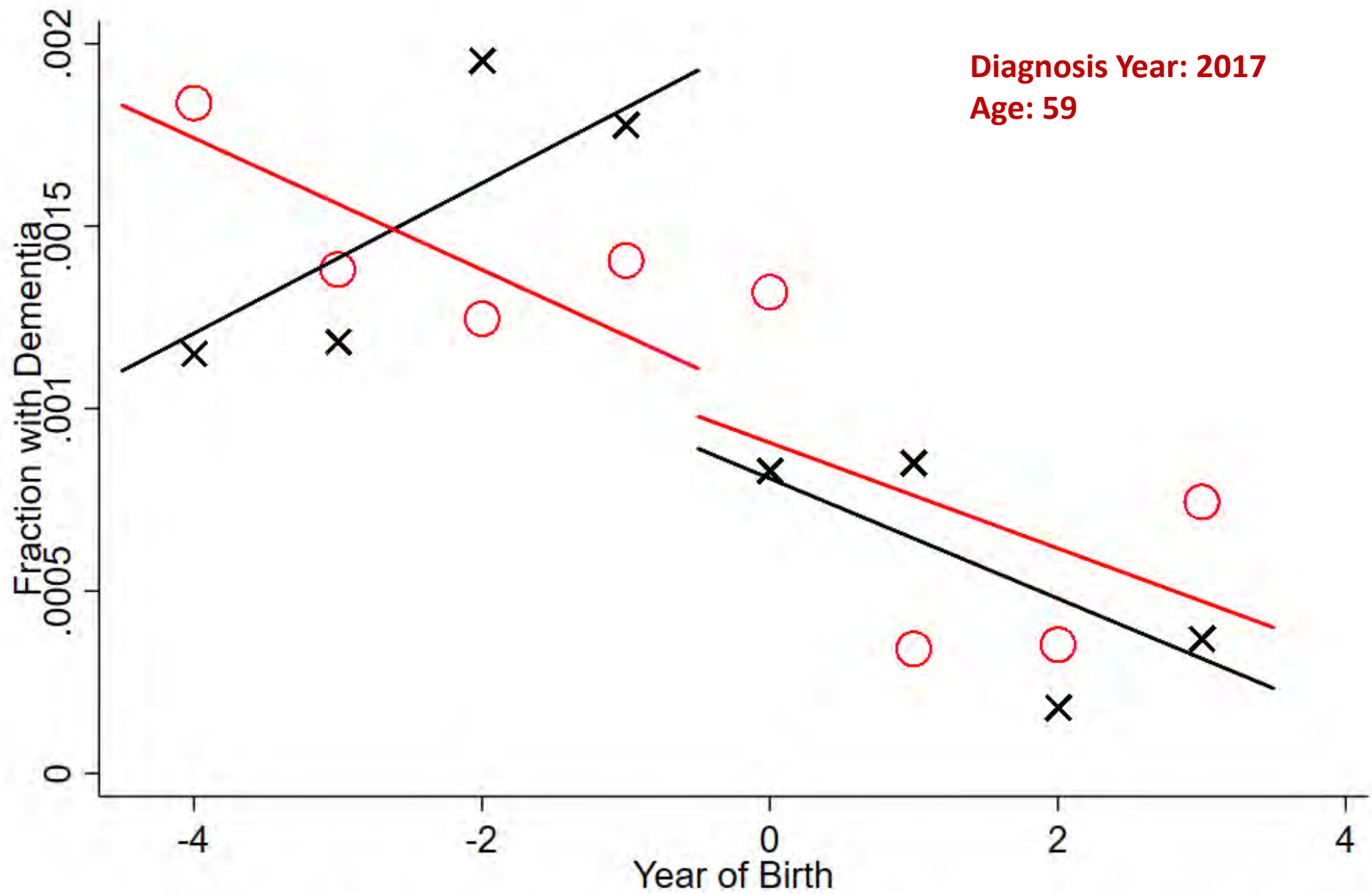


X Bottom Half Composite Genetic Risk O Top Half Composite Genetic Risk

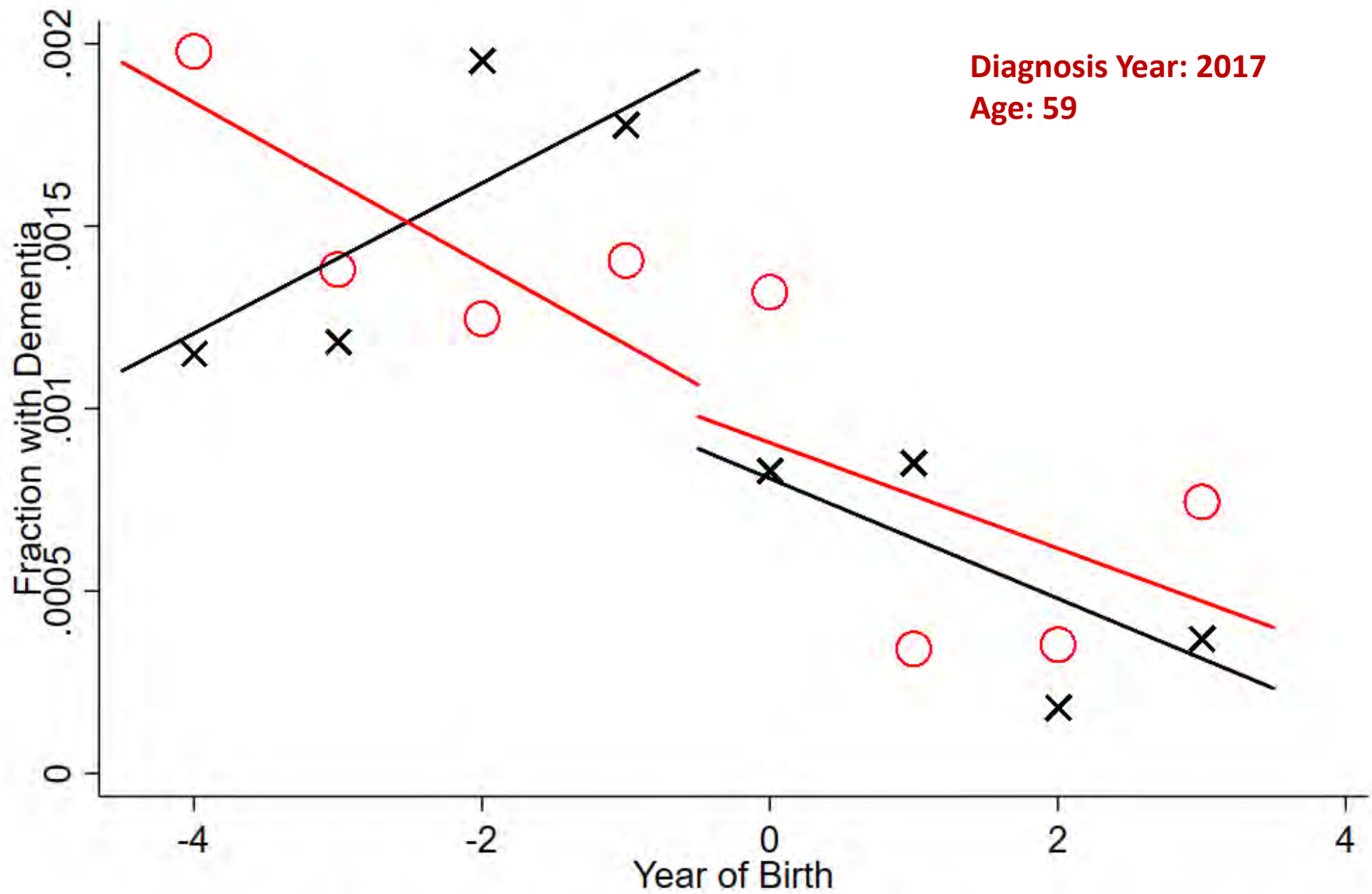




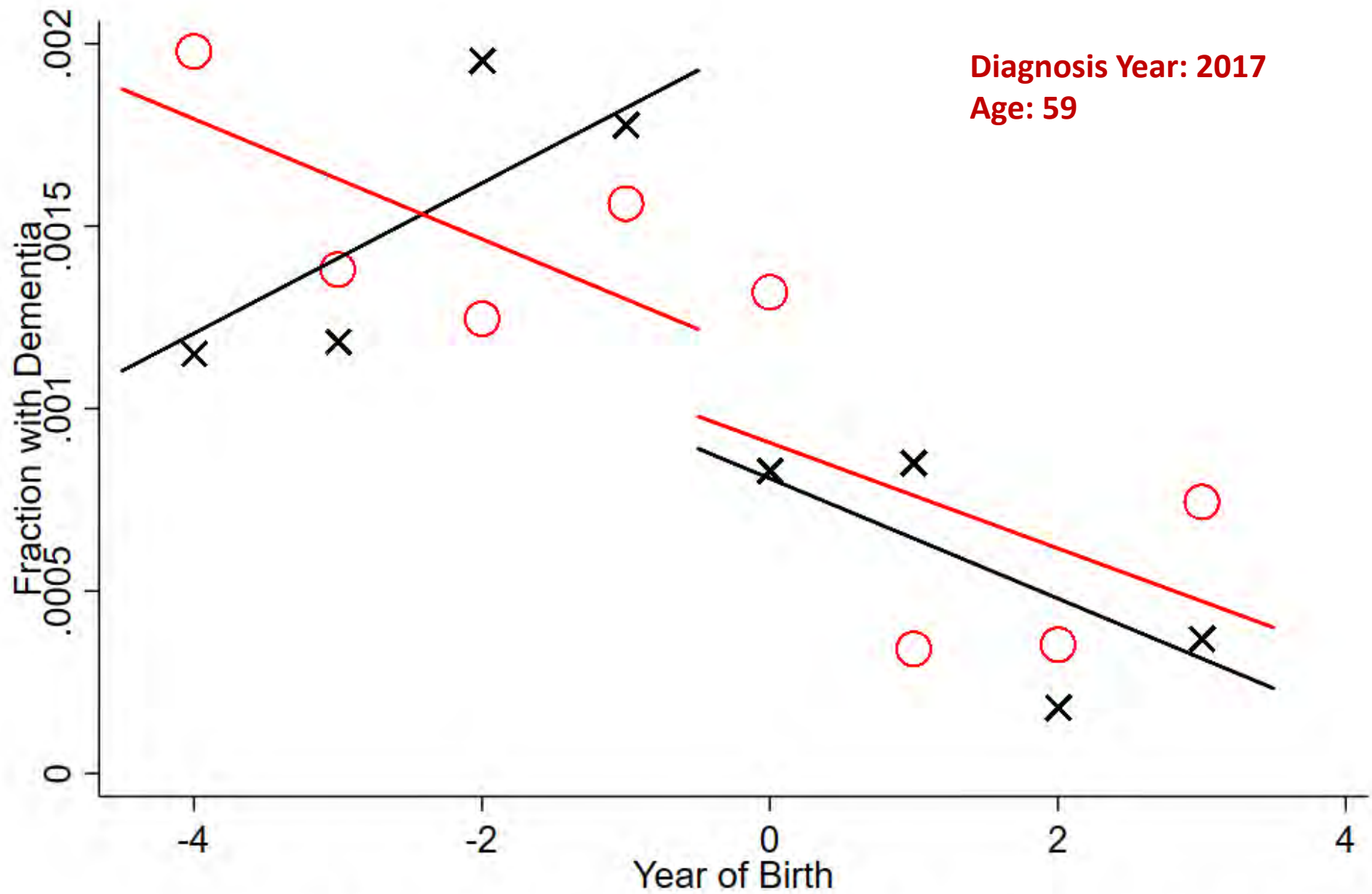
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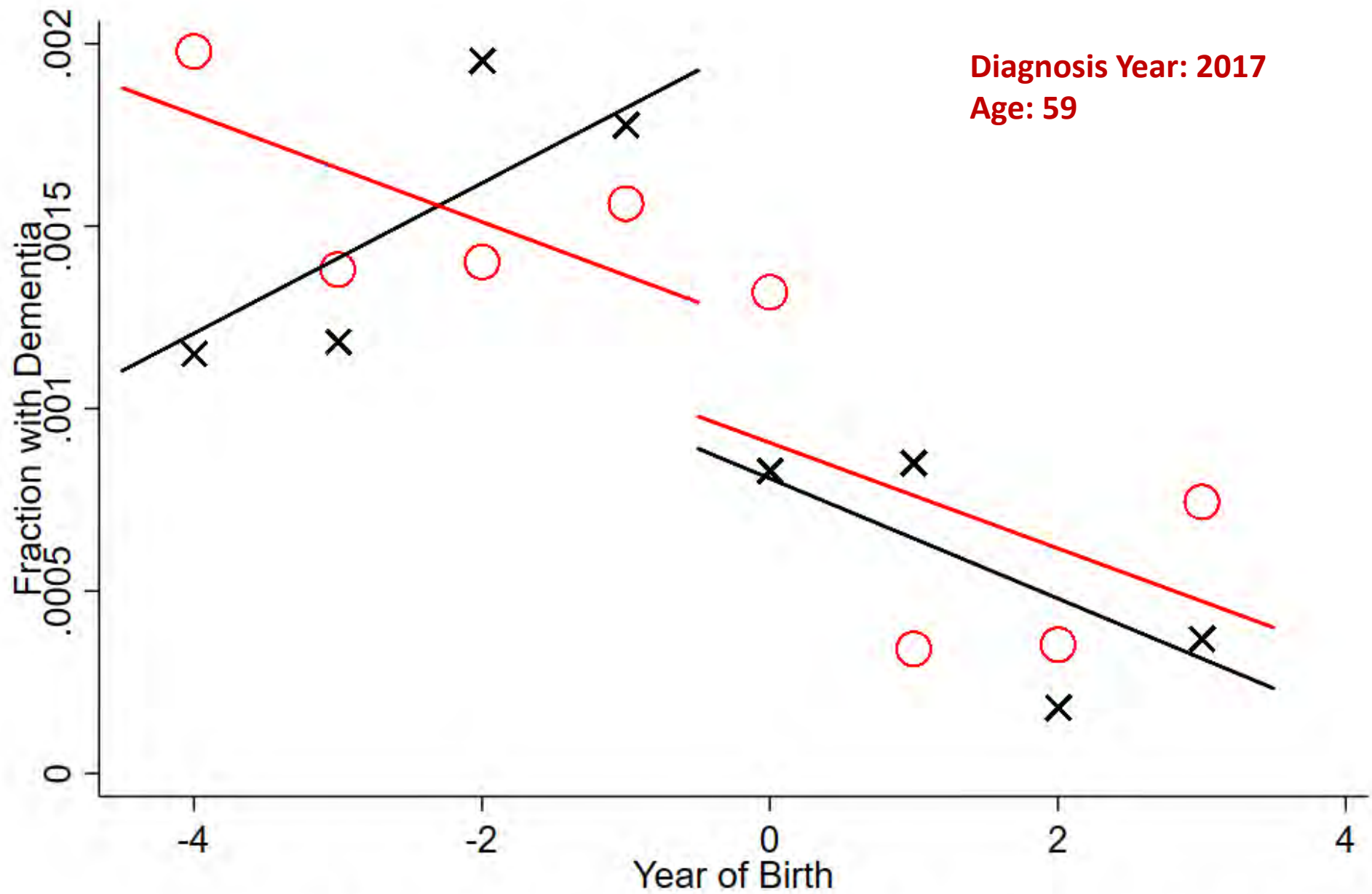
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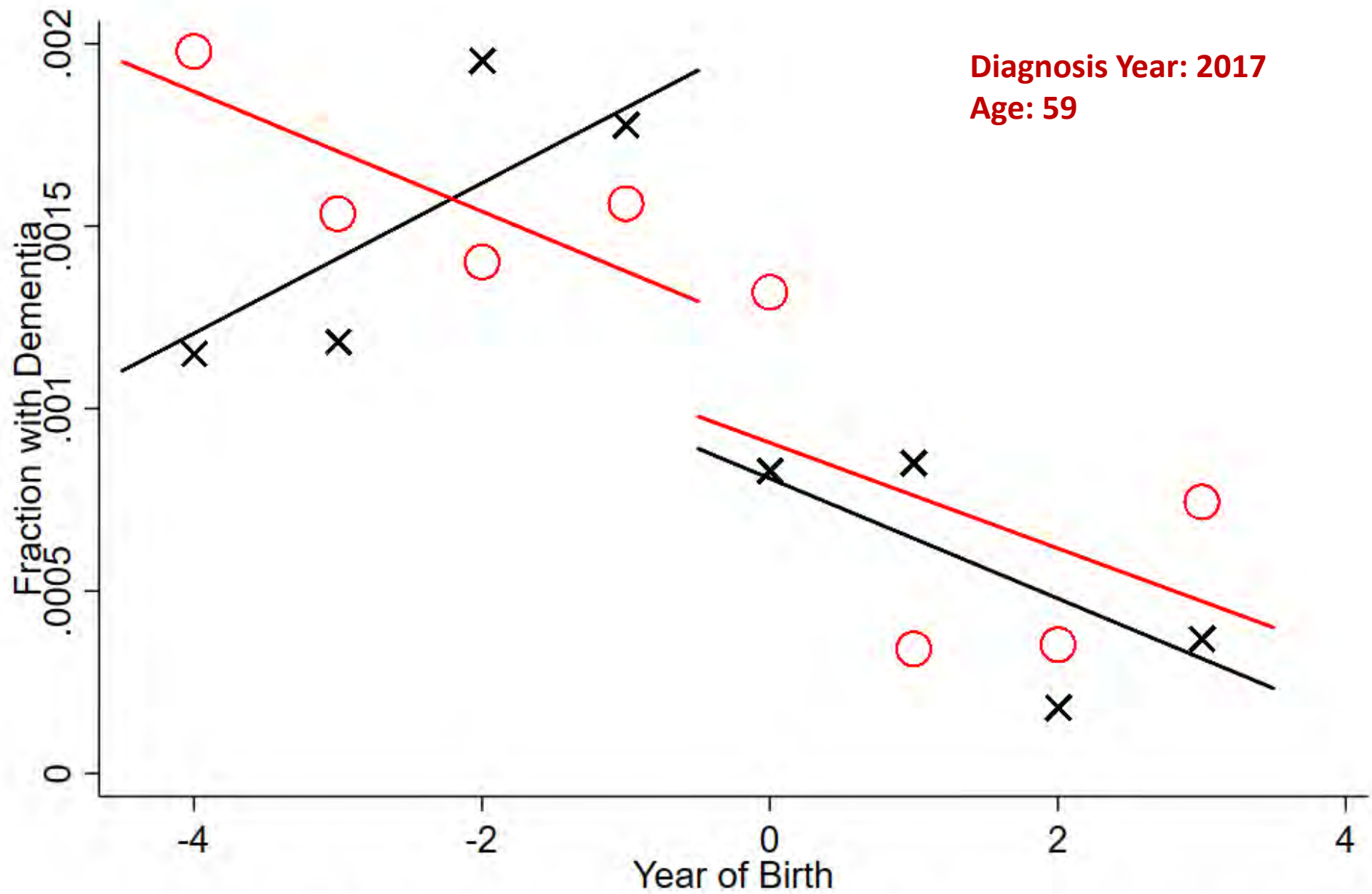
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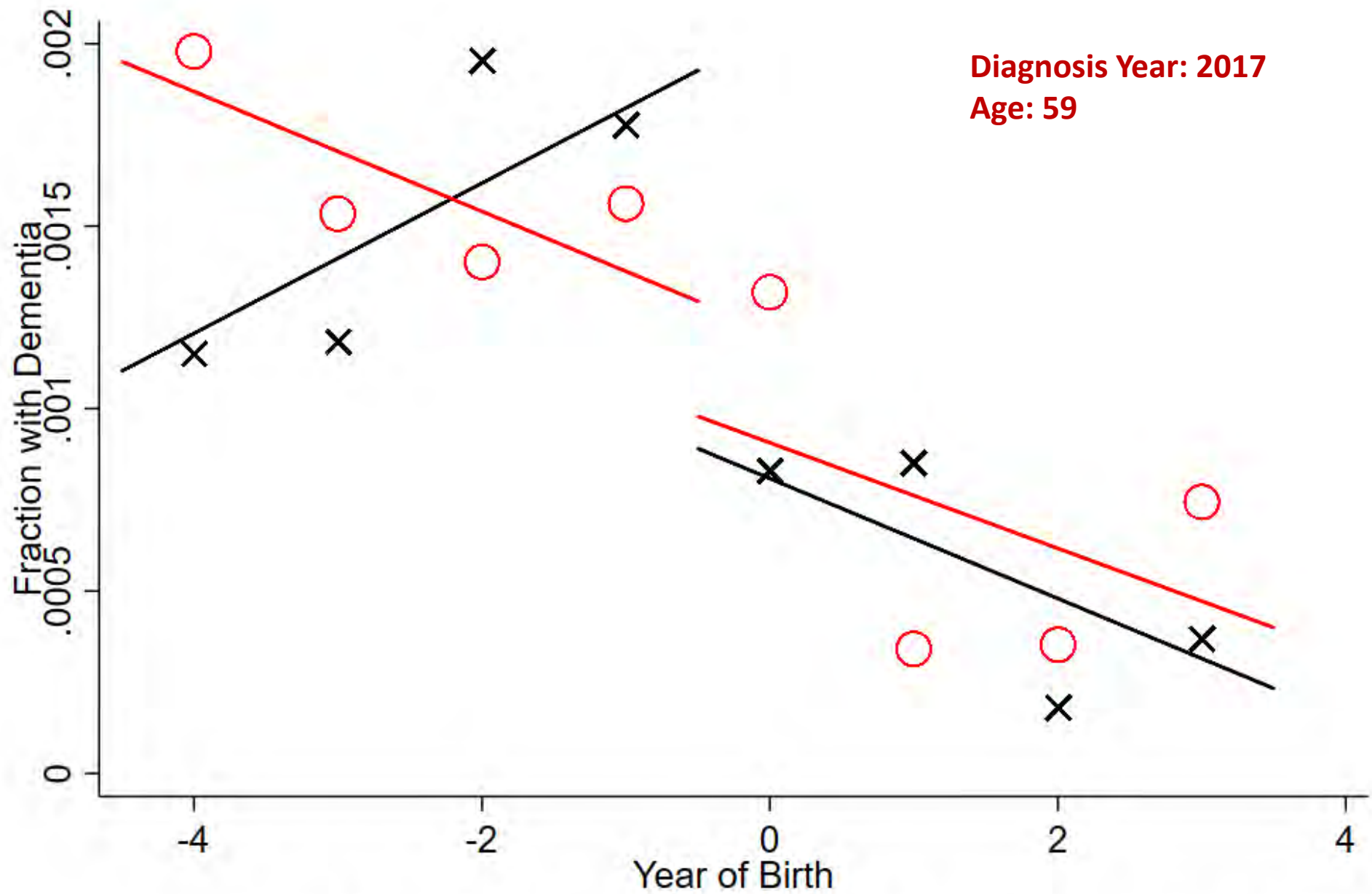
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



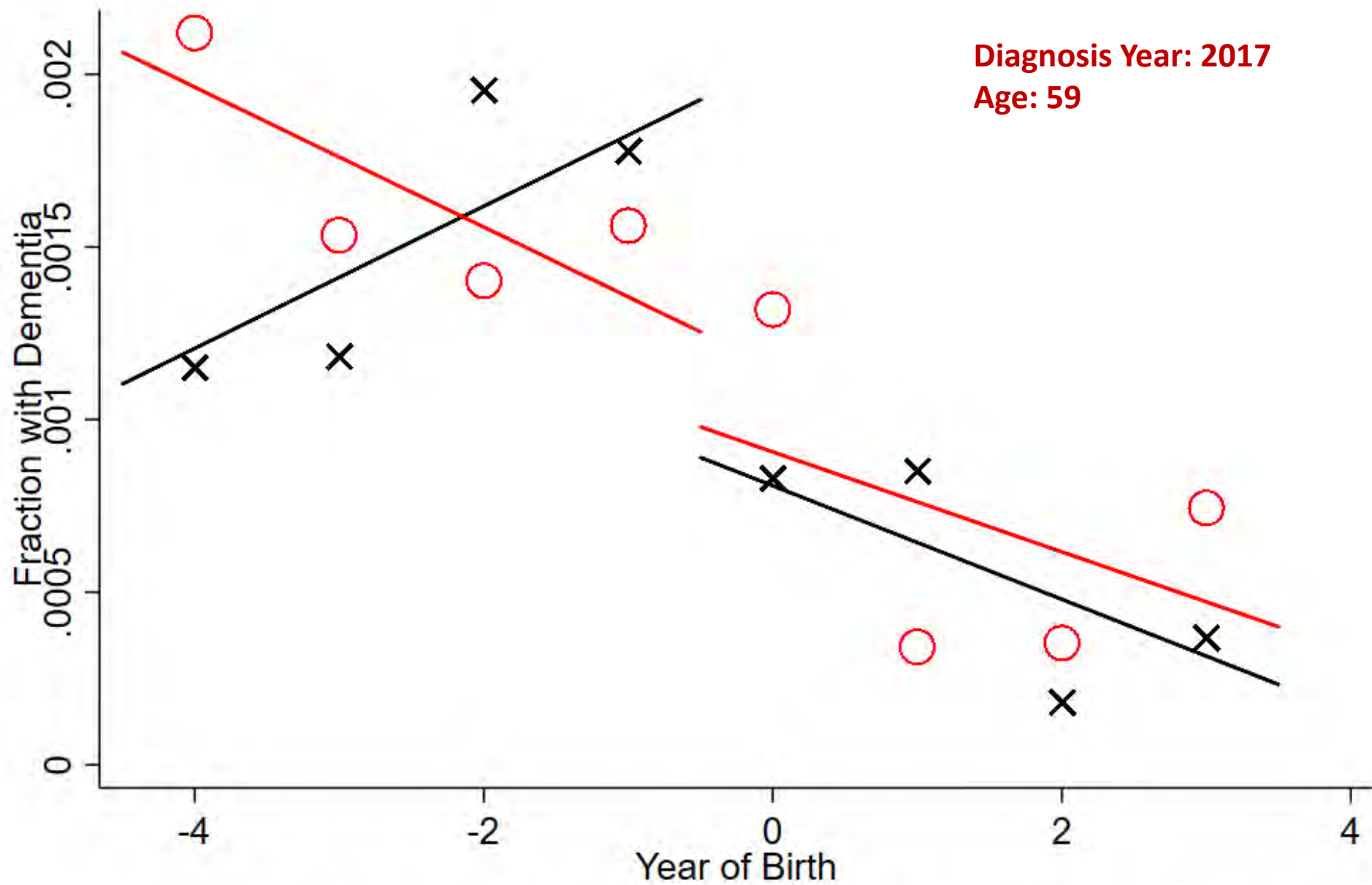
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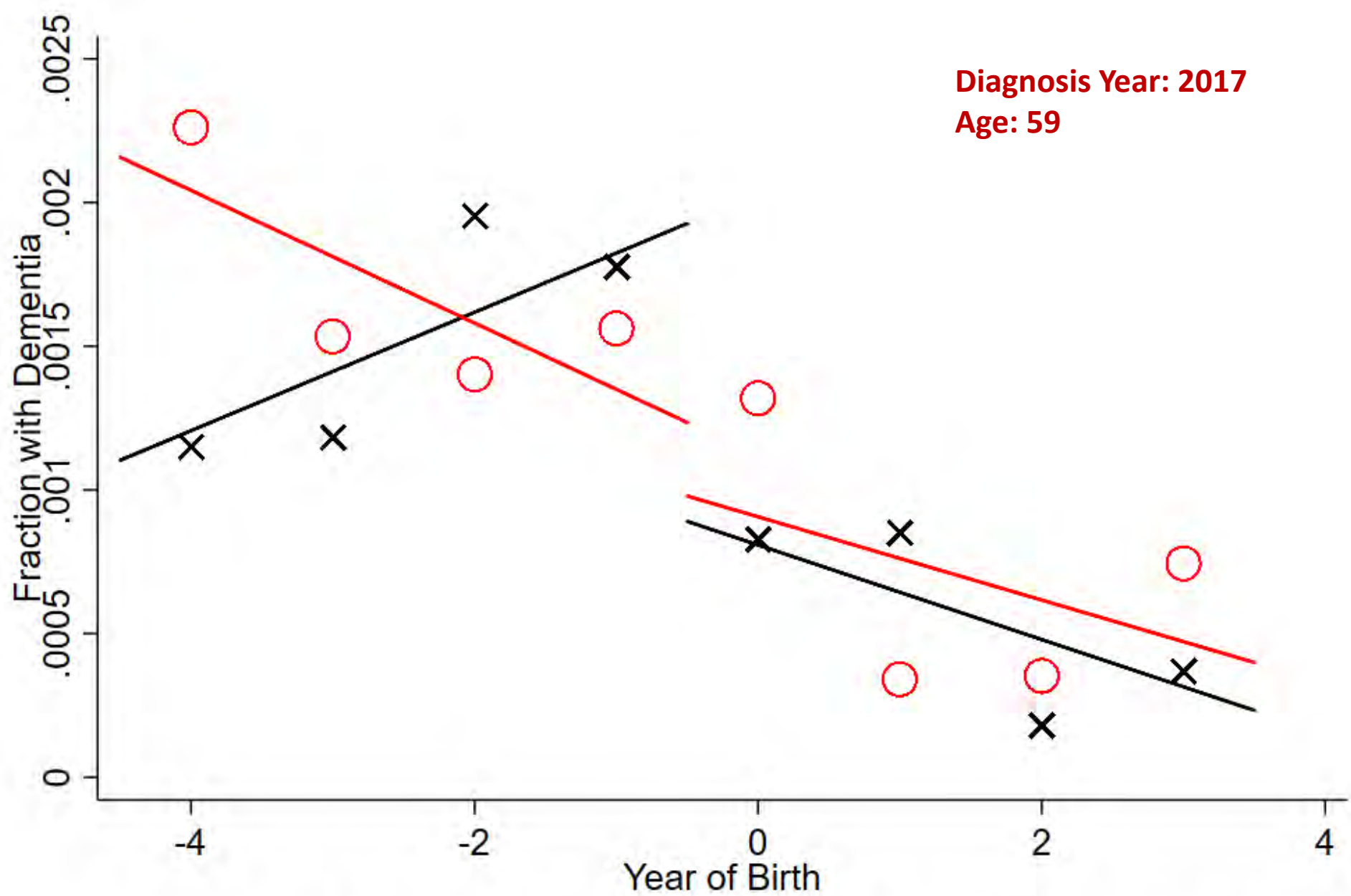
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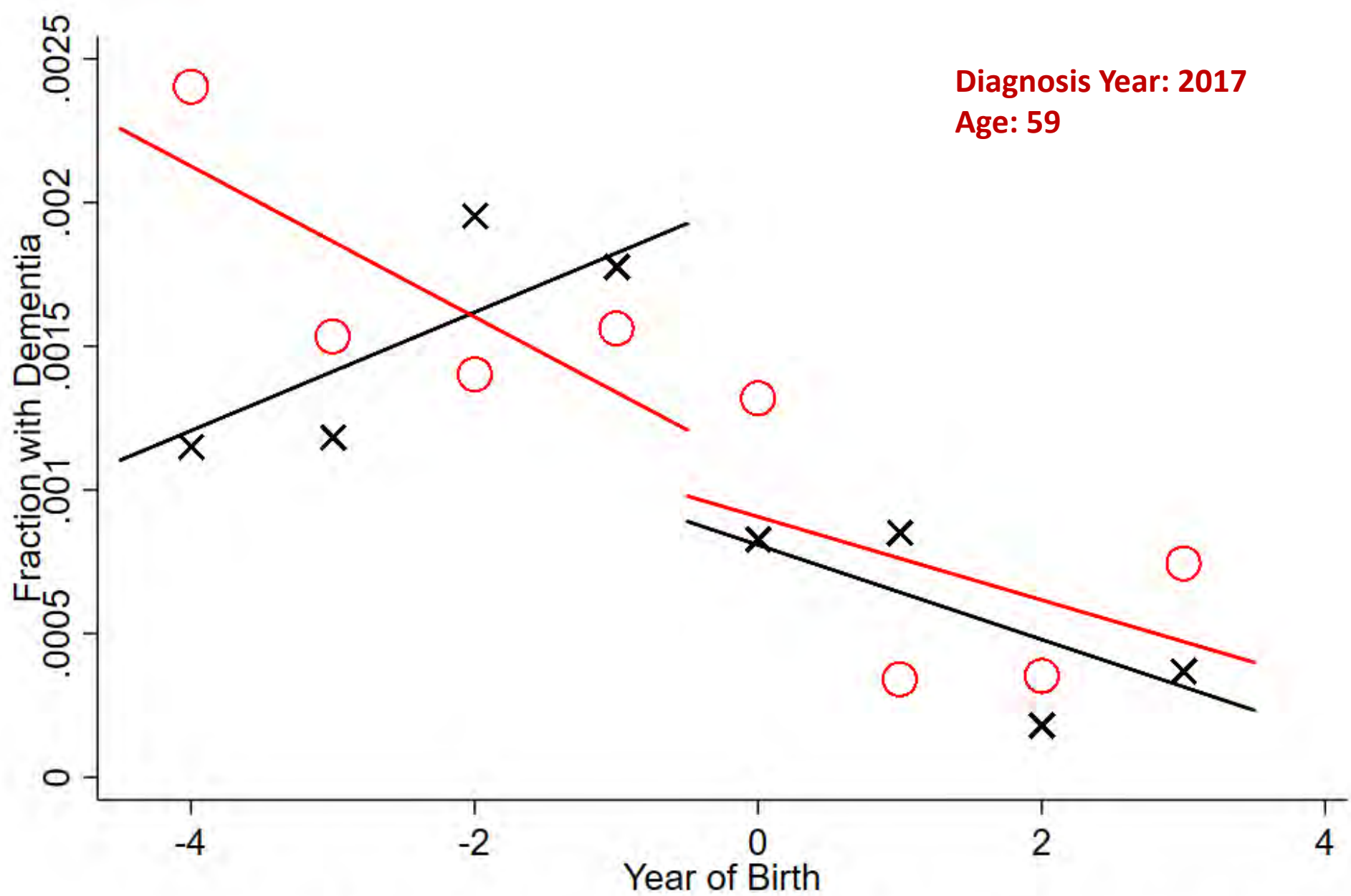


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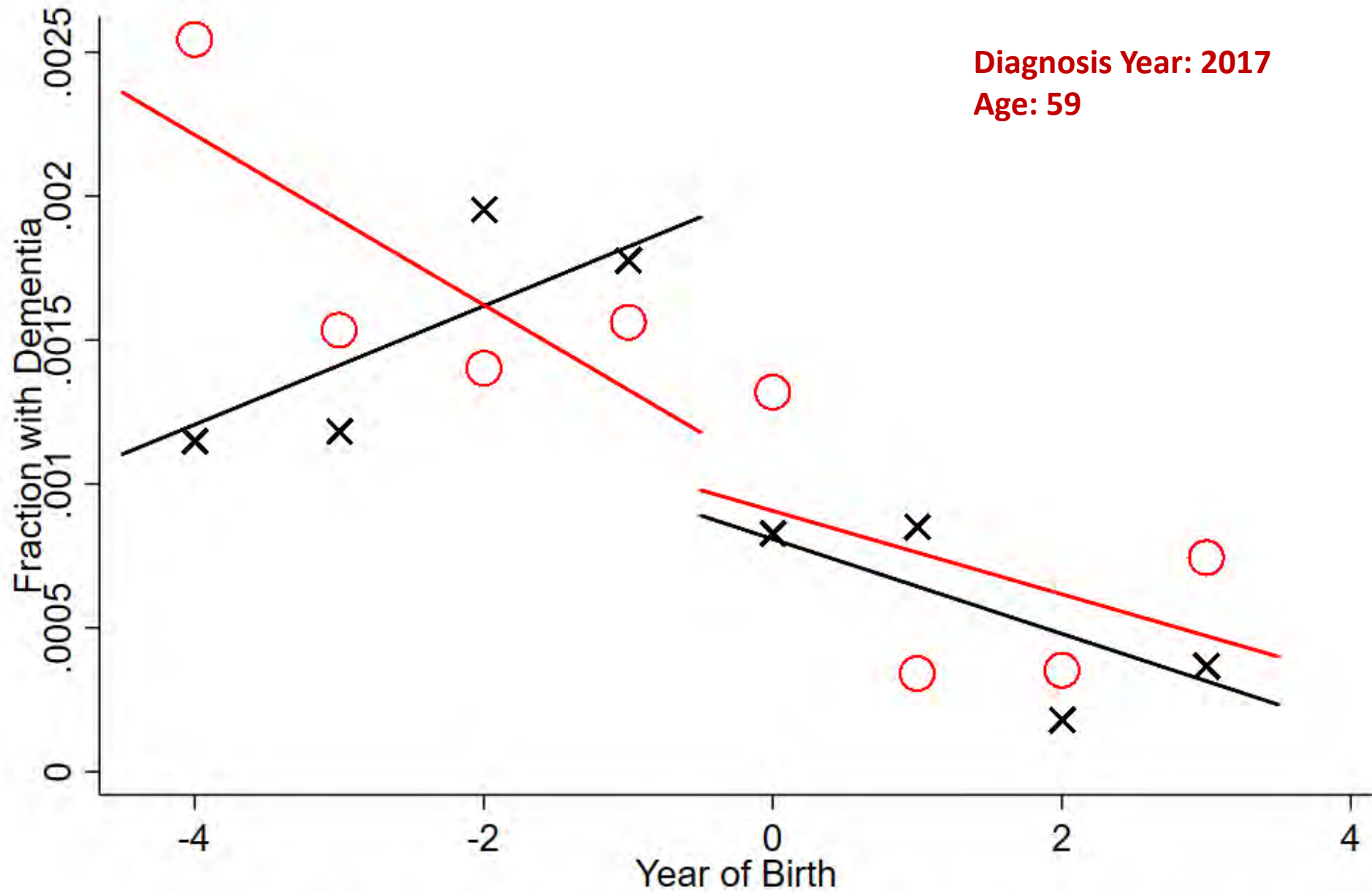


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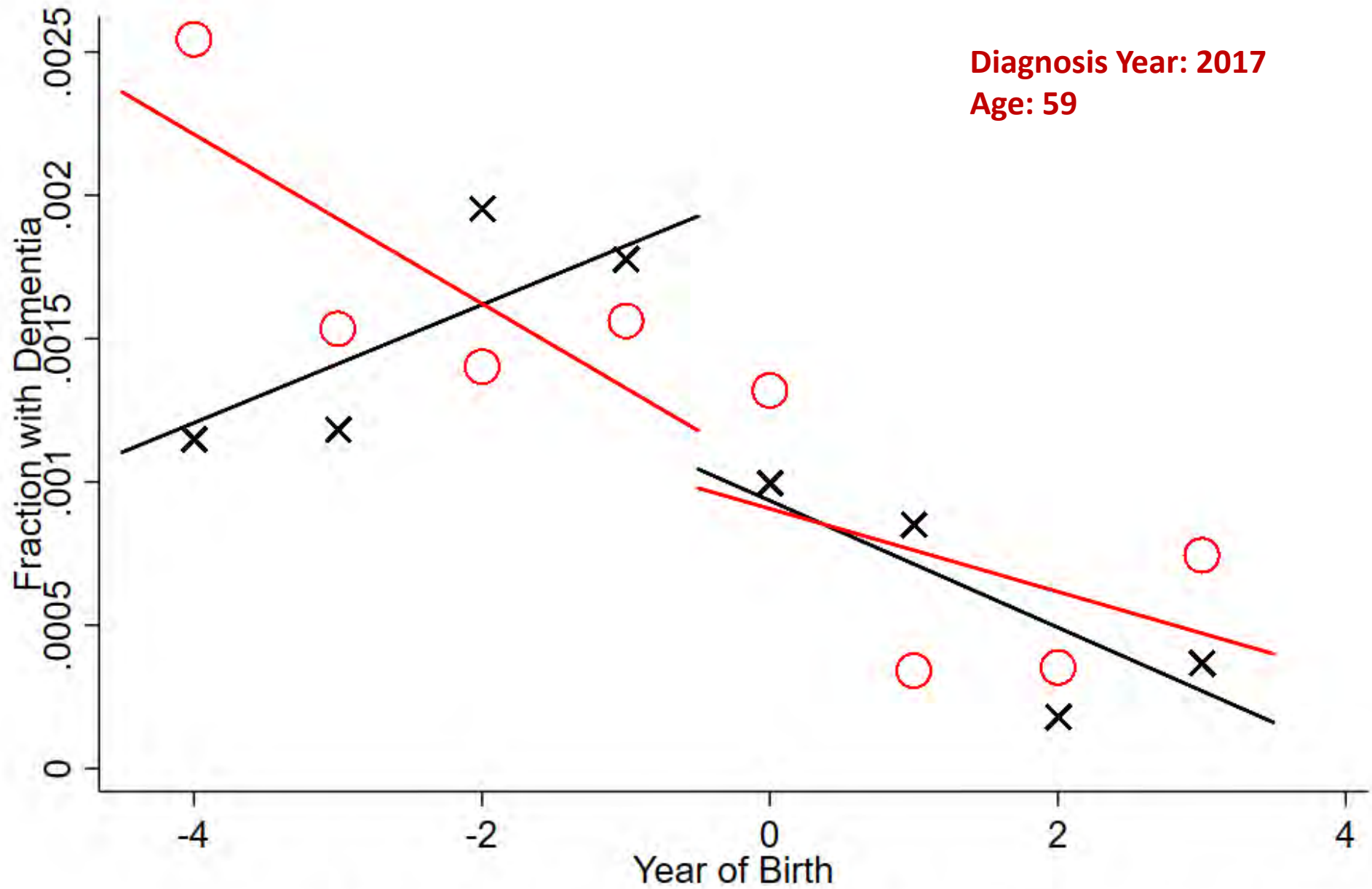


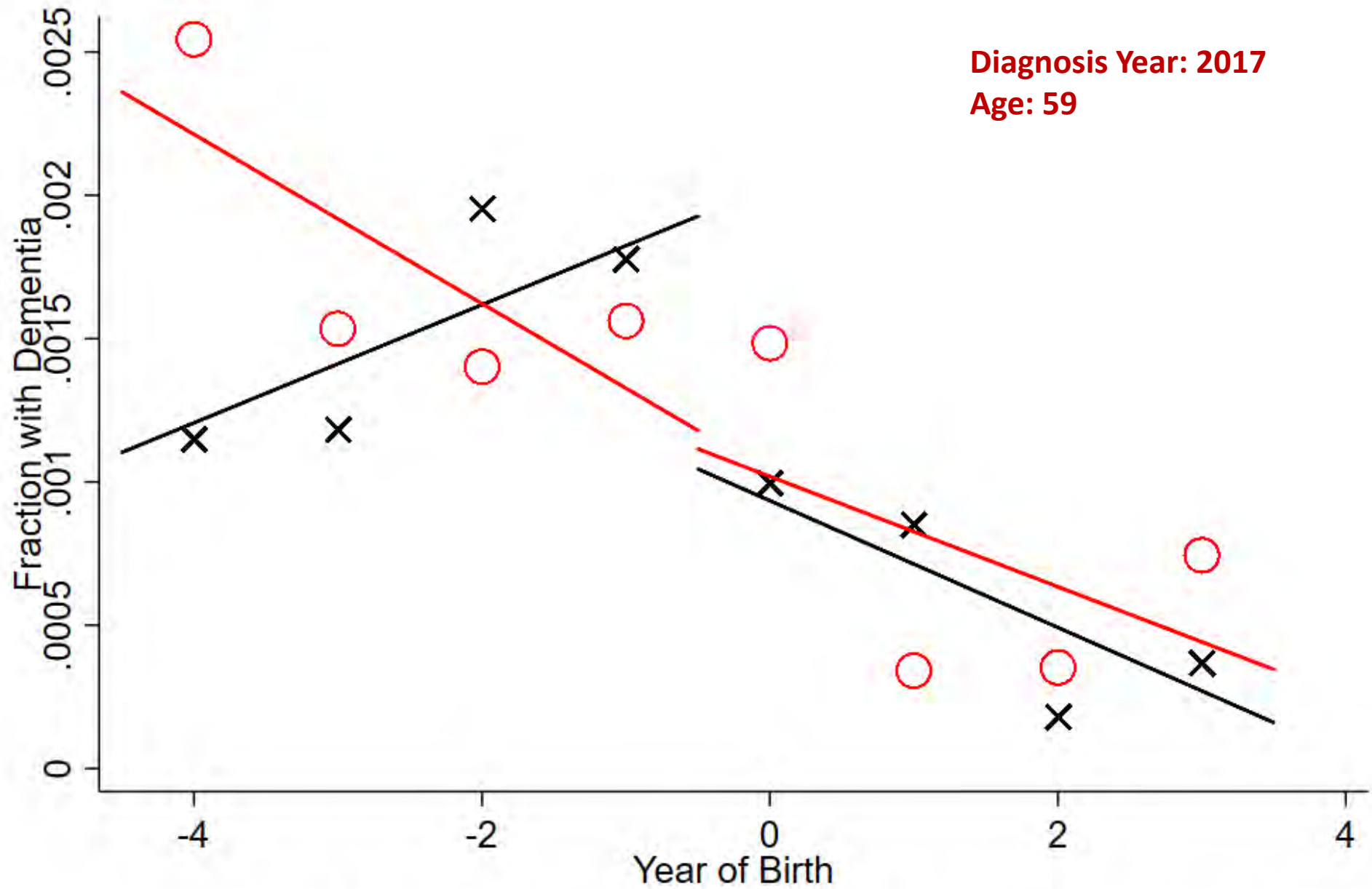


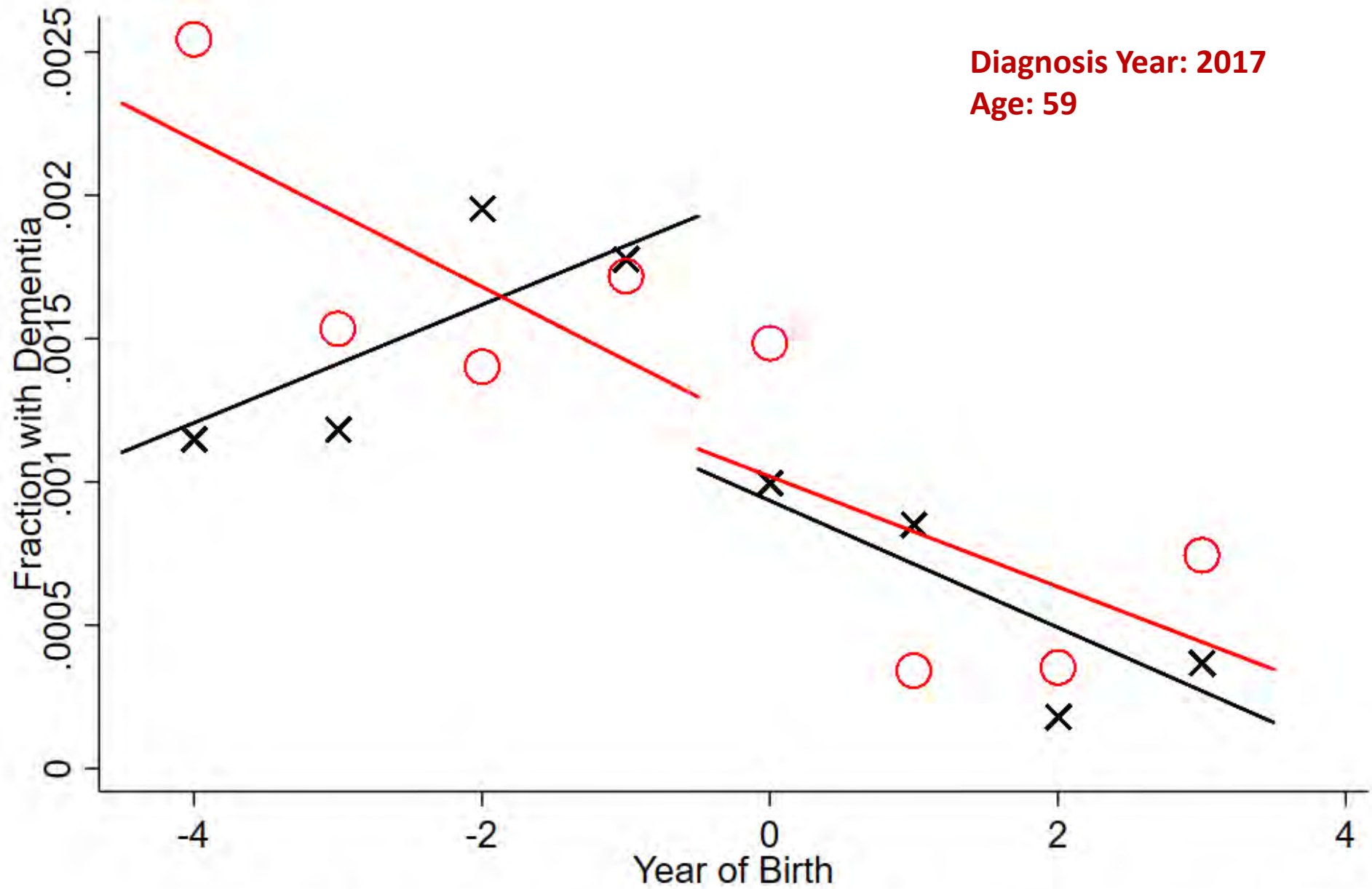
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



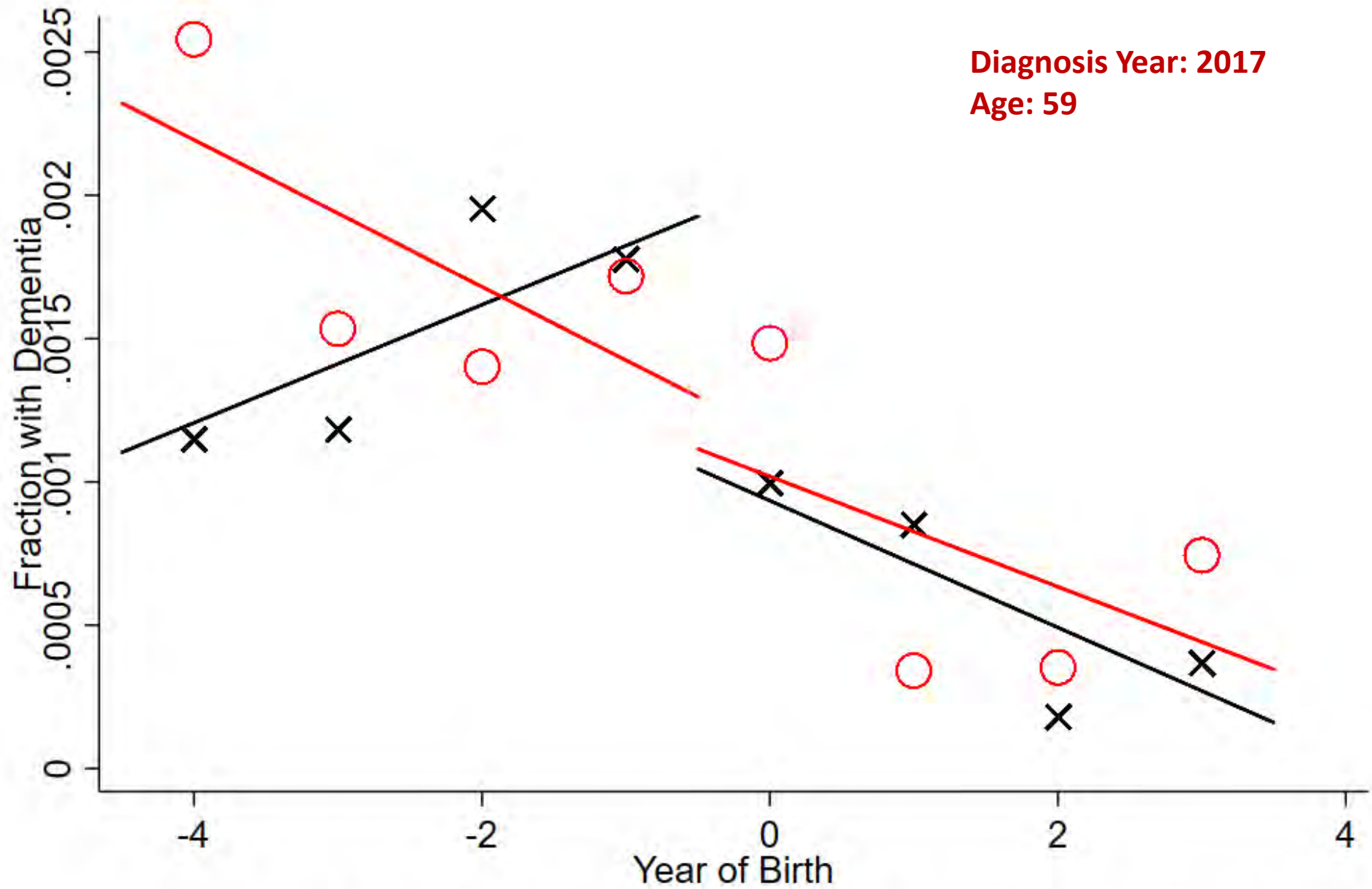
x Bottom Half Composite Genetic Risk o Top Half Composite Genetic Risk



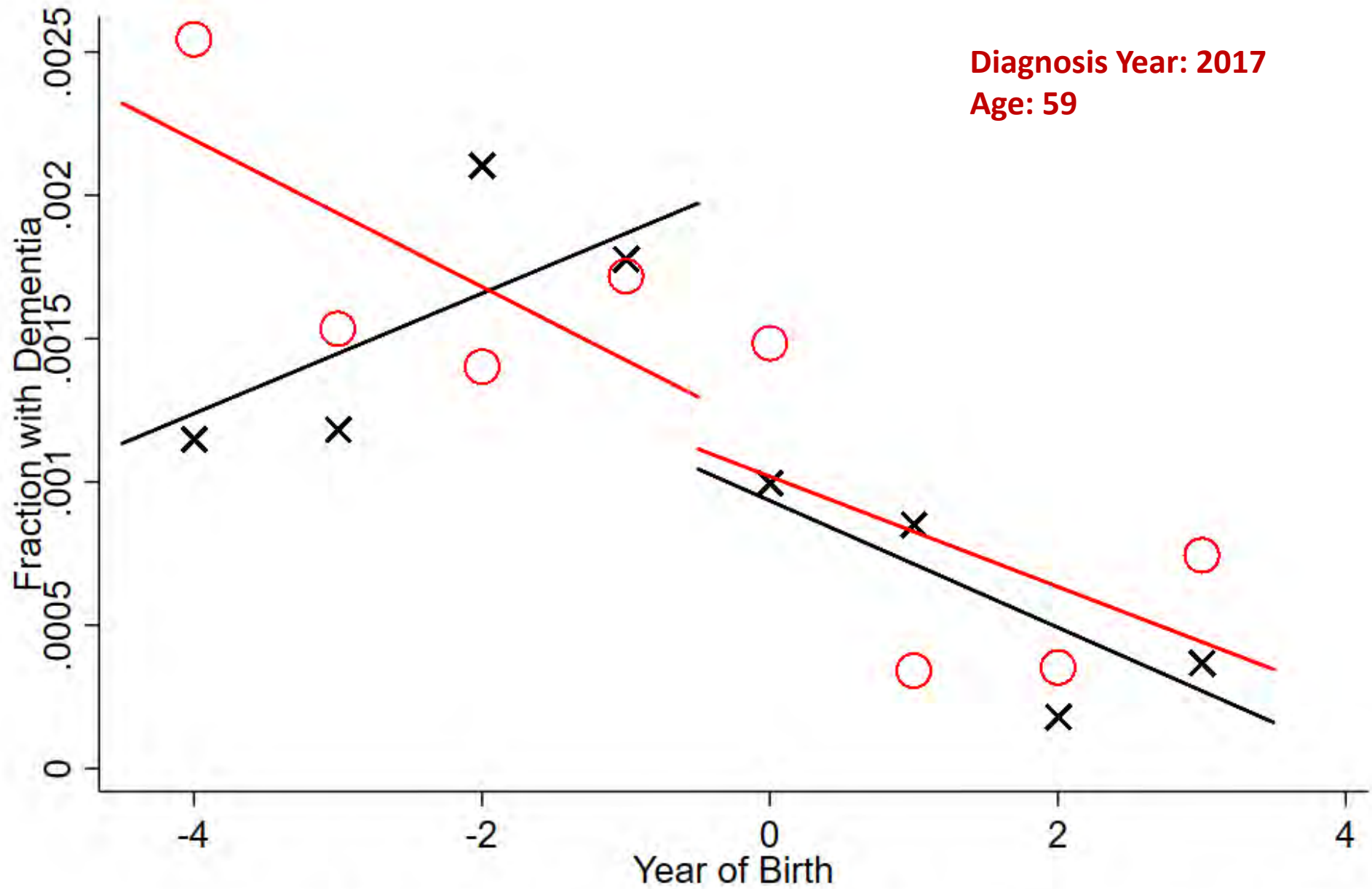




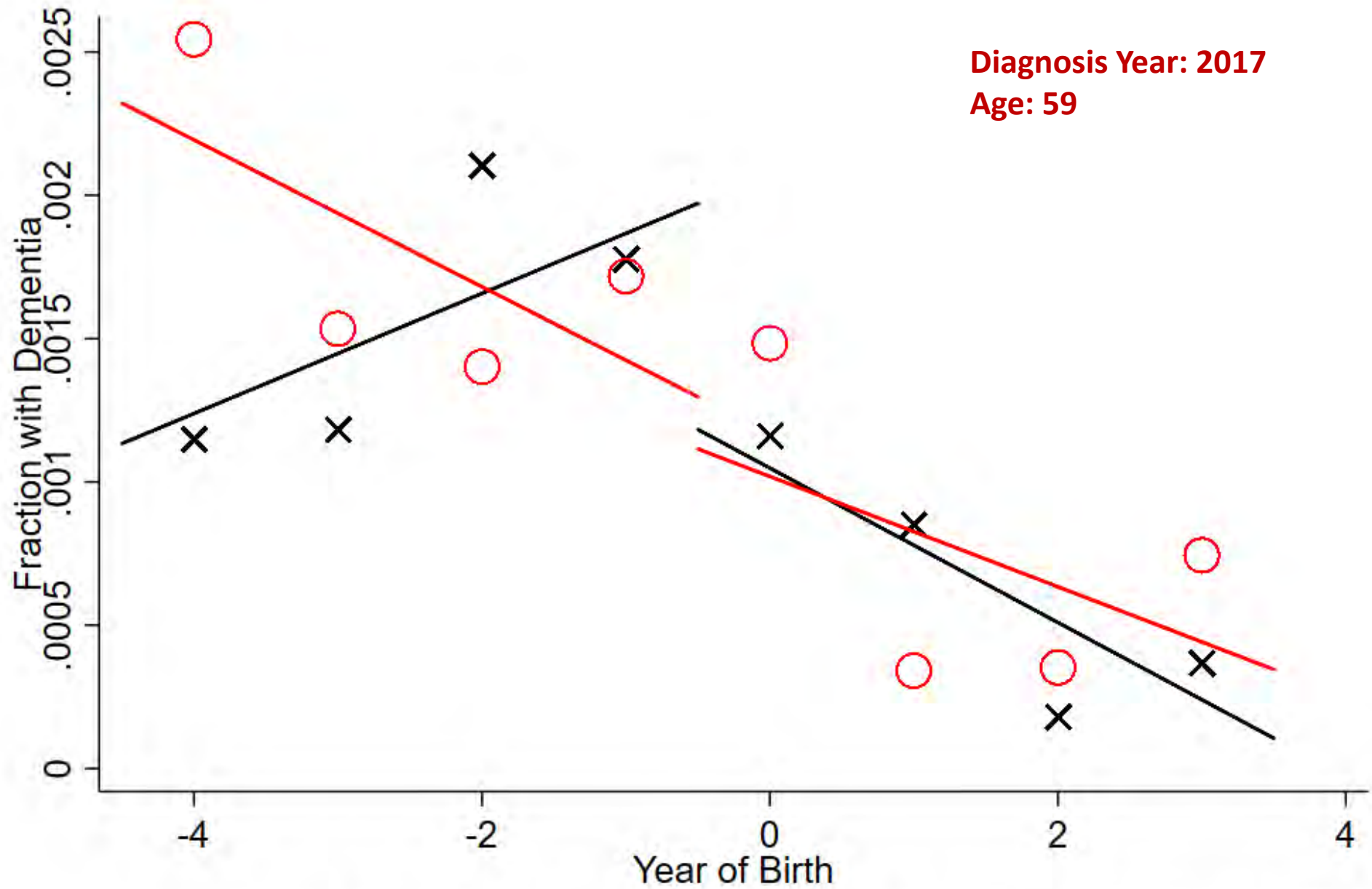
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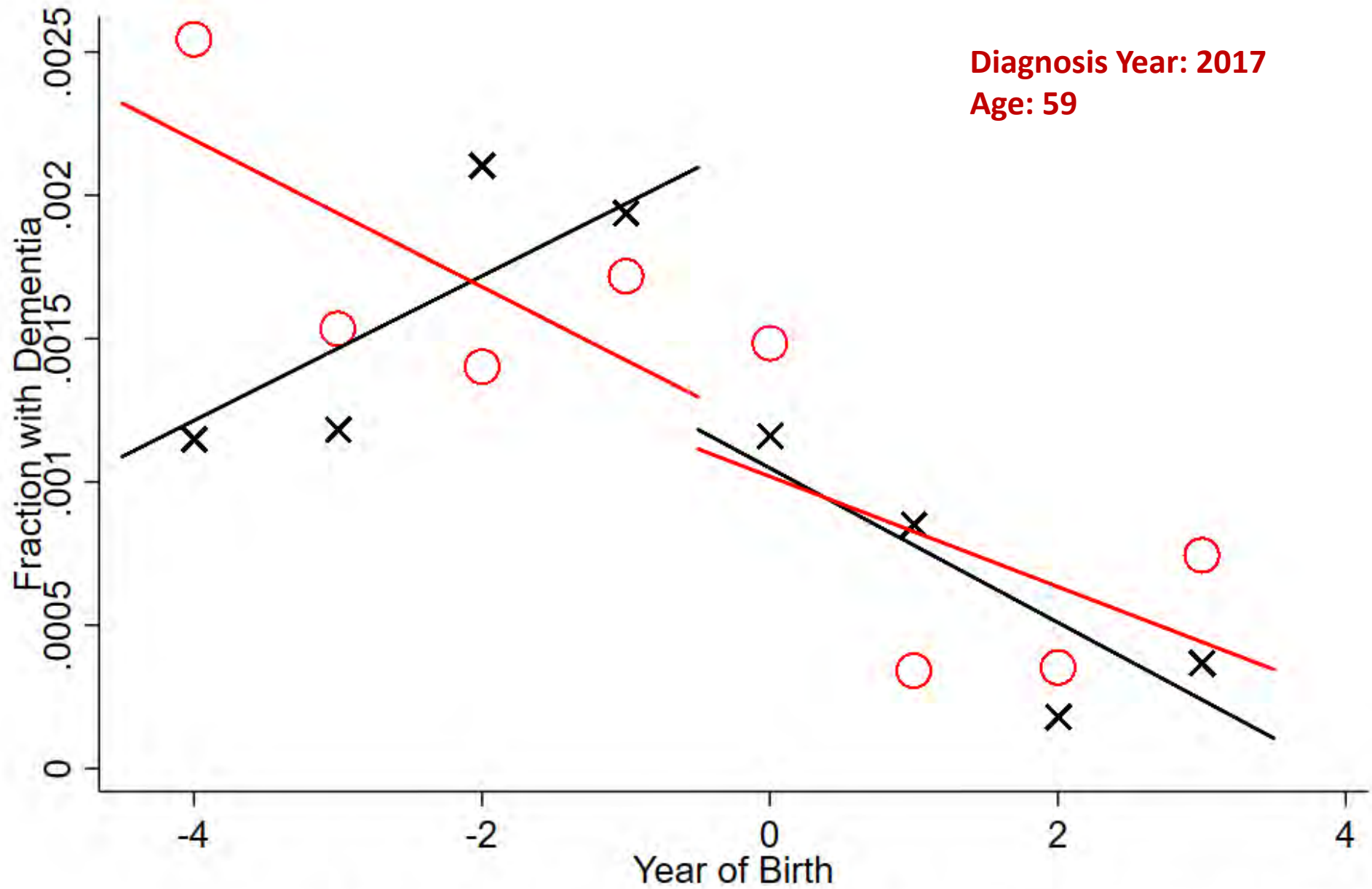


× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

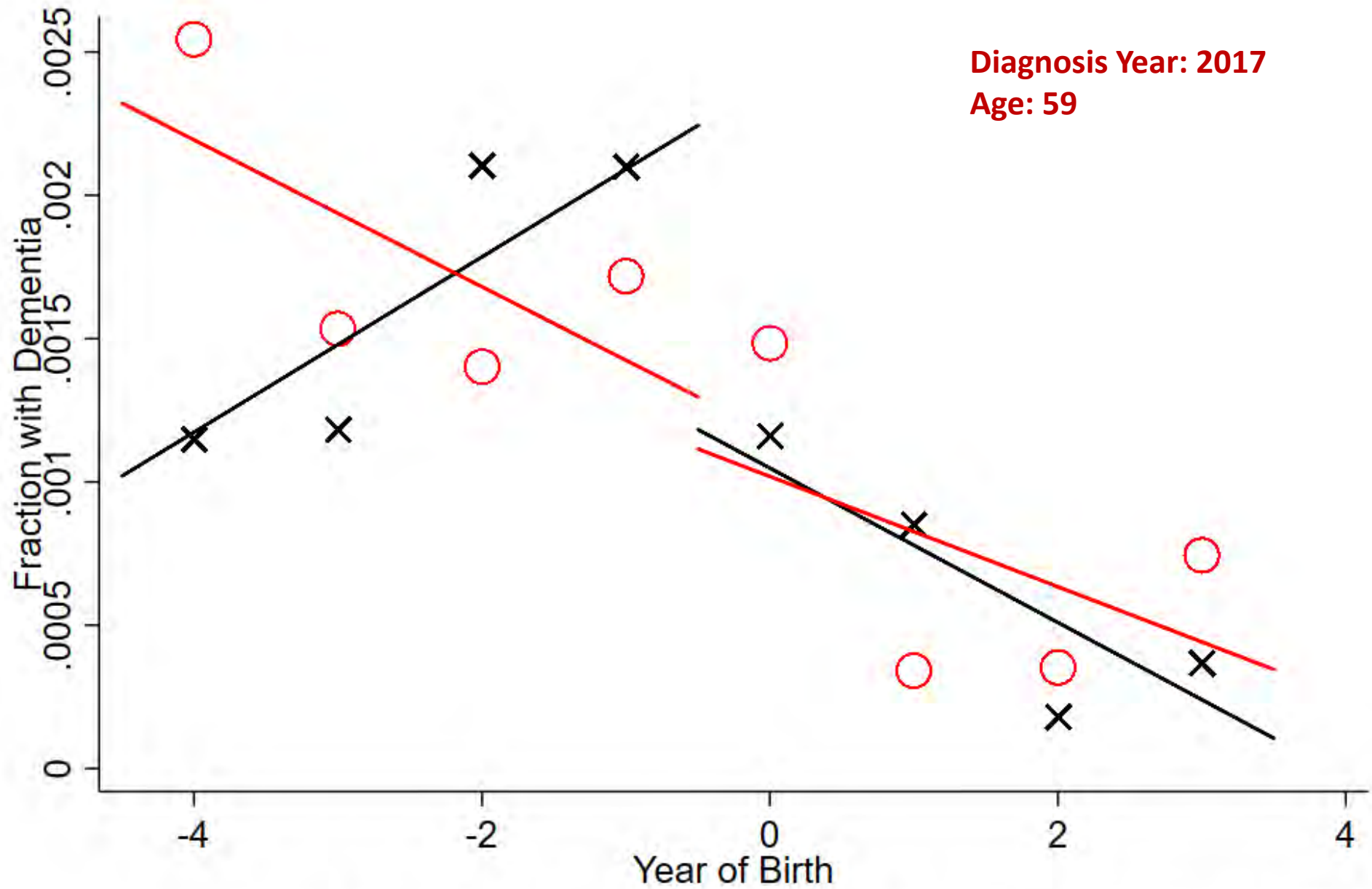


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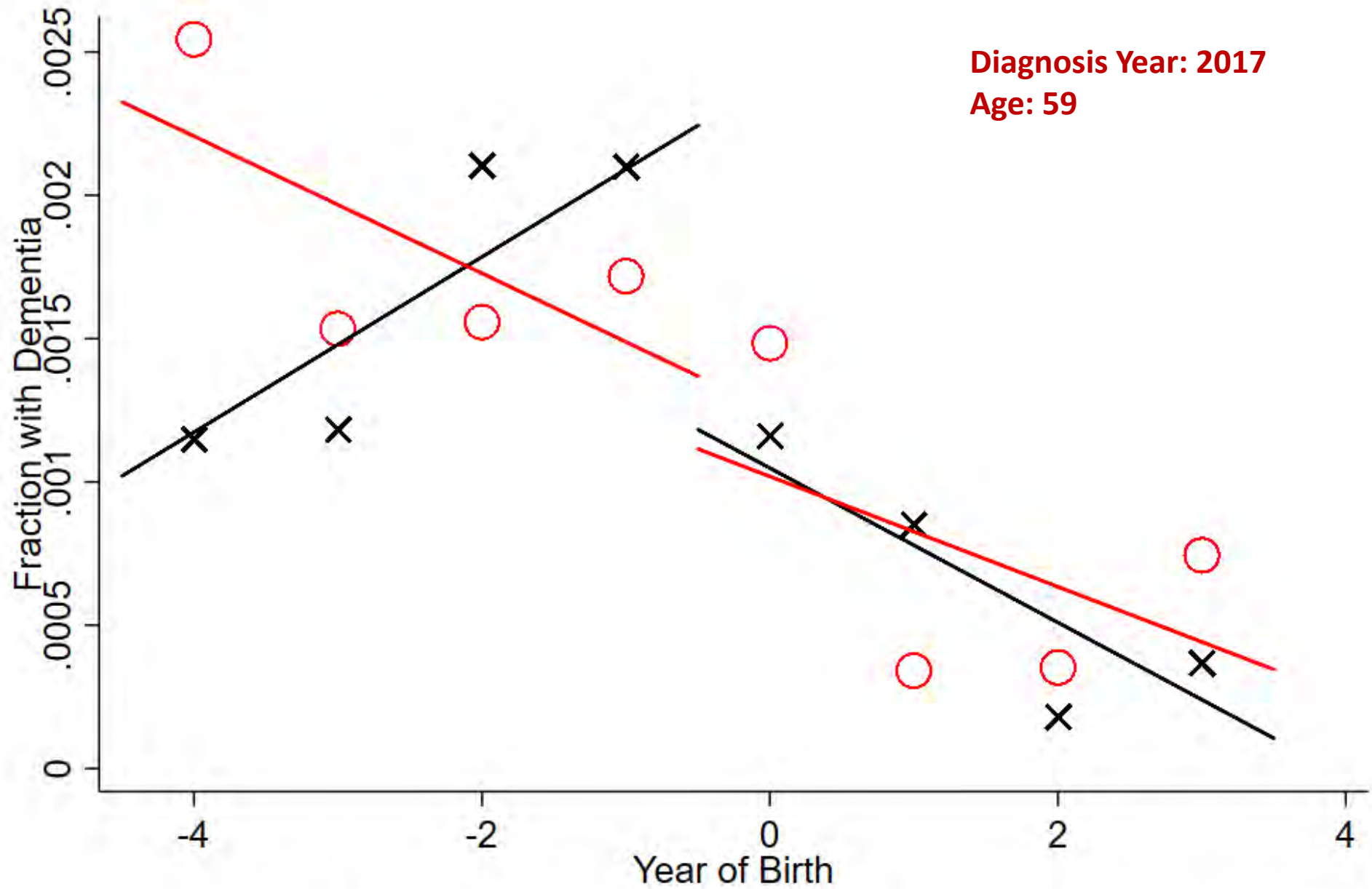




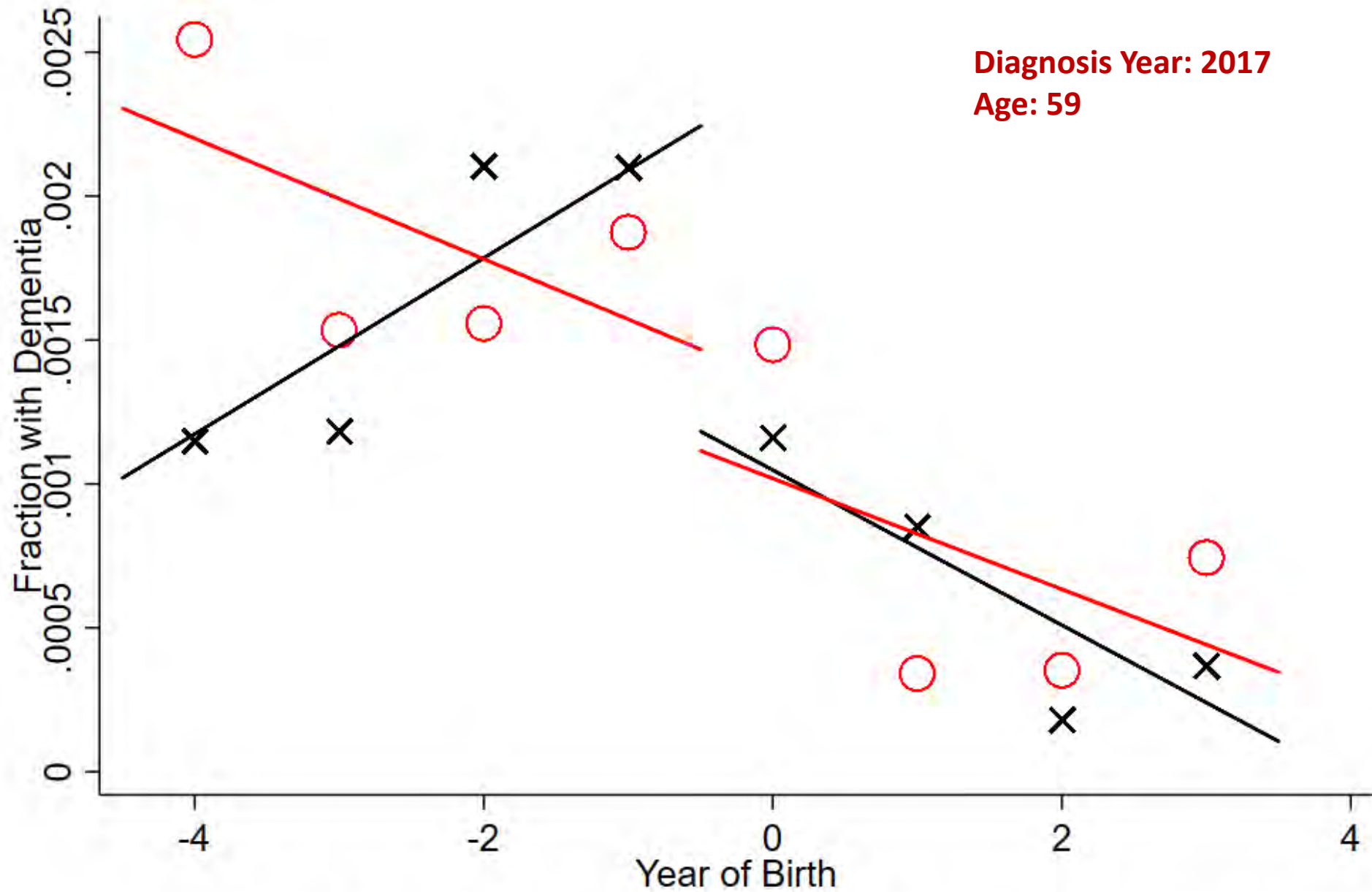
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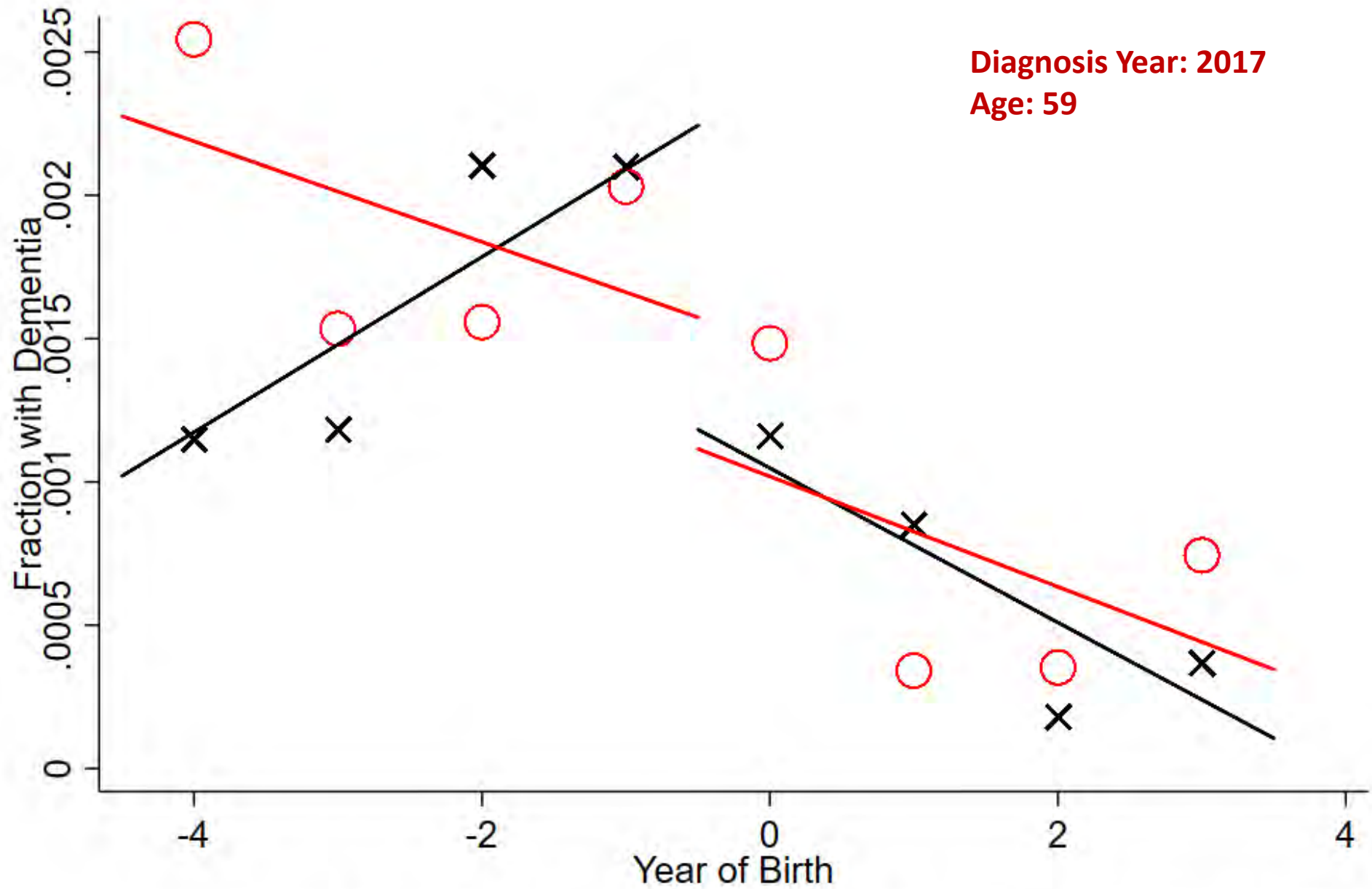


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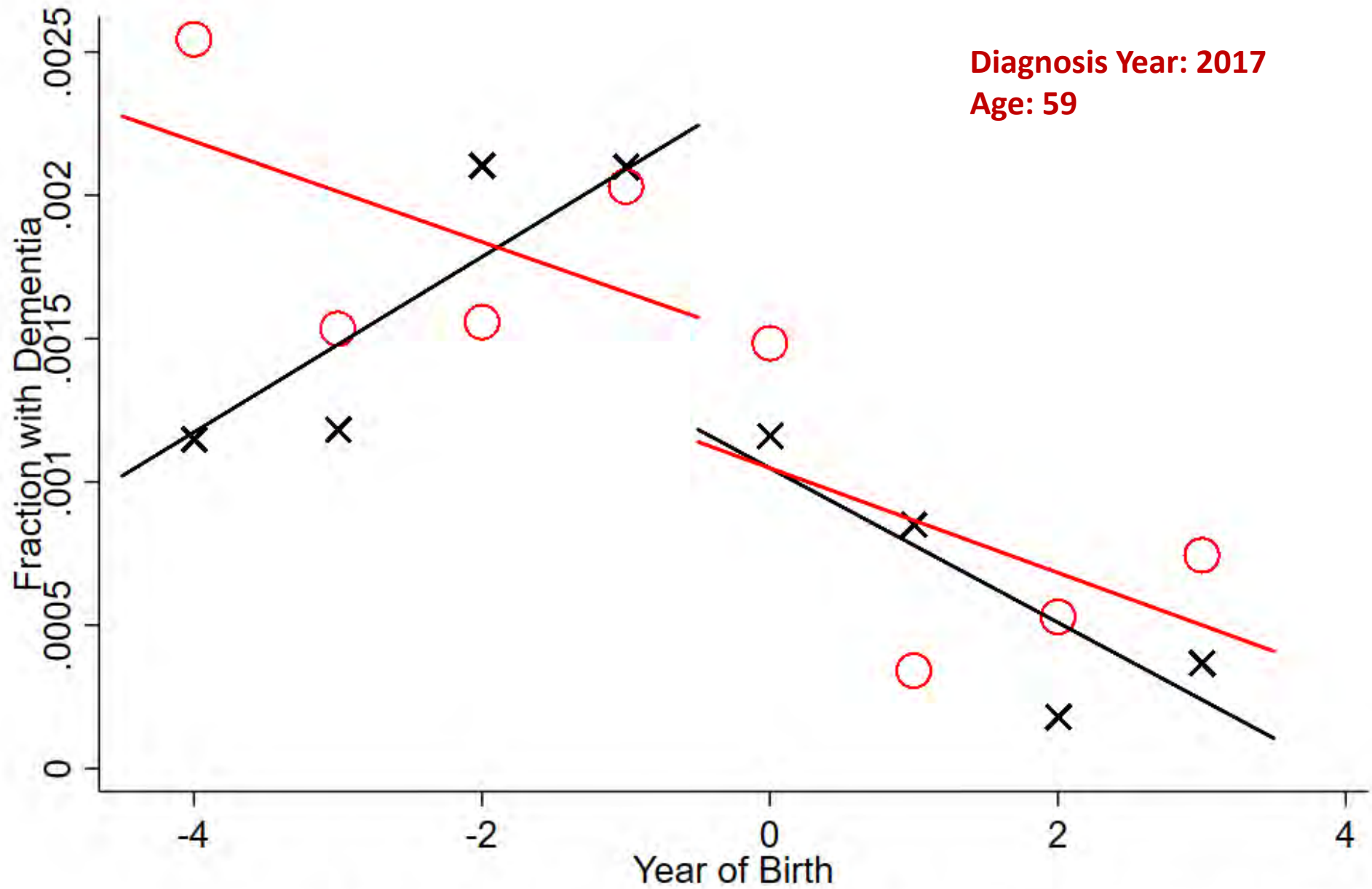


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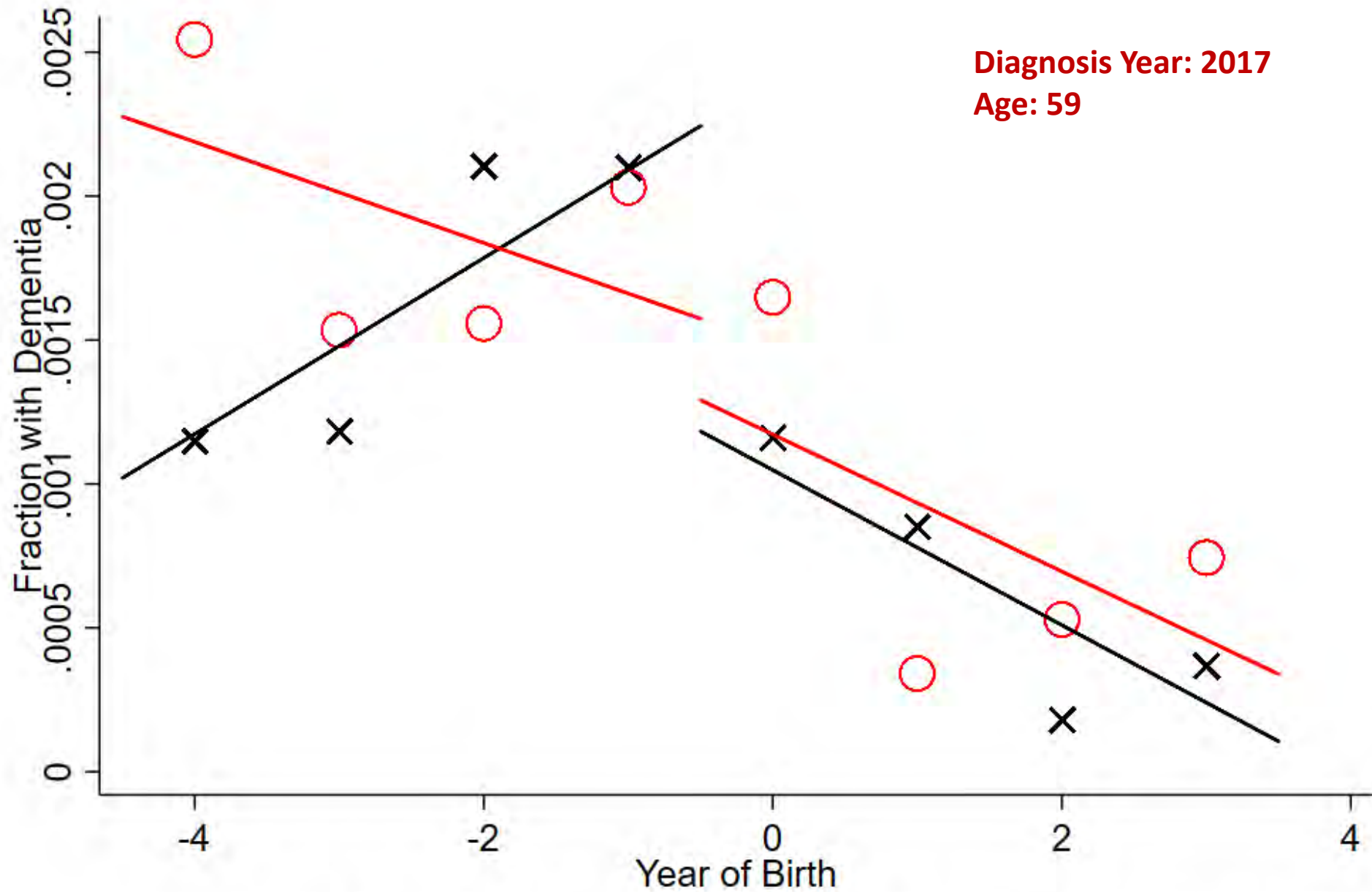




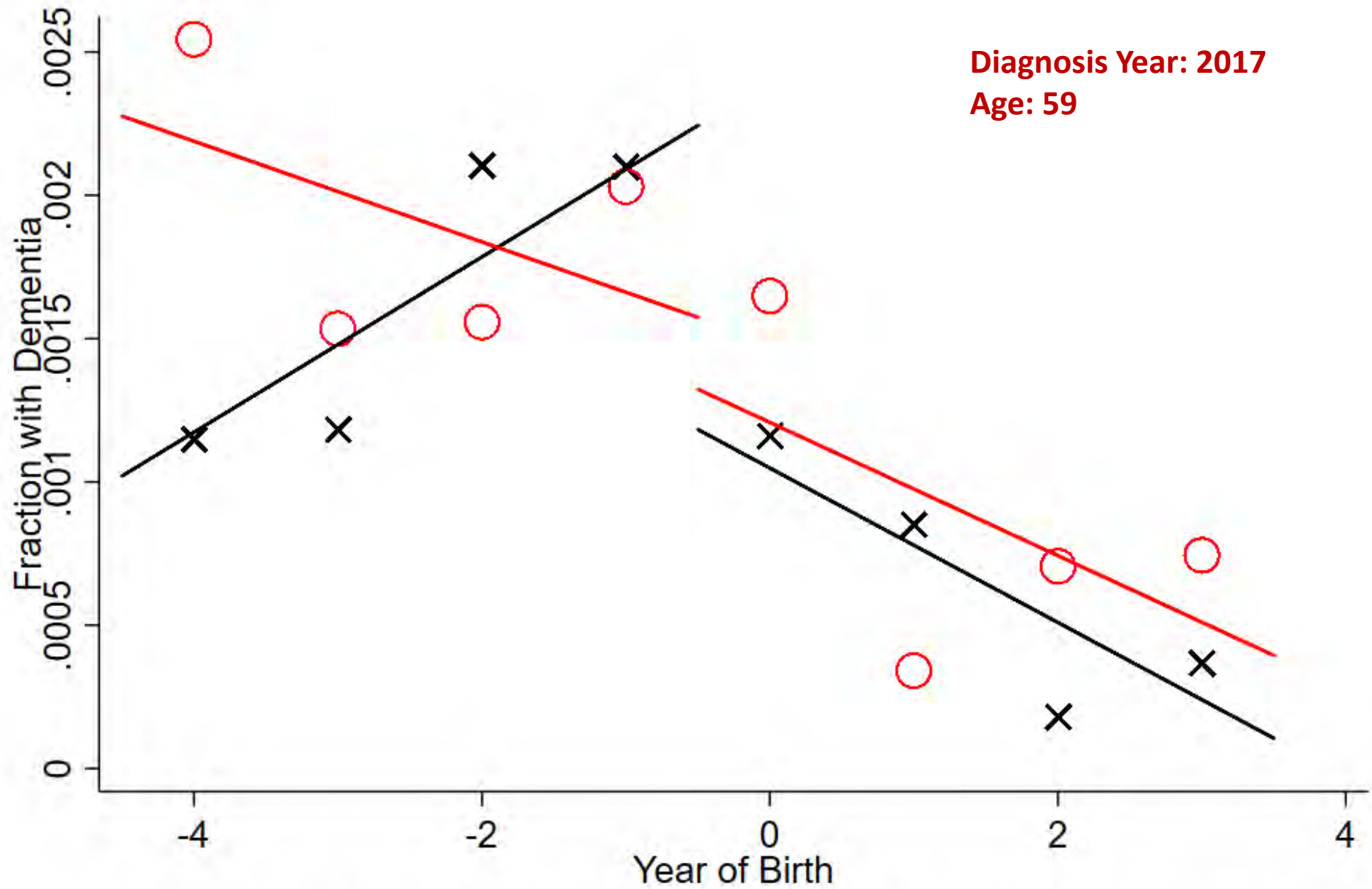
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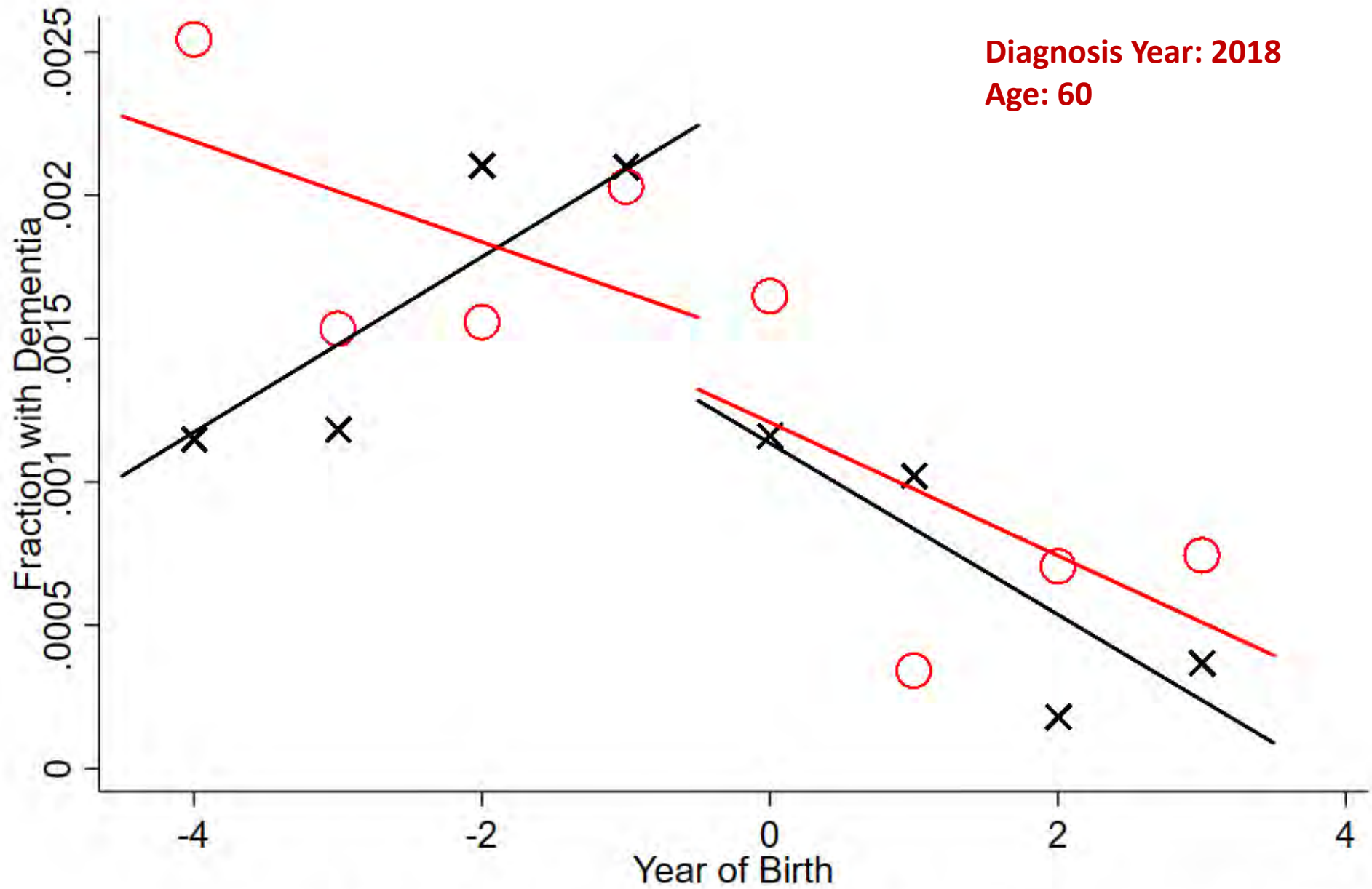
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



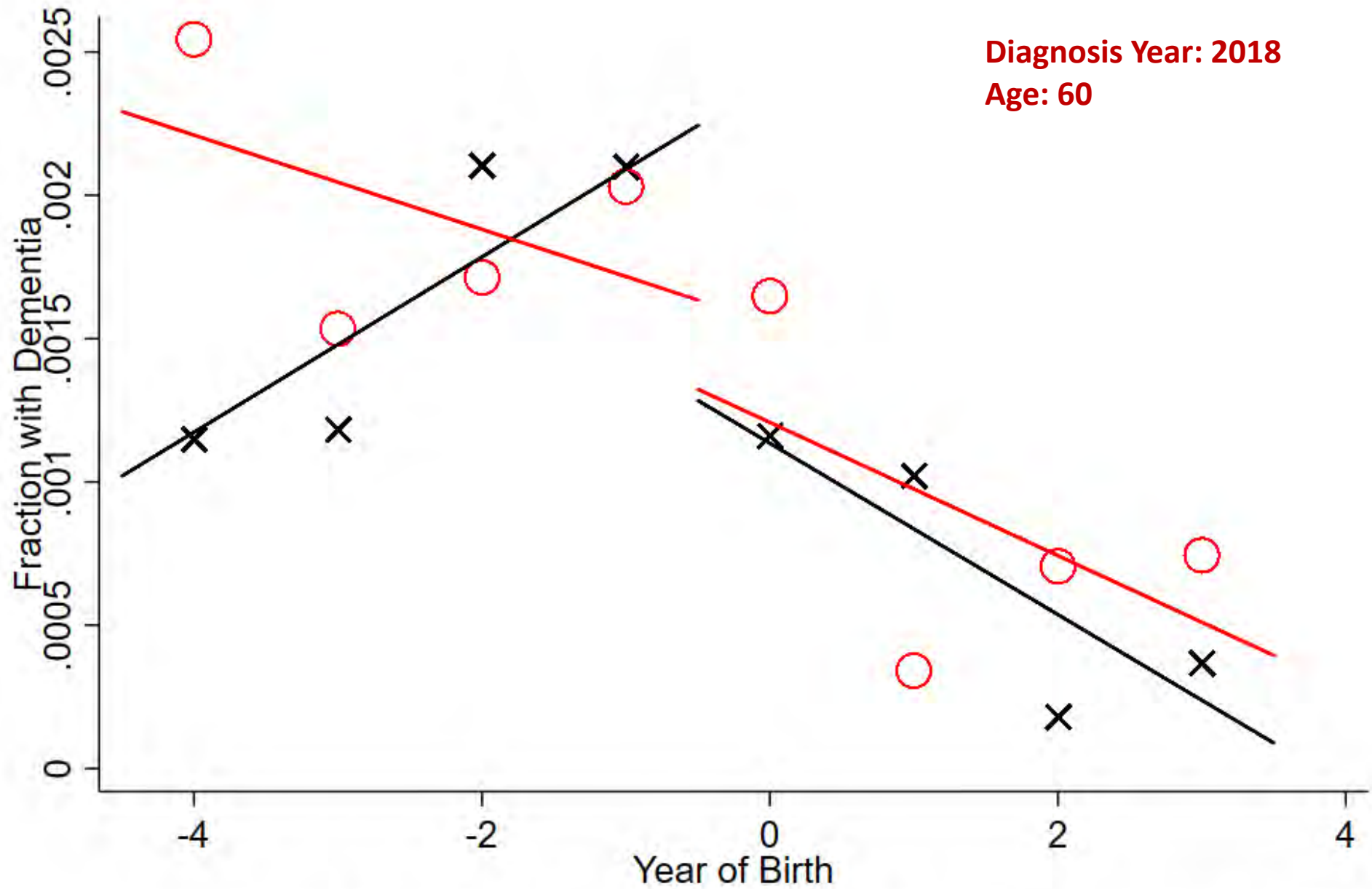
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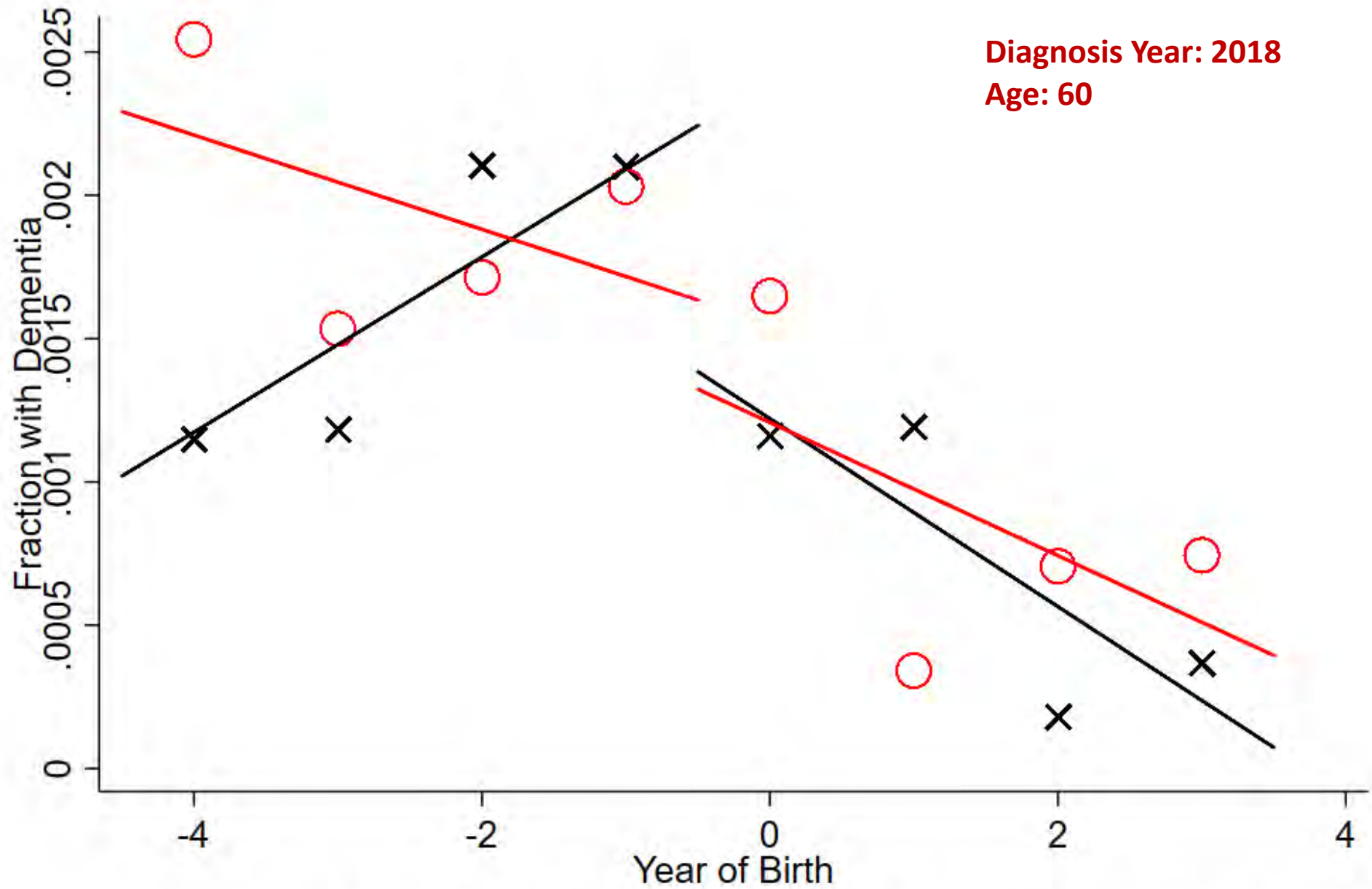
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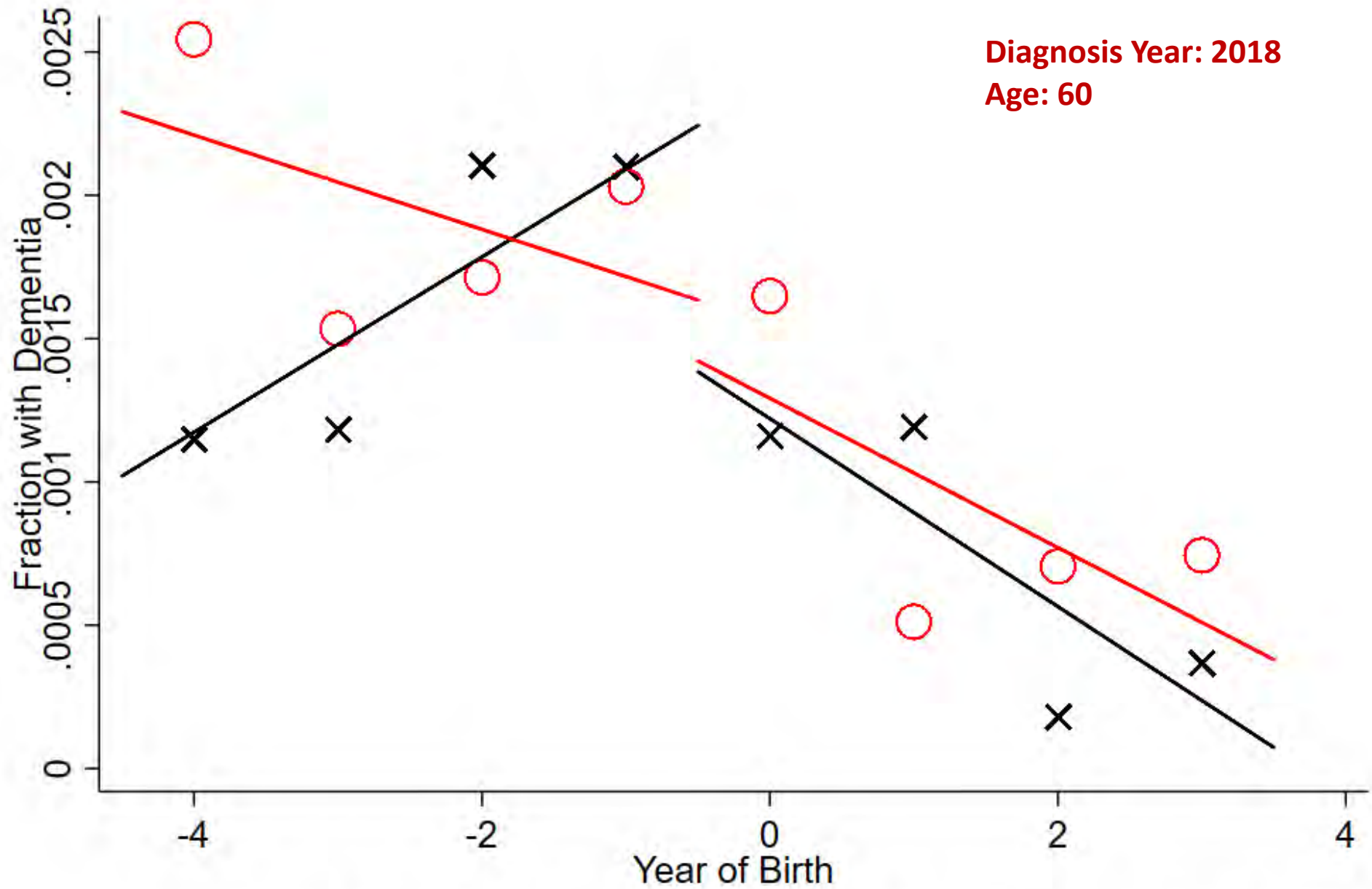
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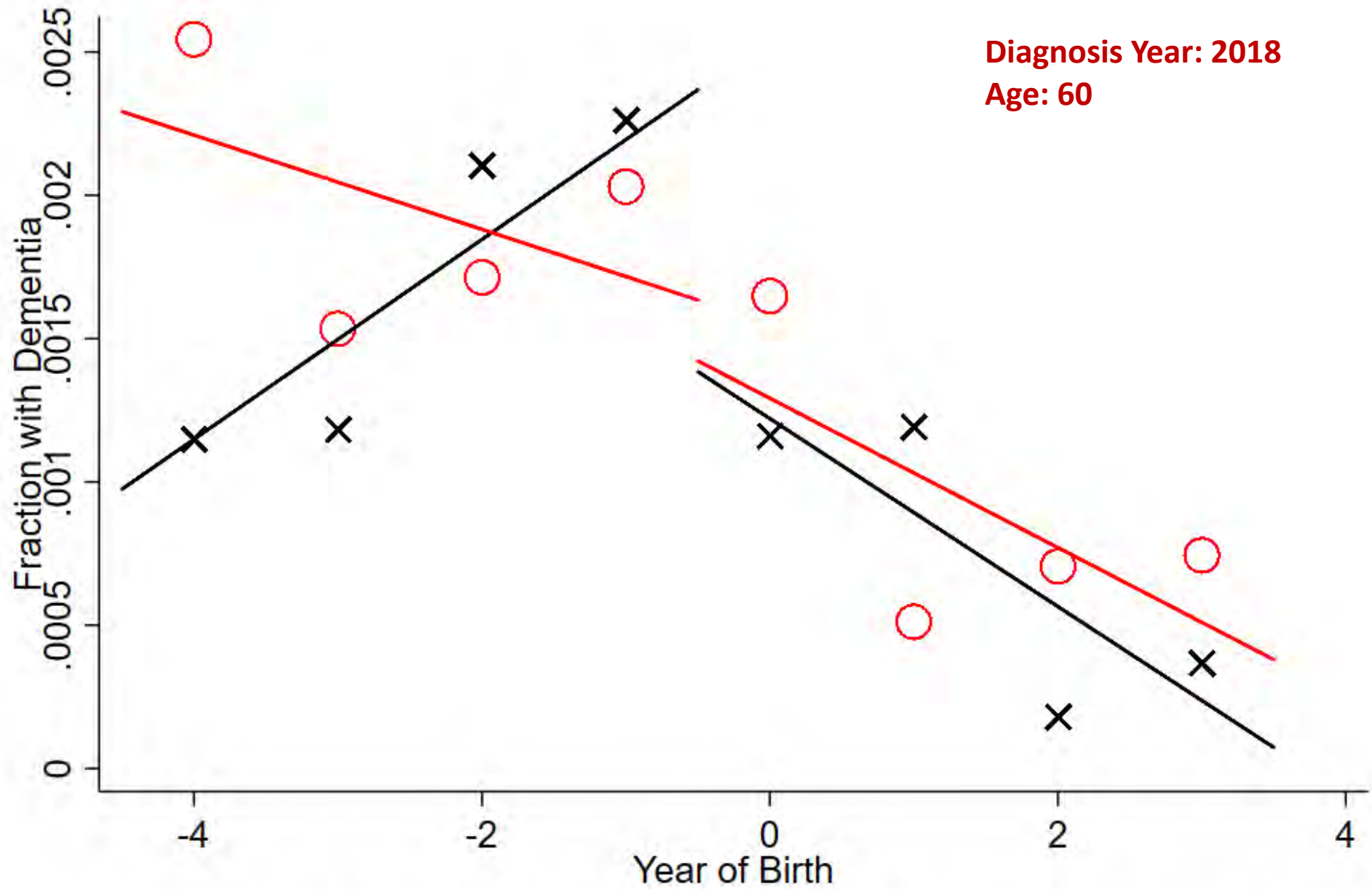
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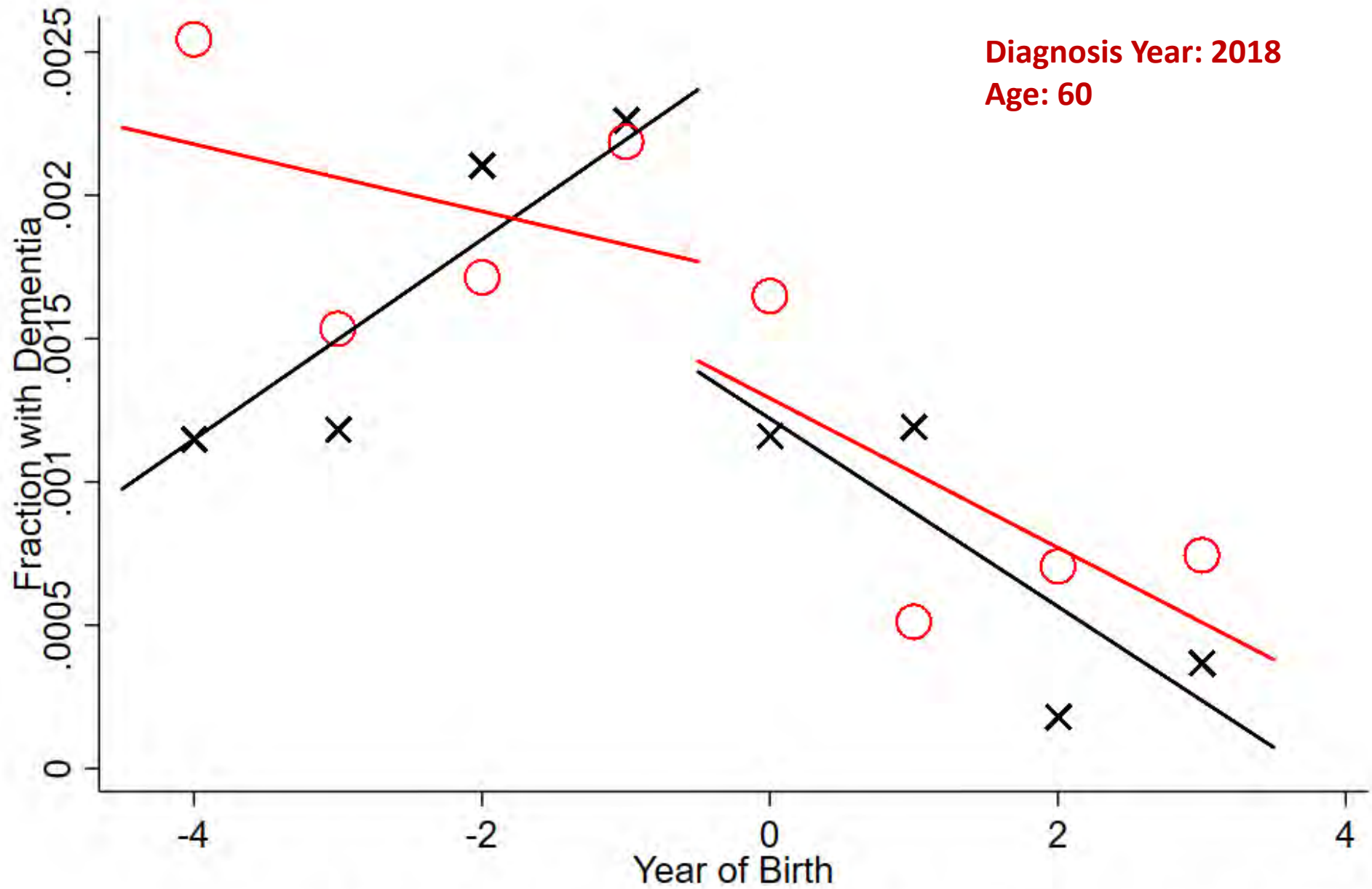


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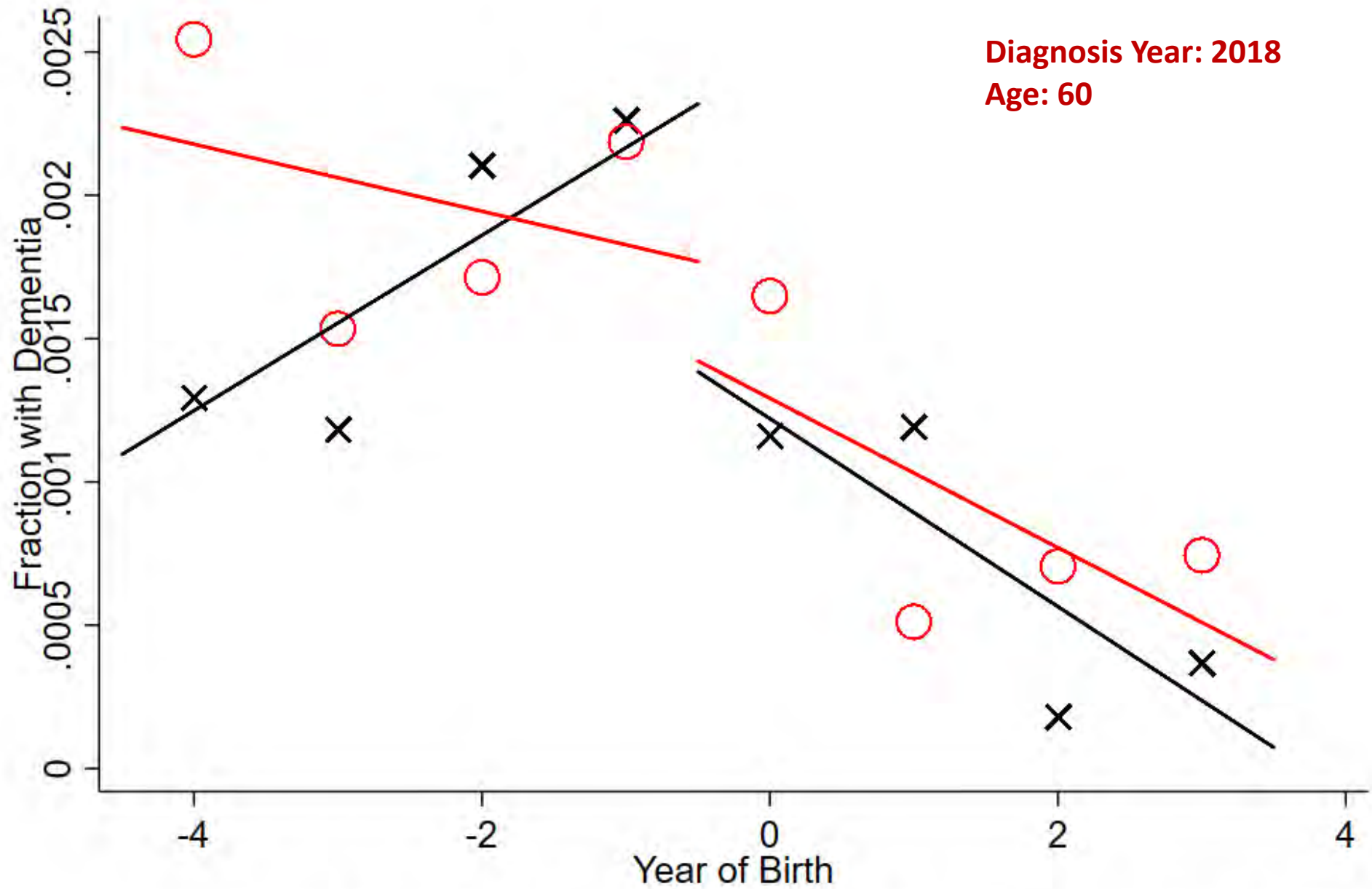


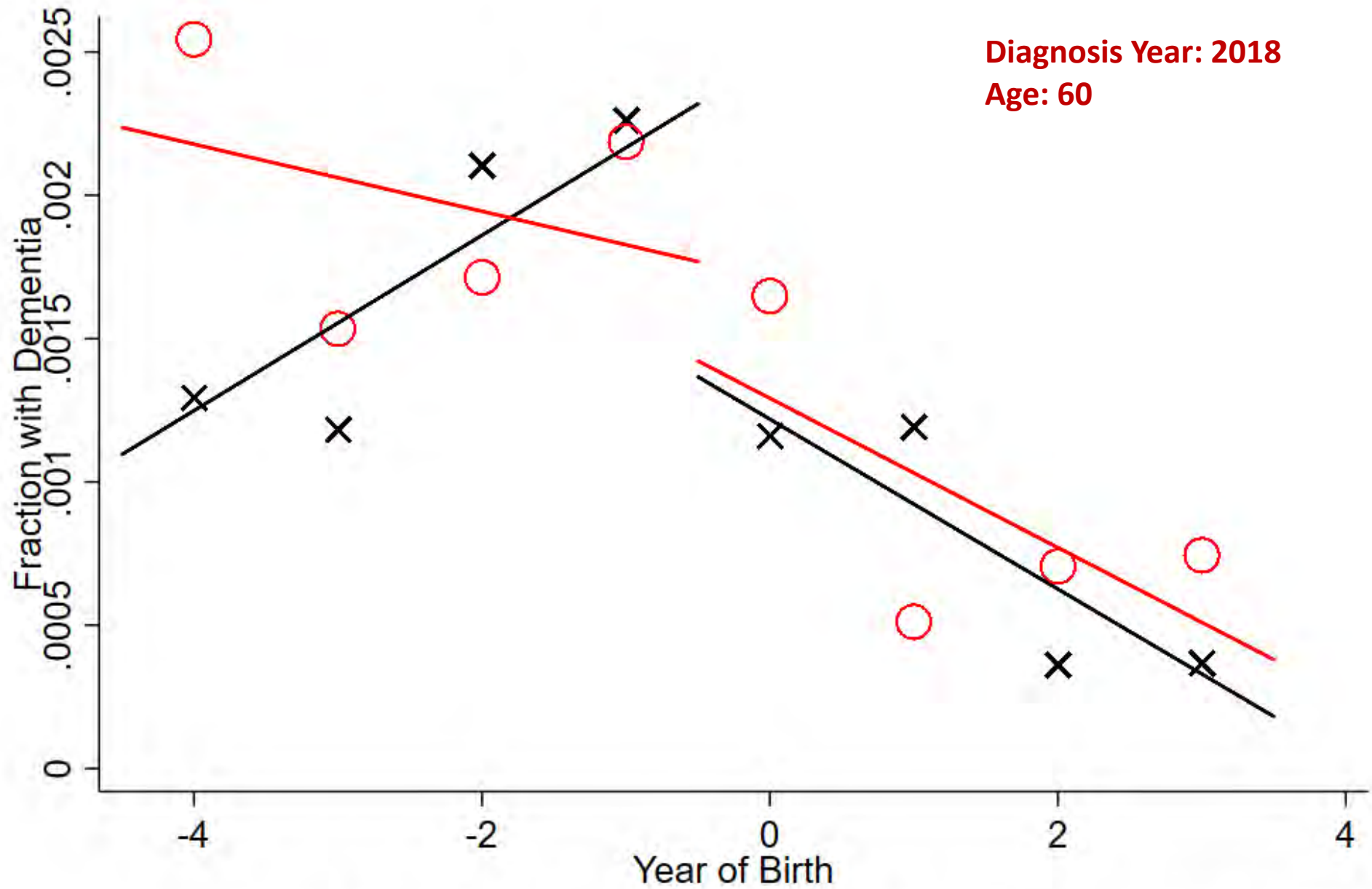
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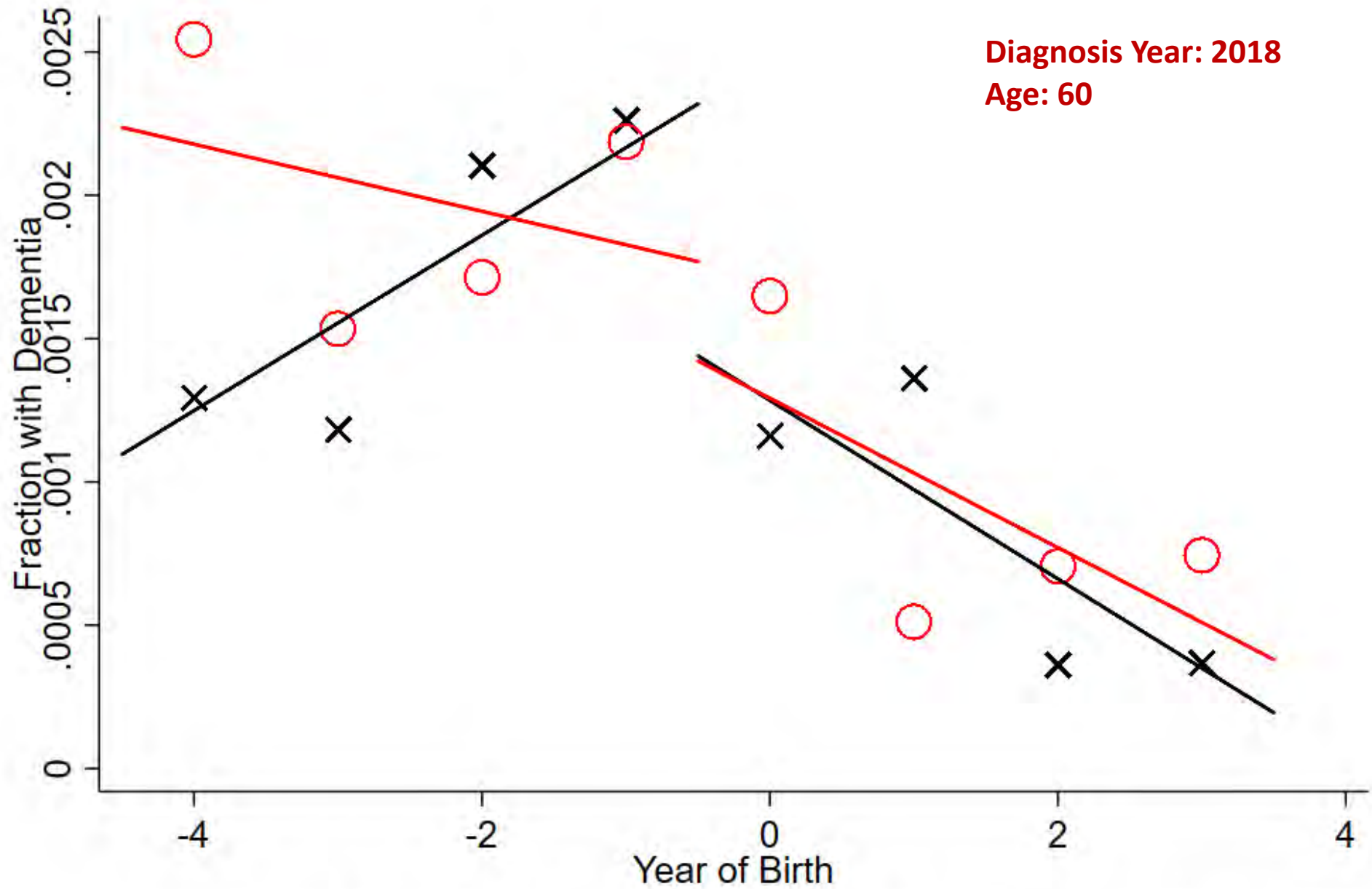


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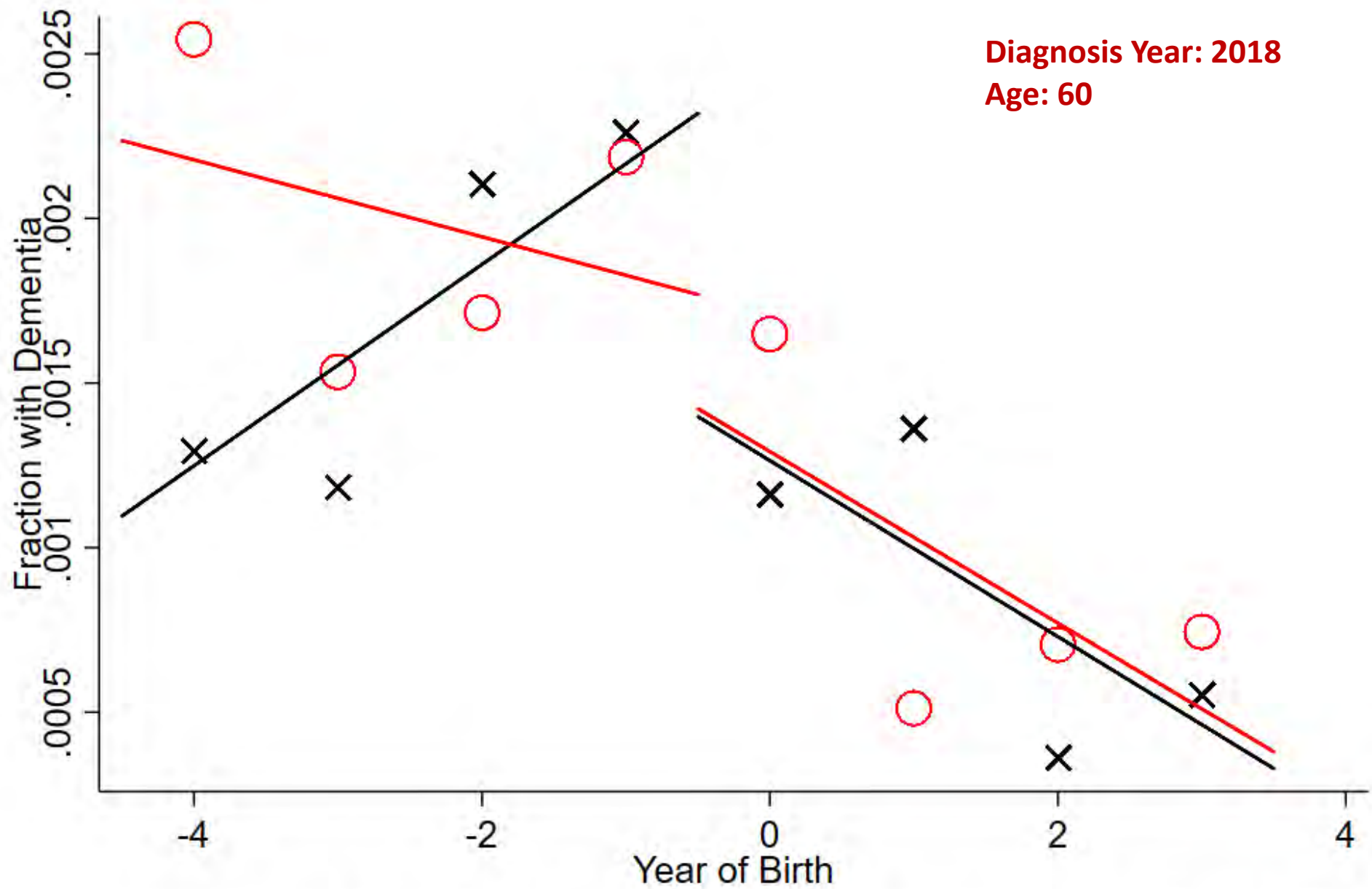


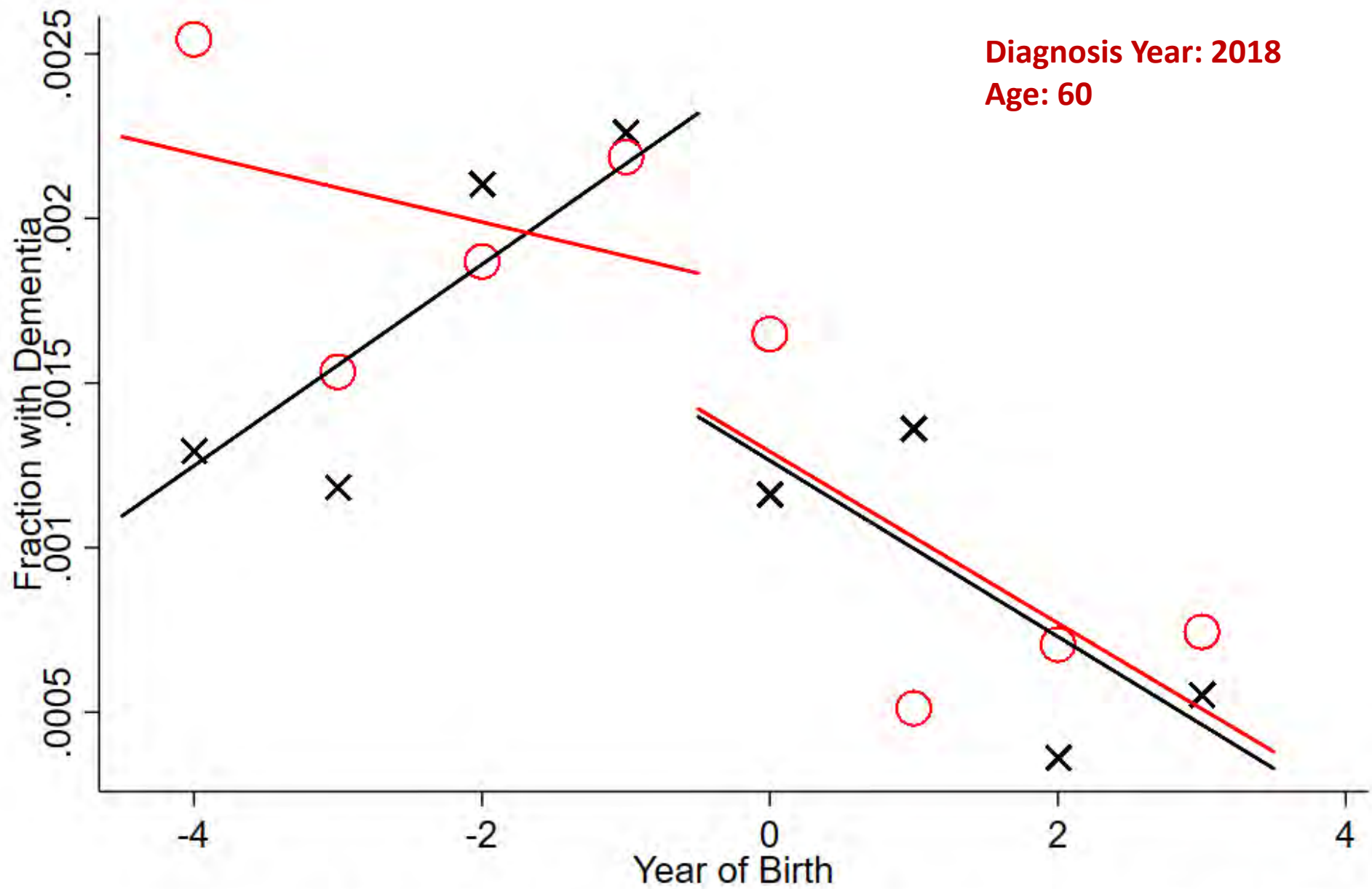


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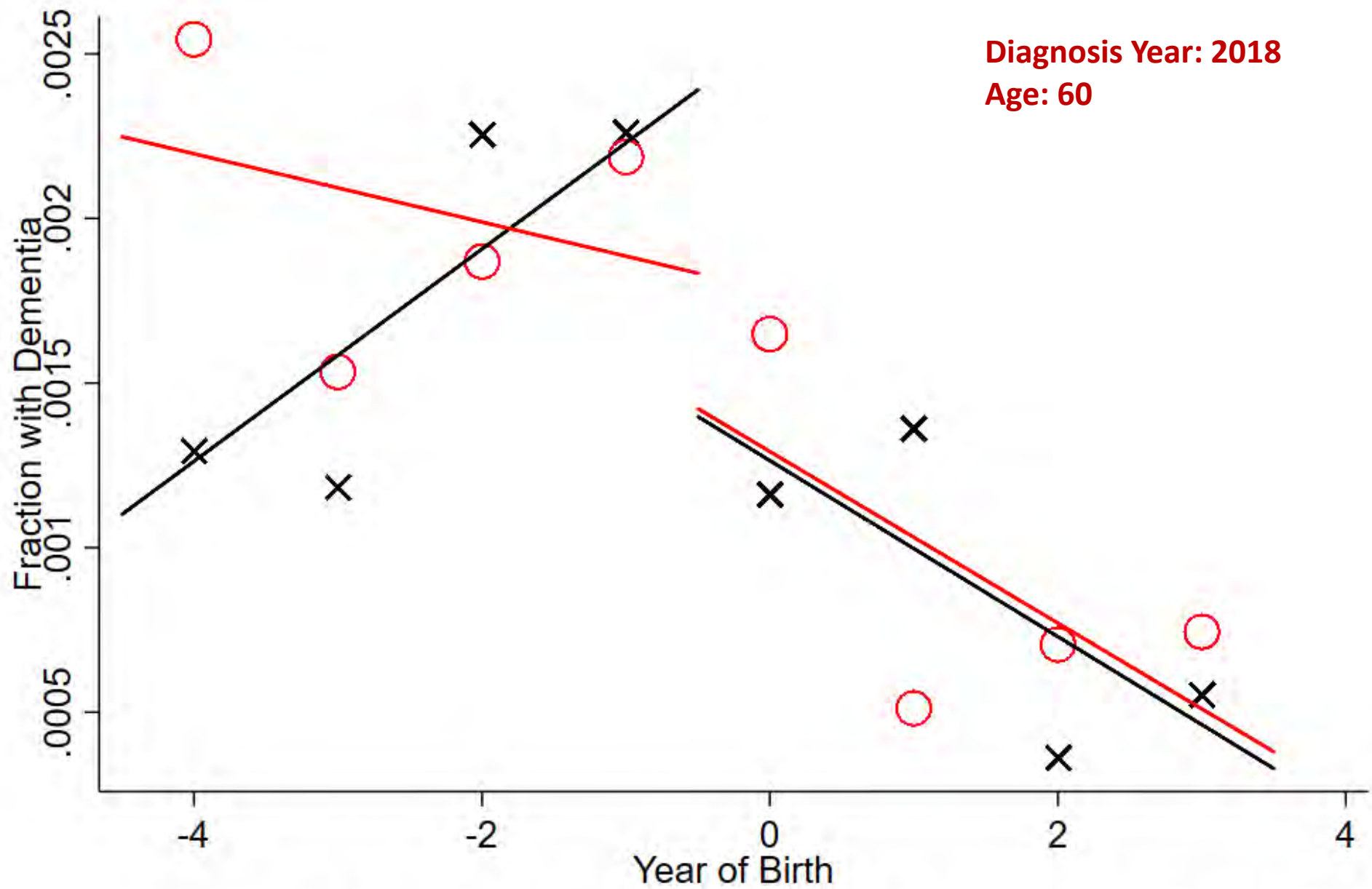


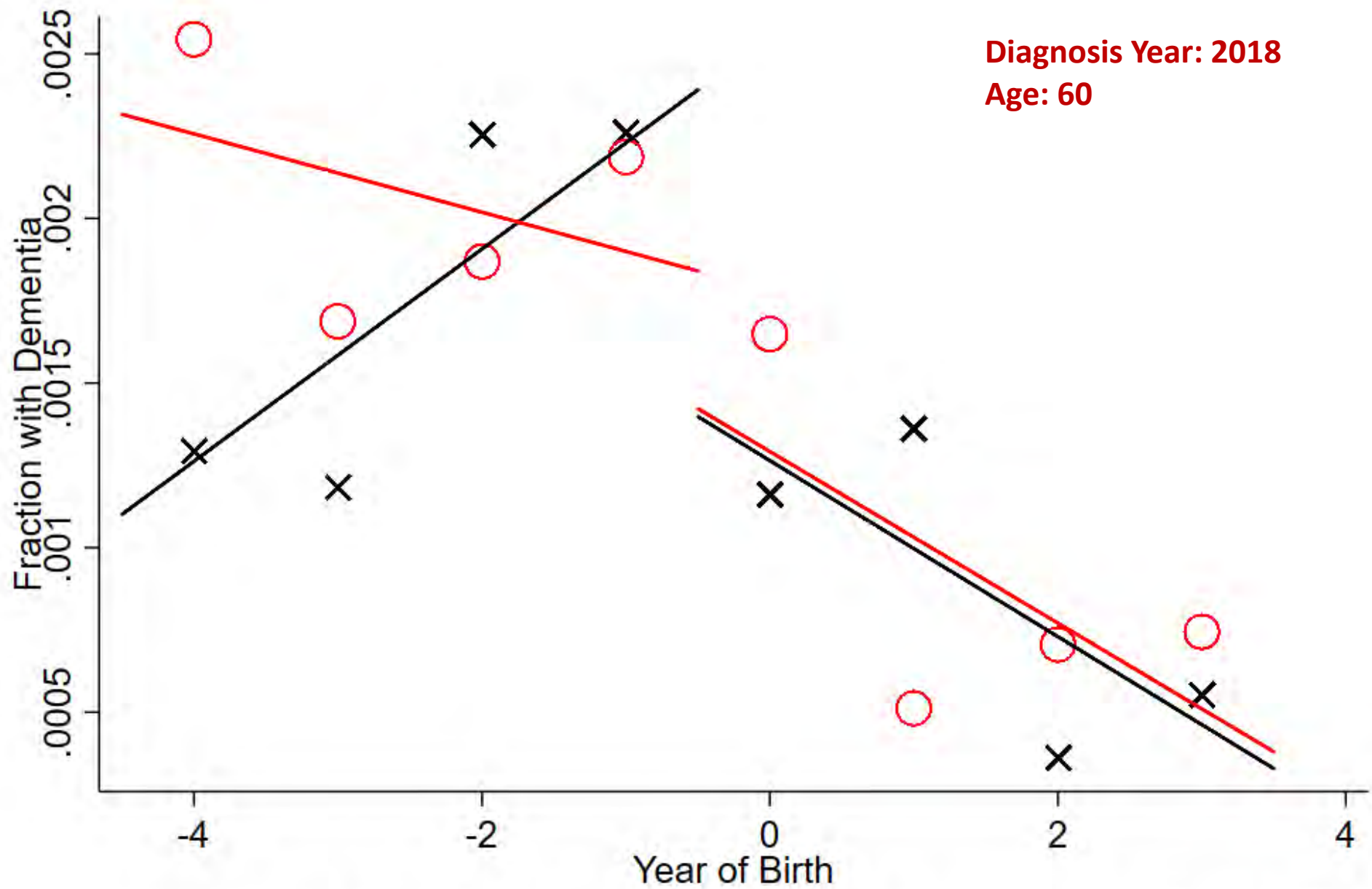
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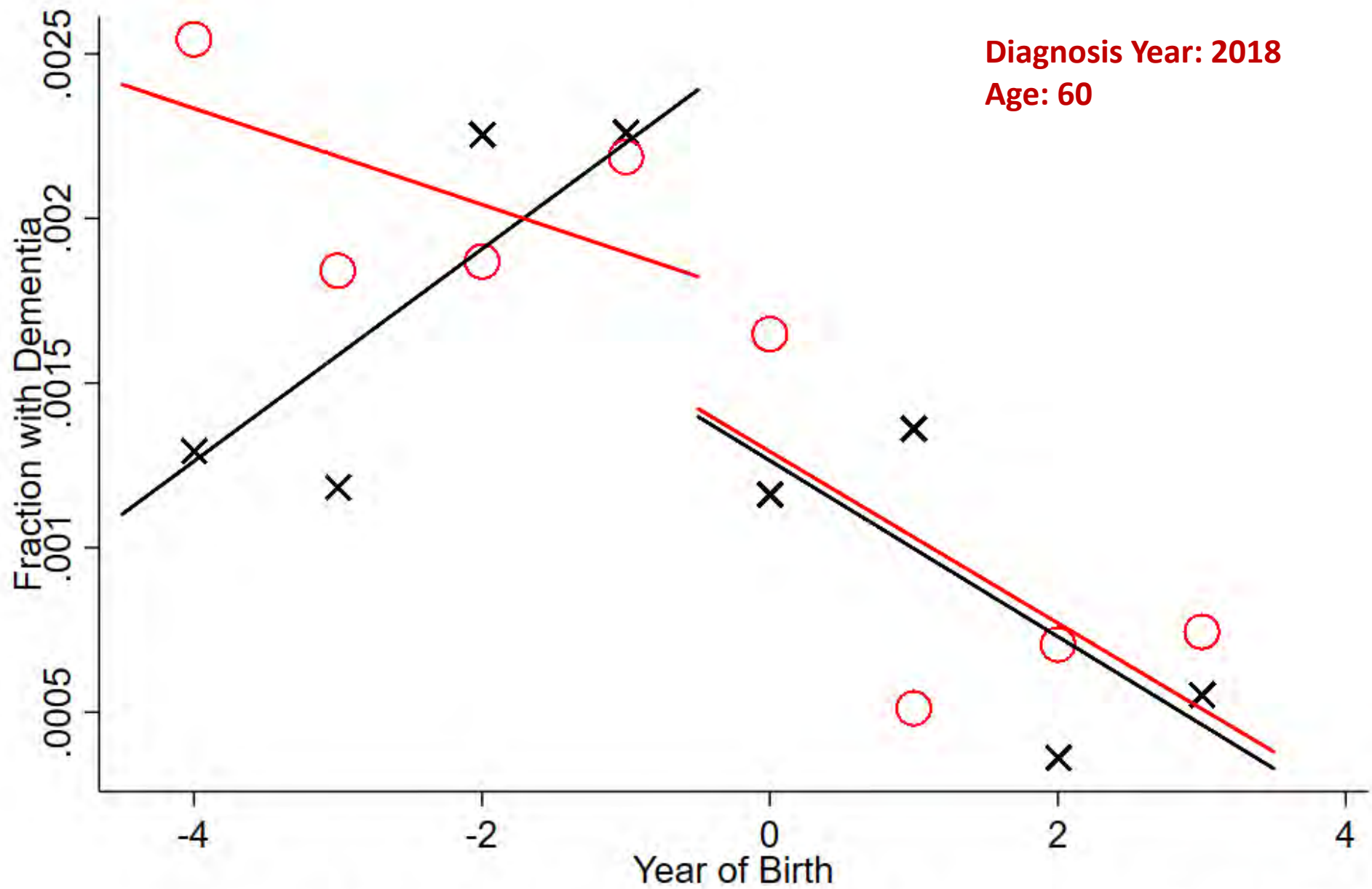




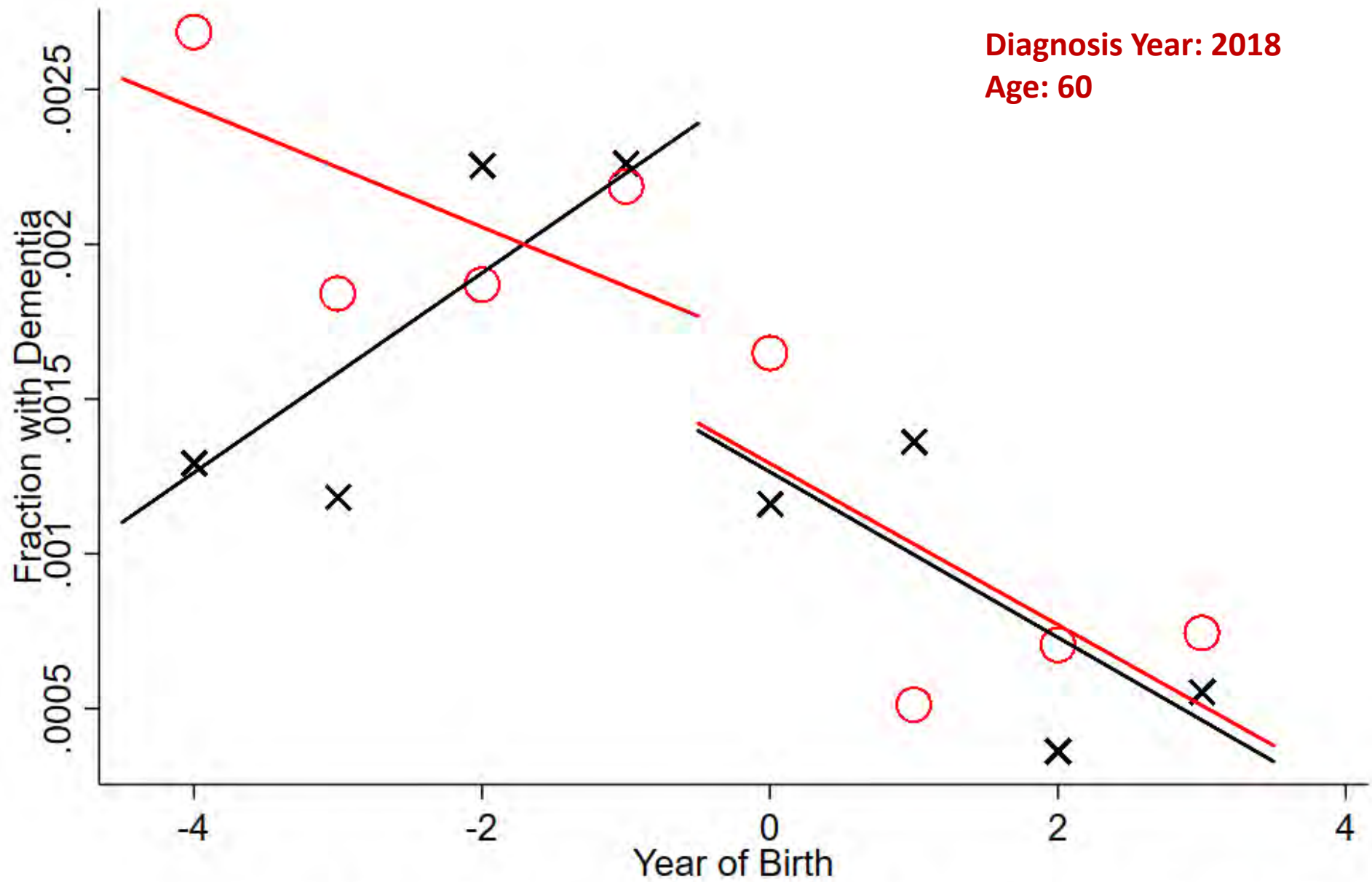
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



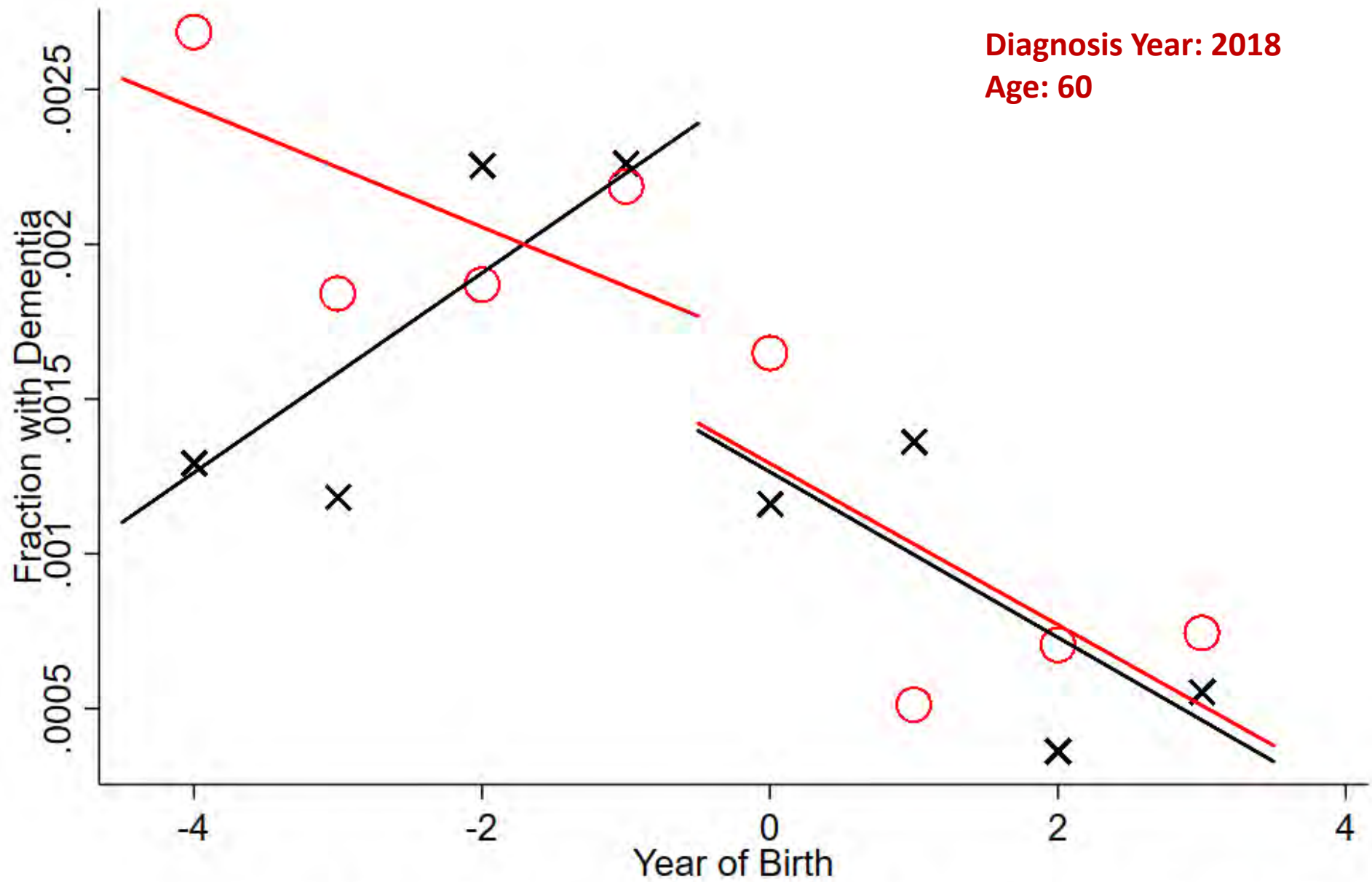


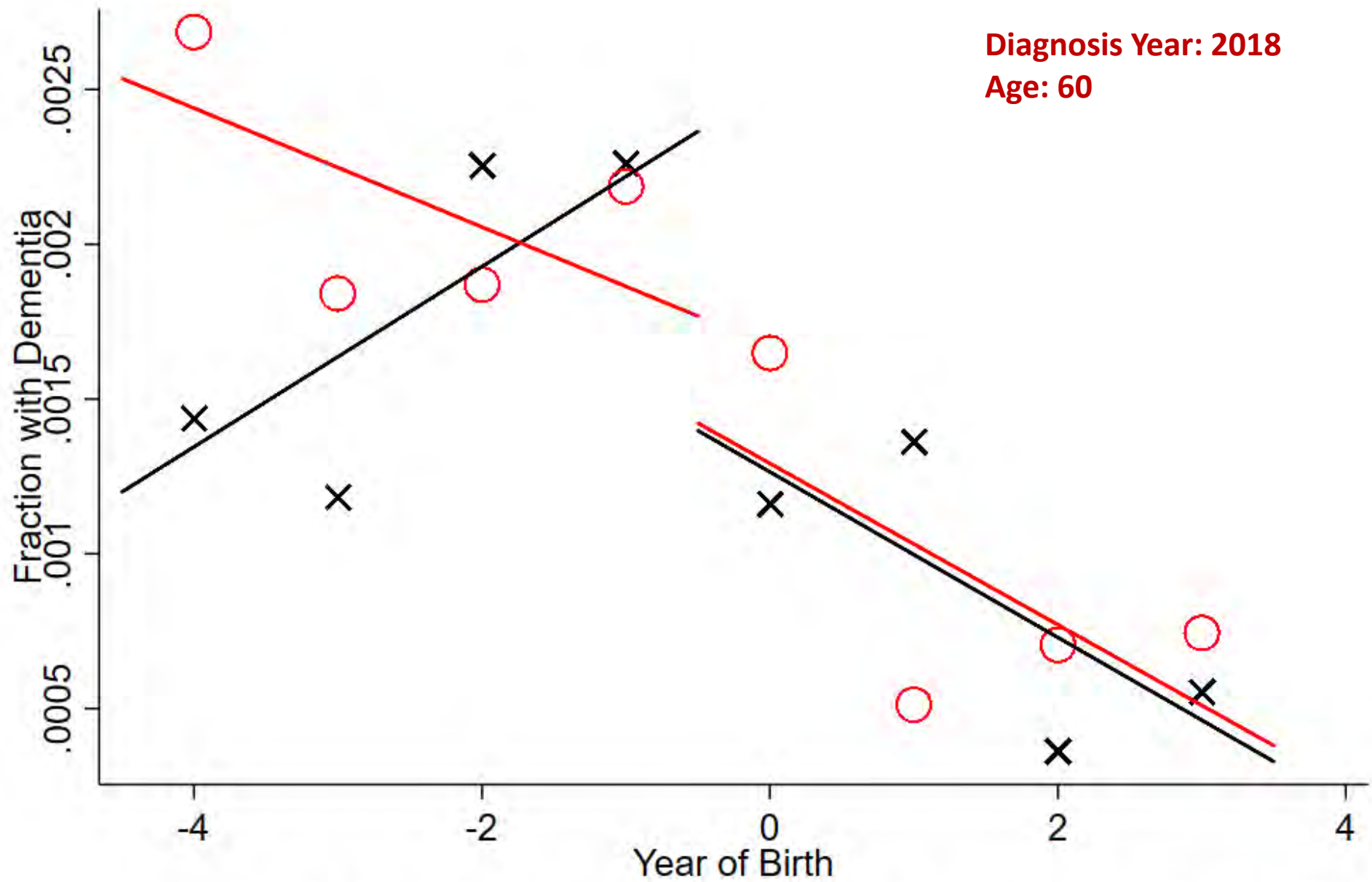


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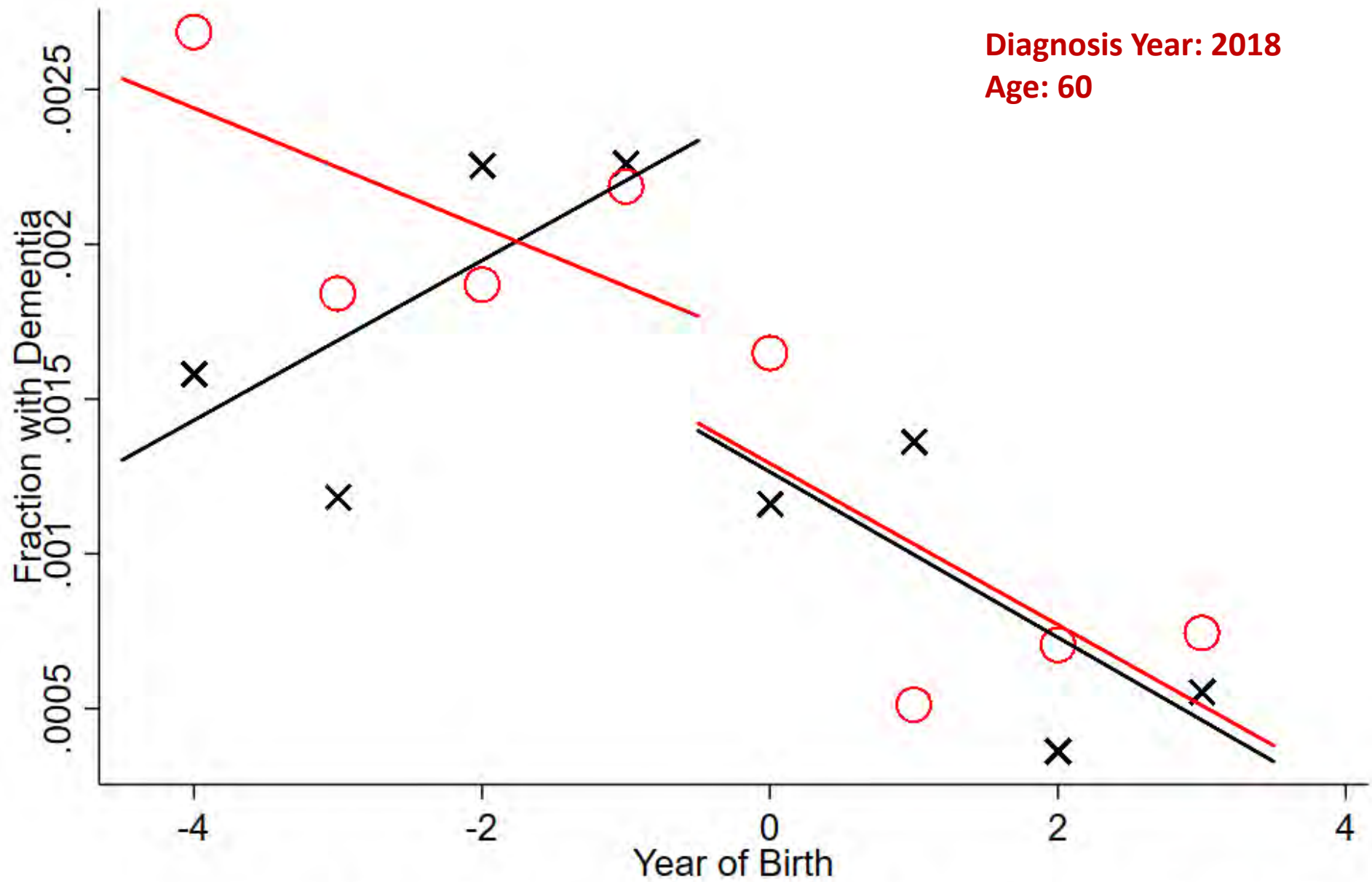


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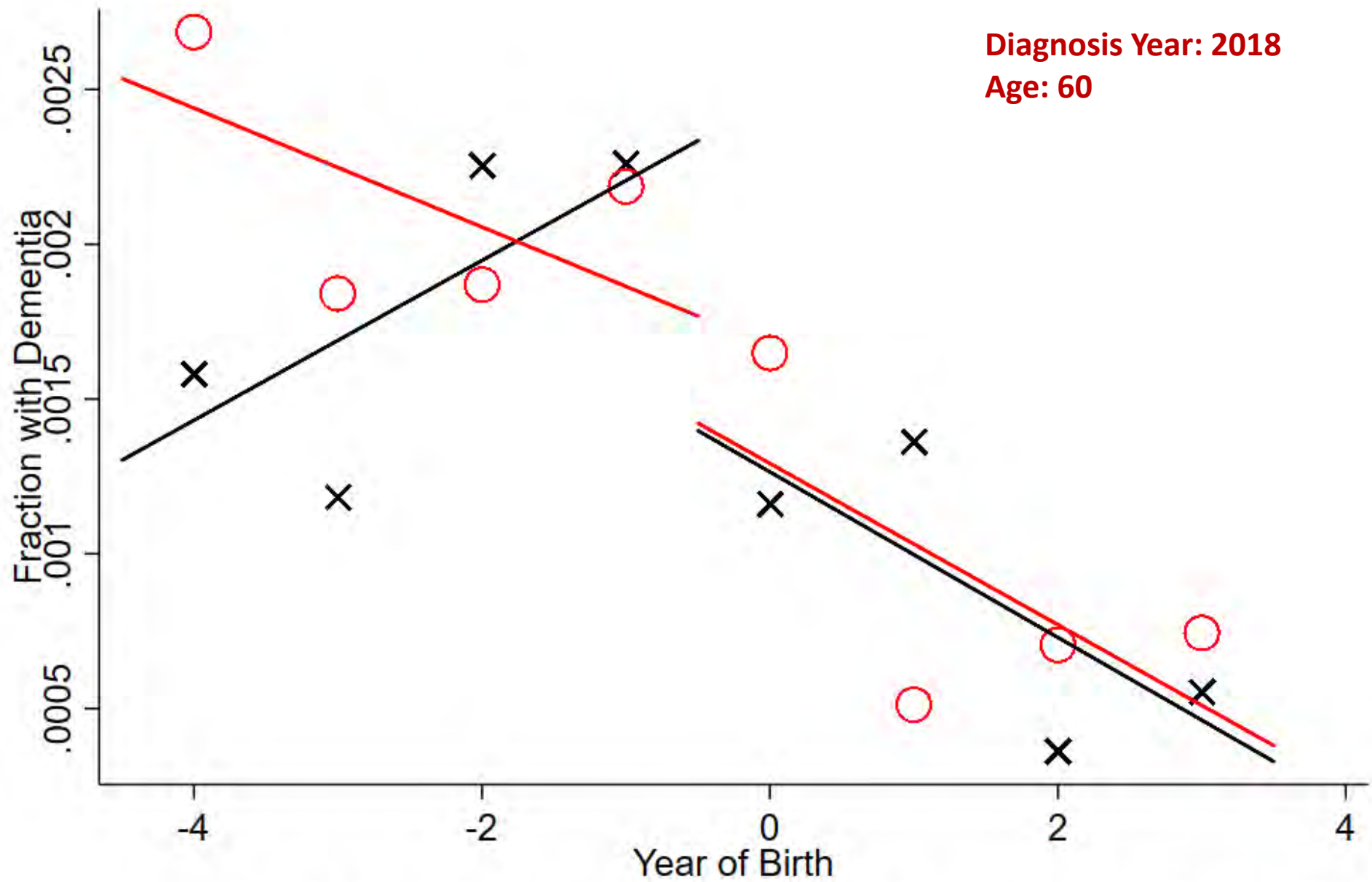




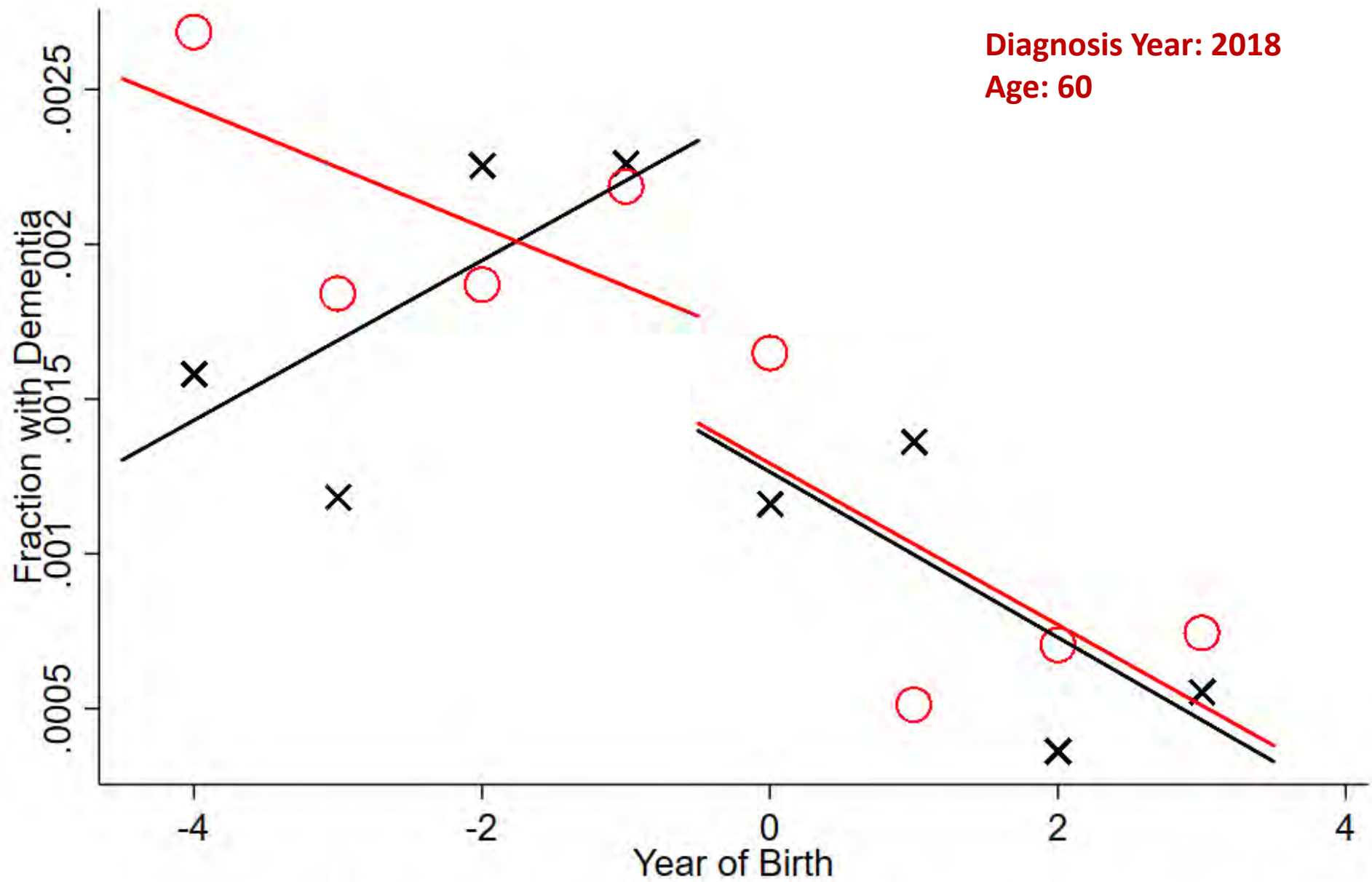
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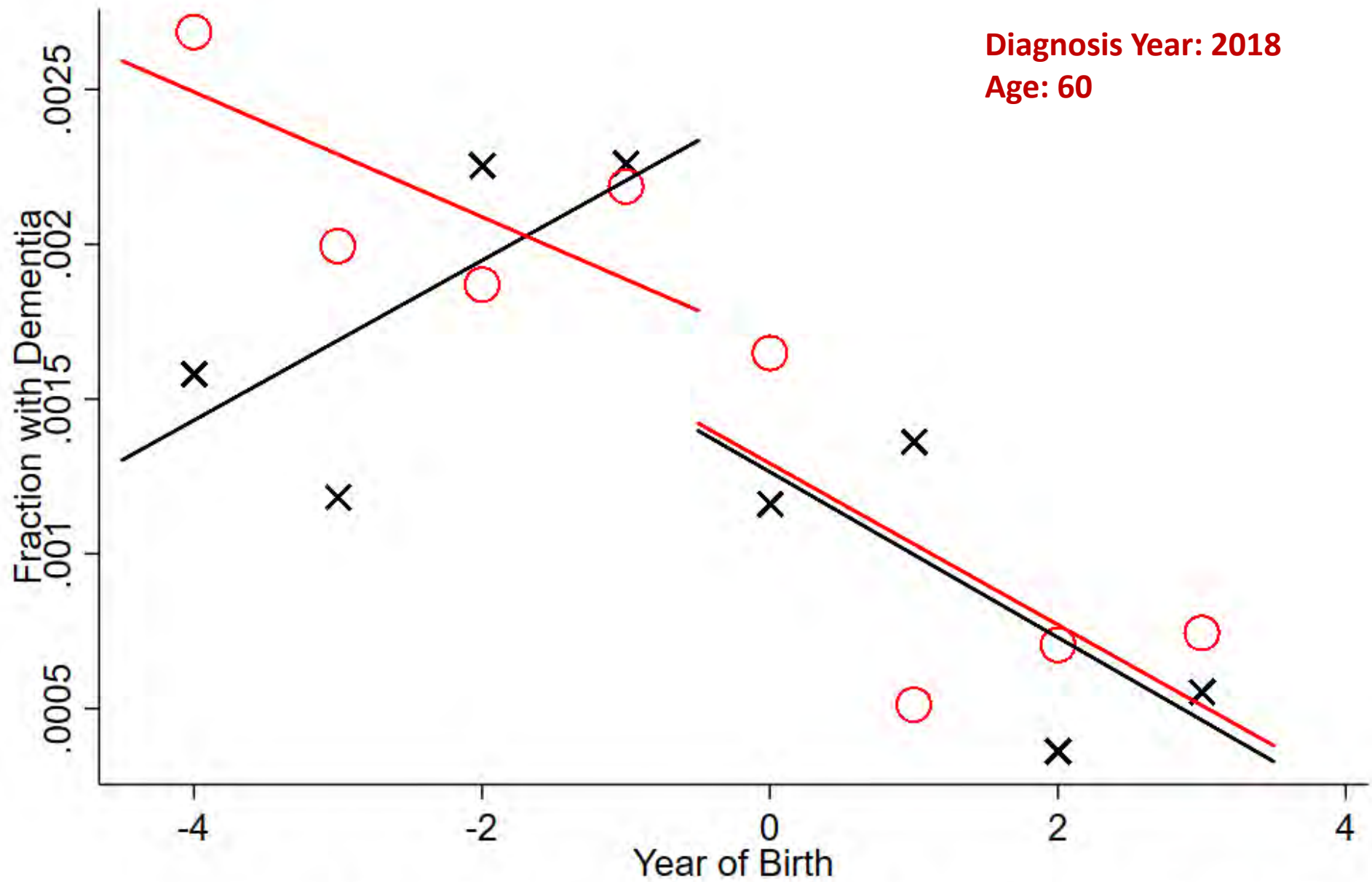
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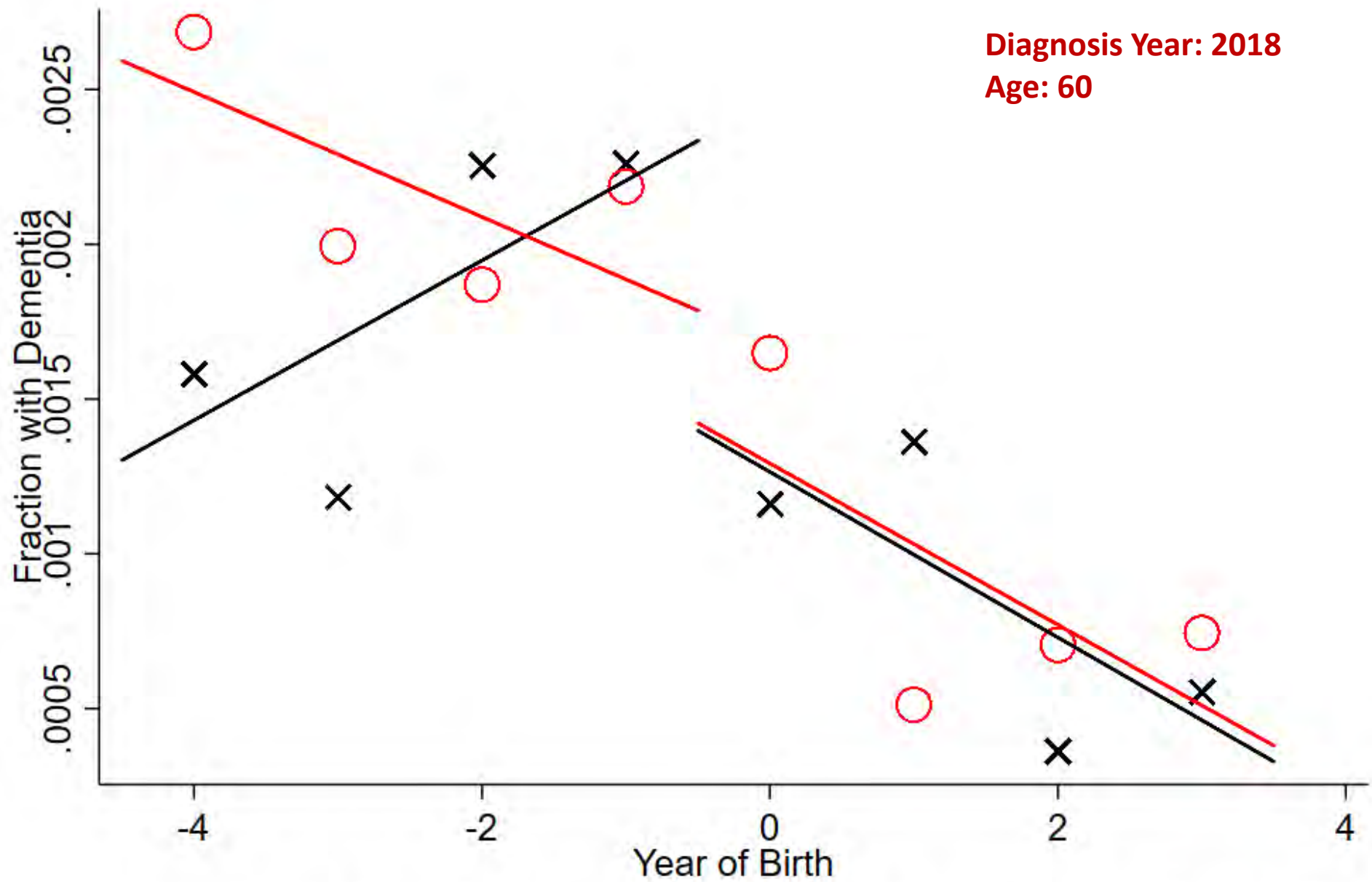
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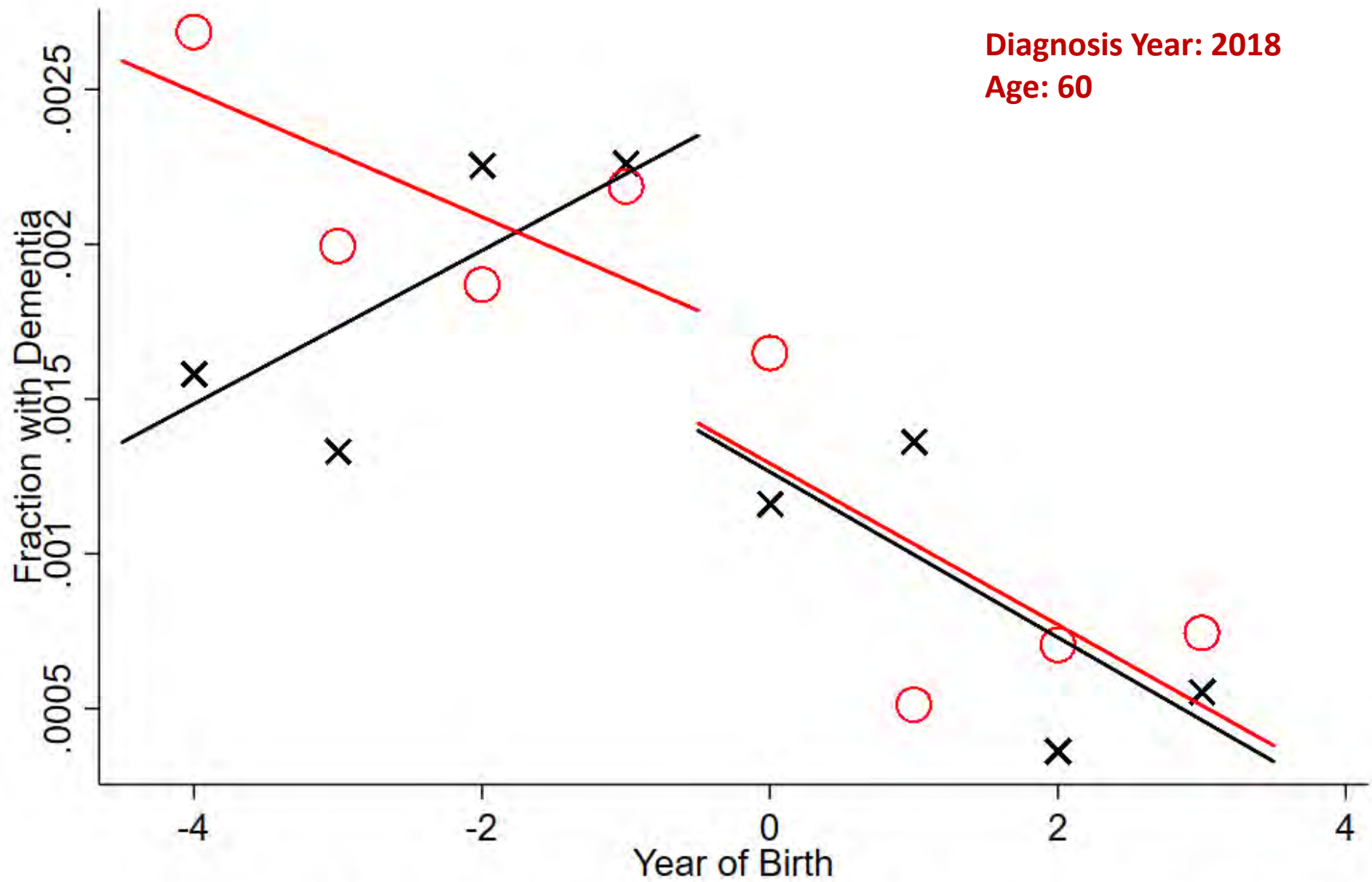


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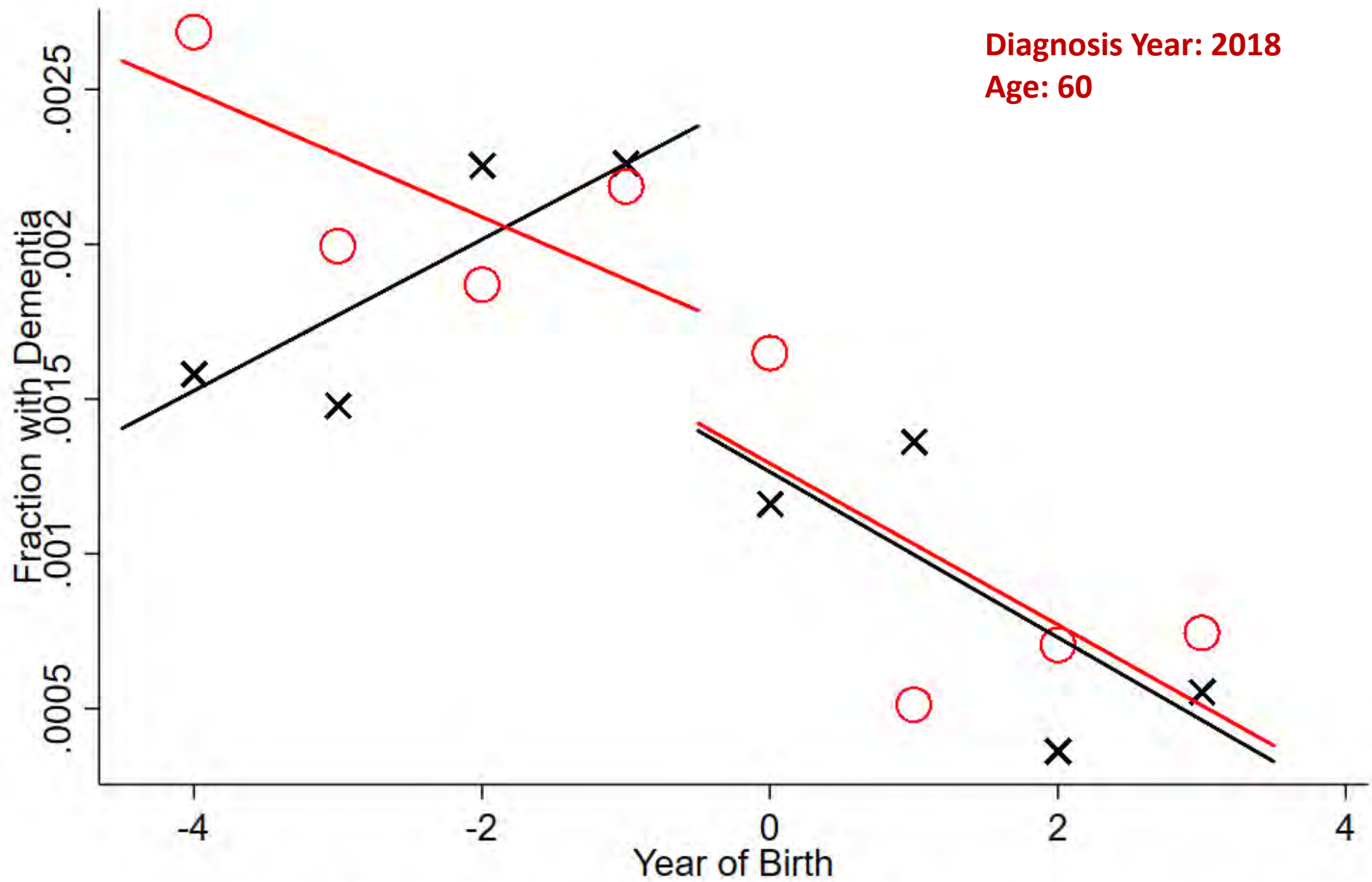


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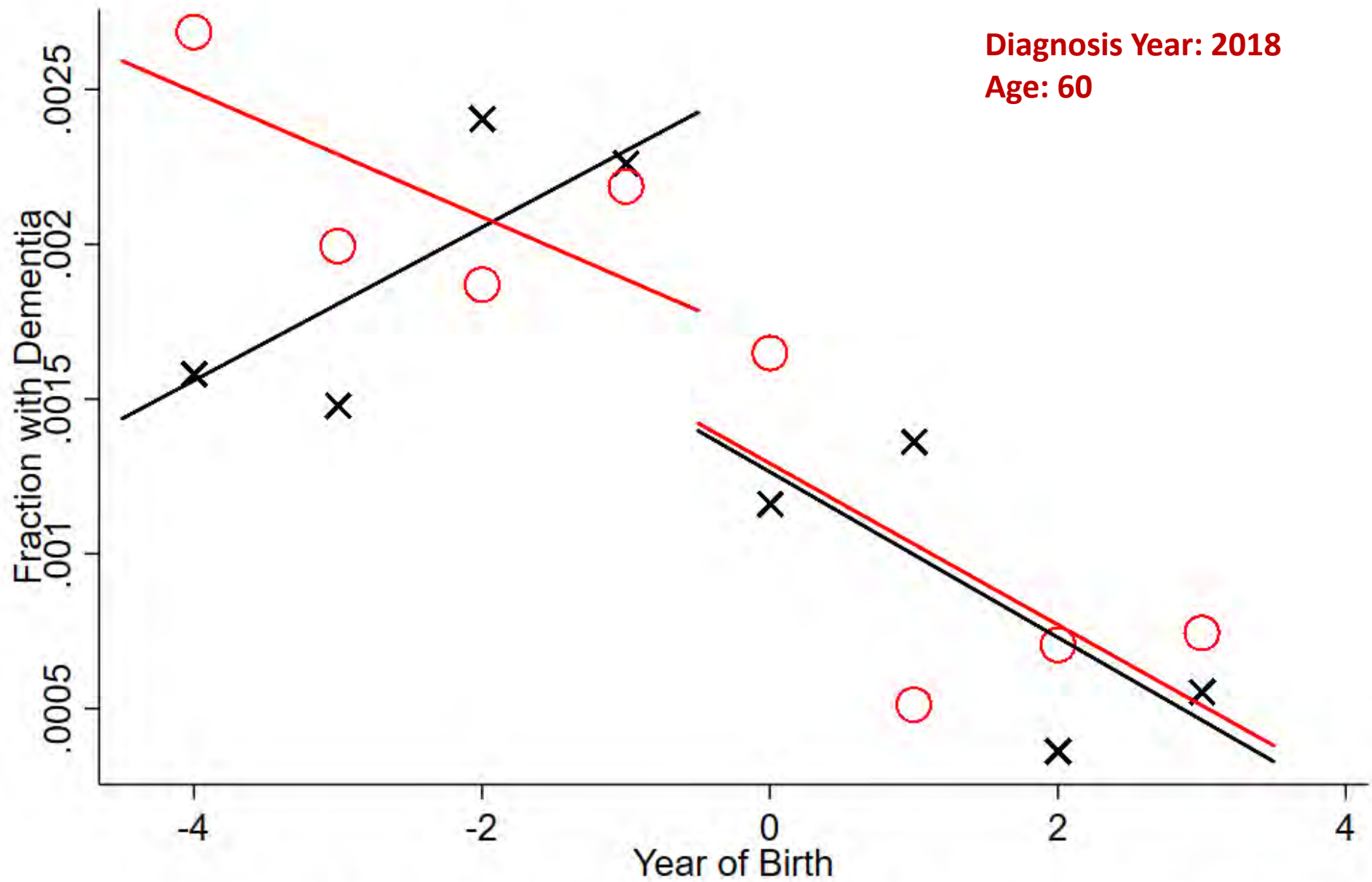




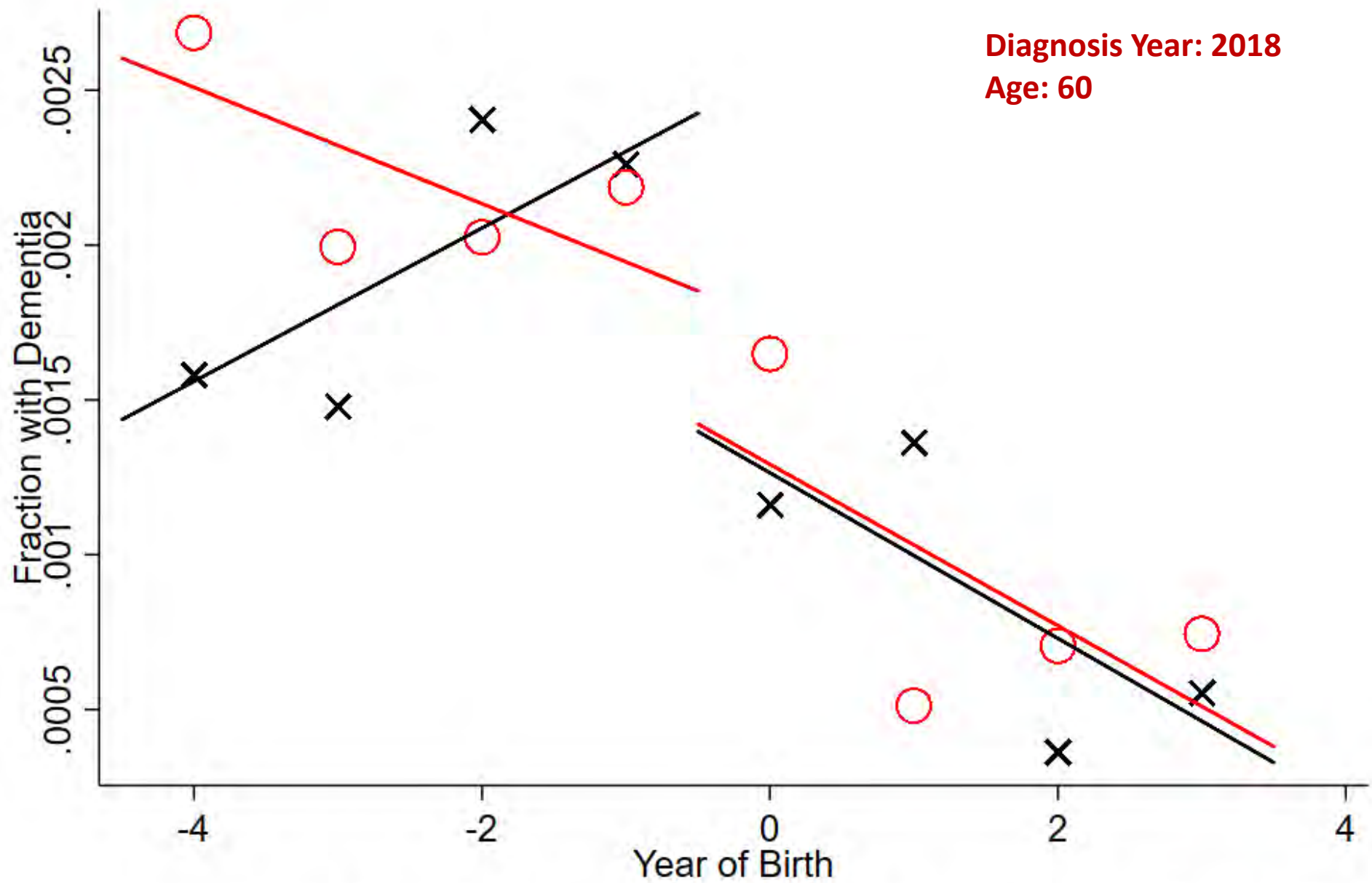
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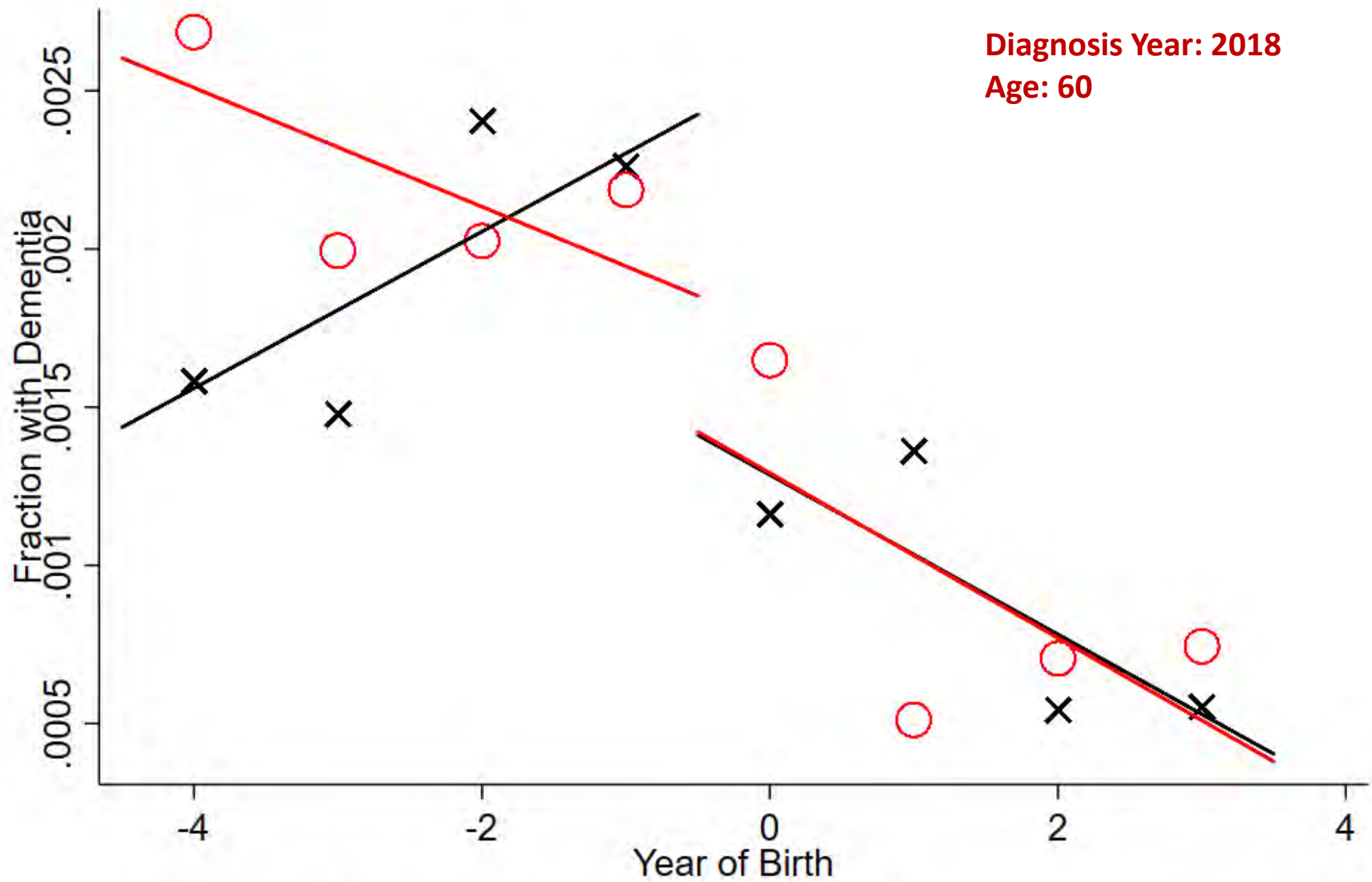
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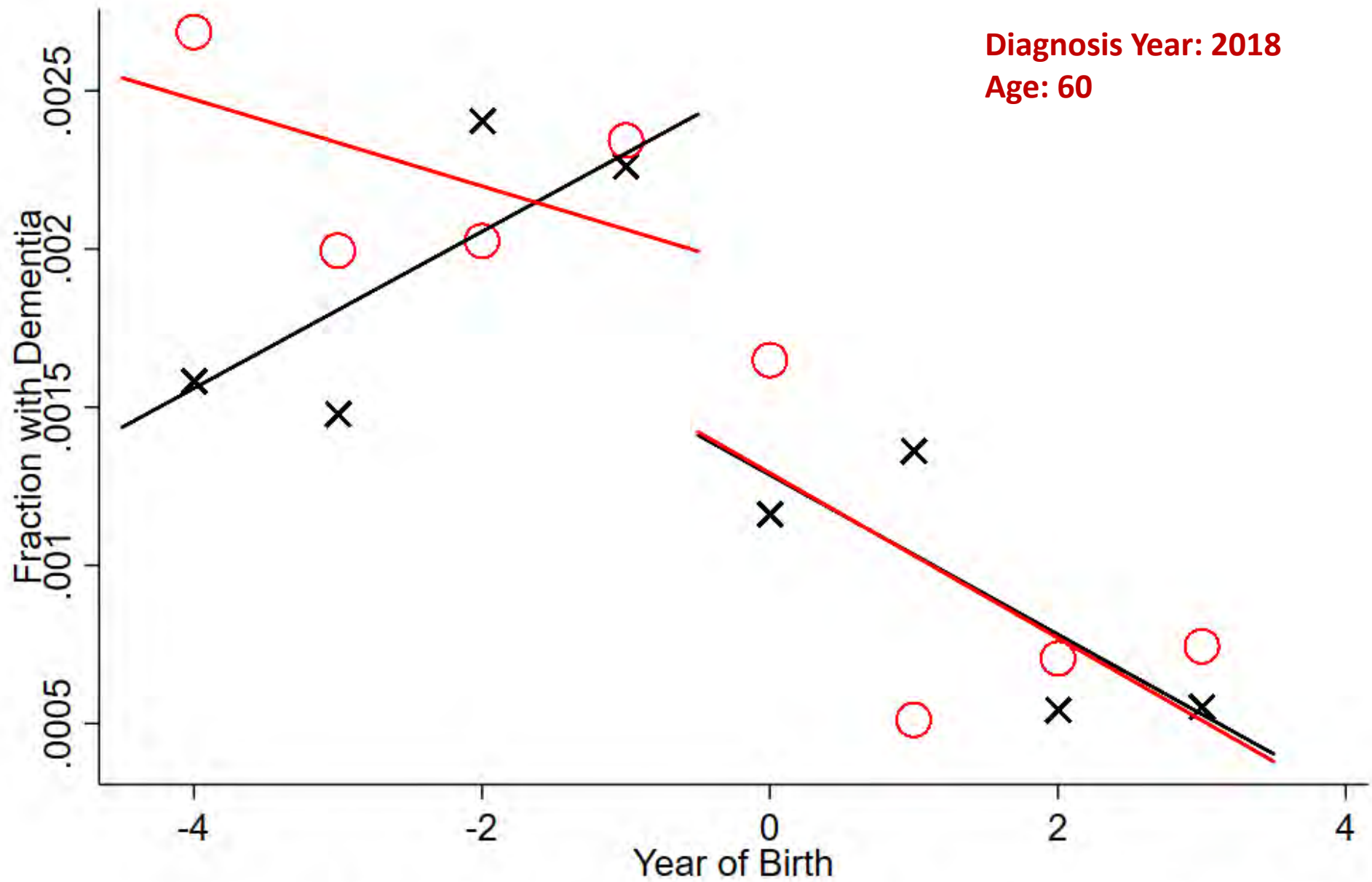
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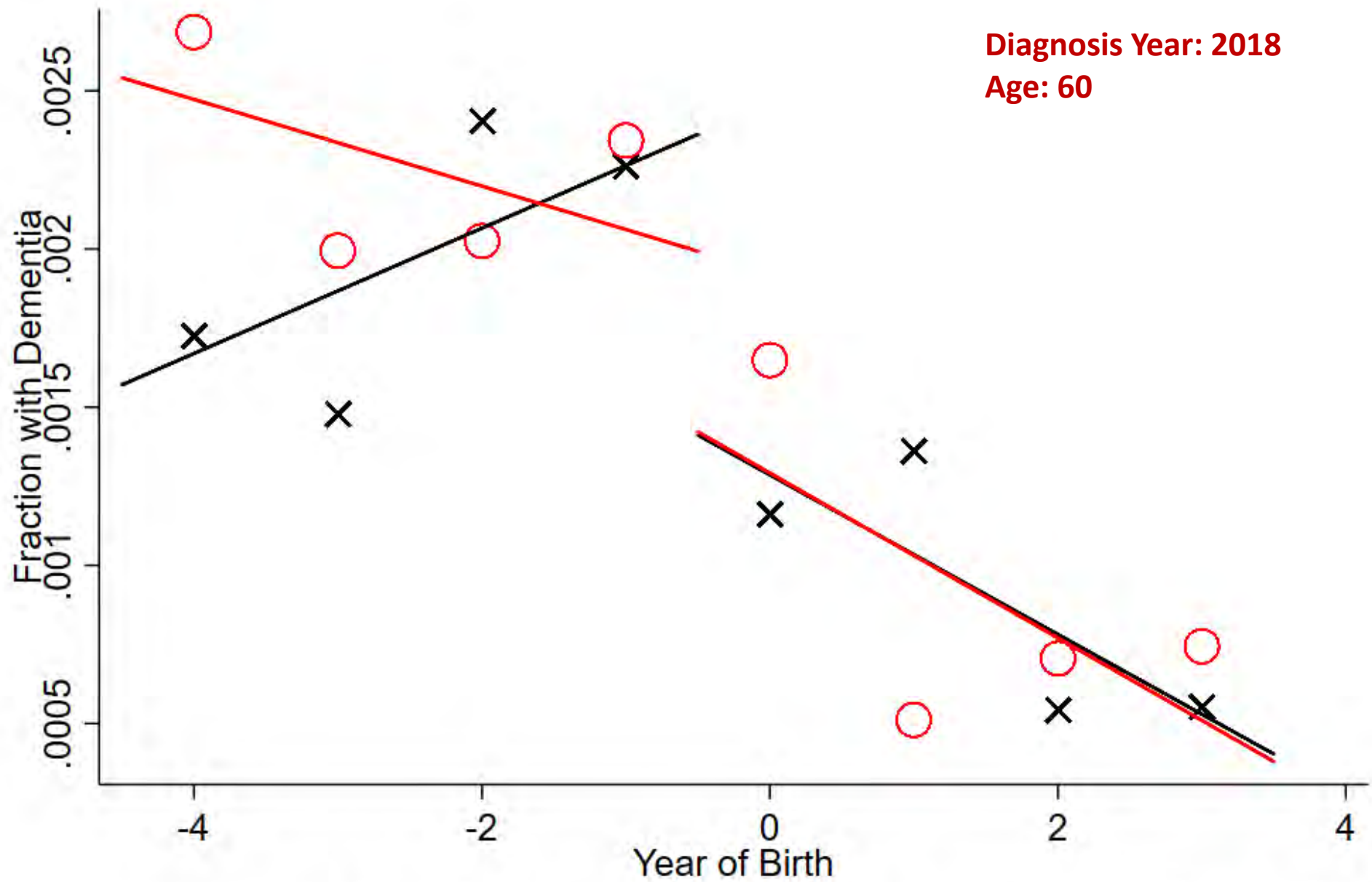
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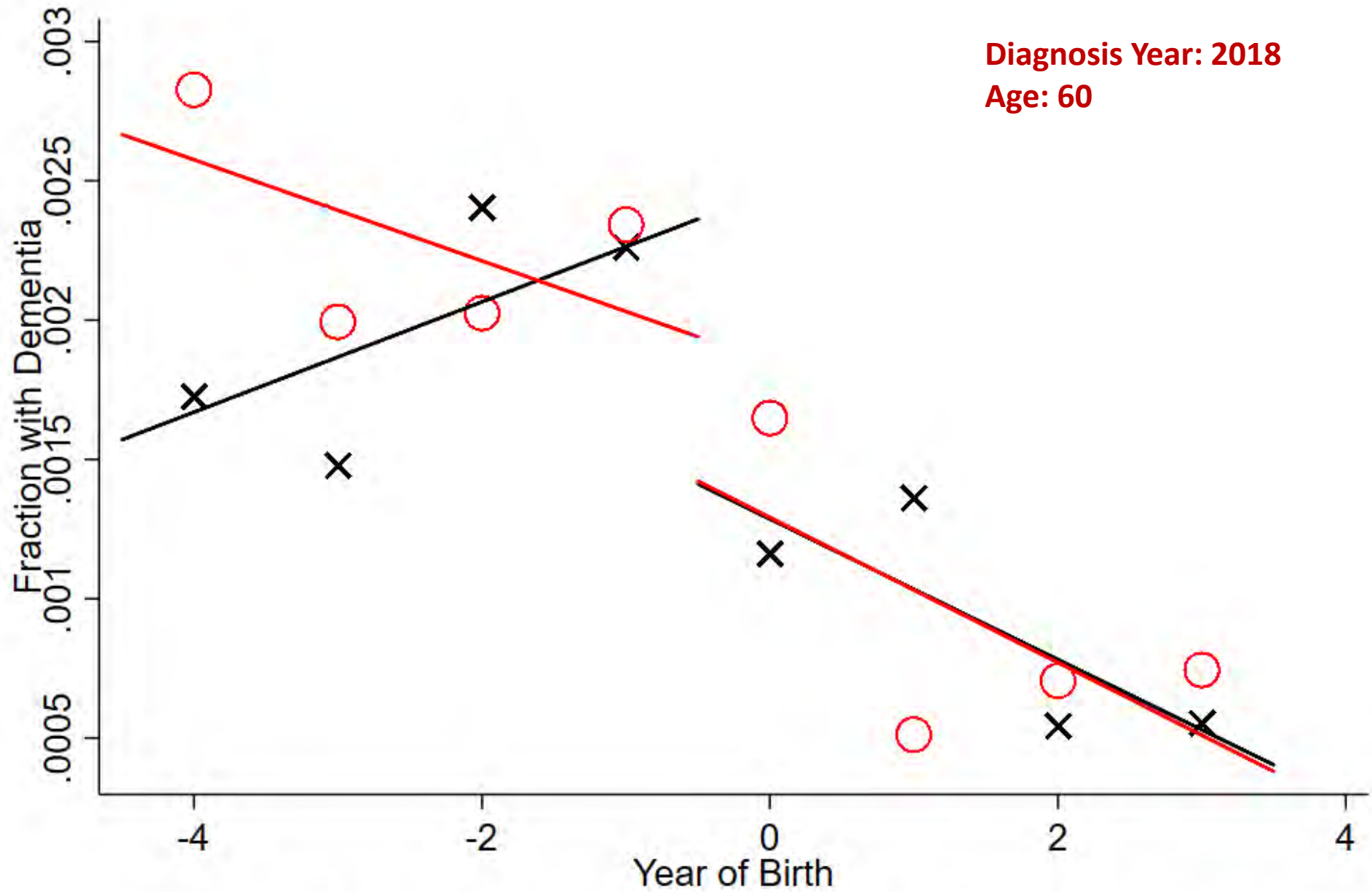
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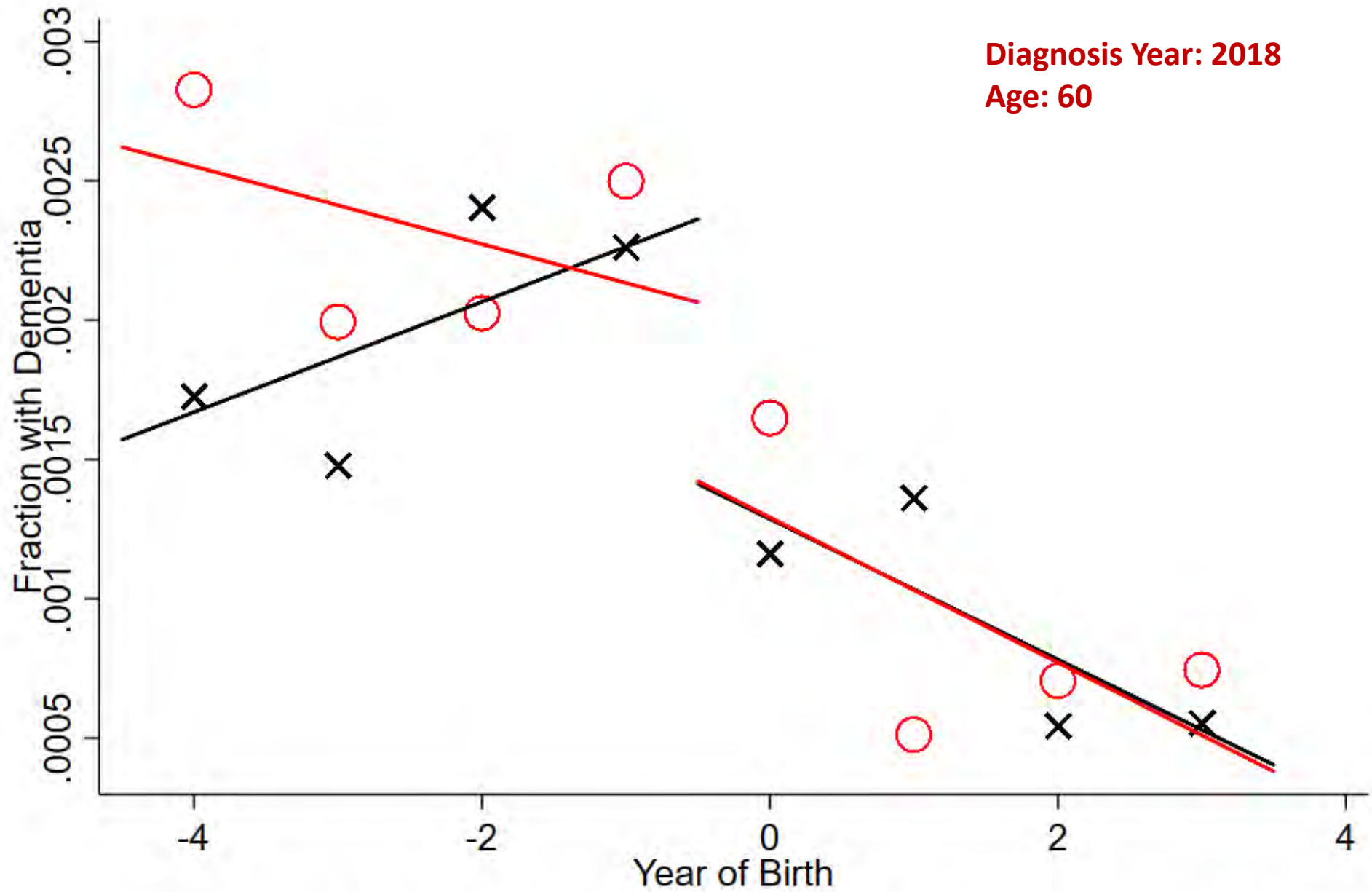
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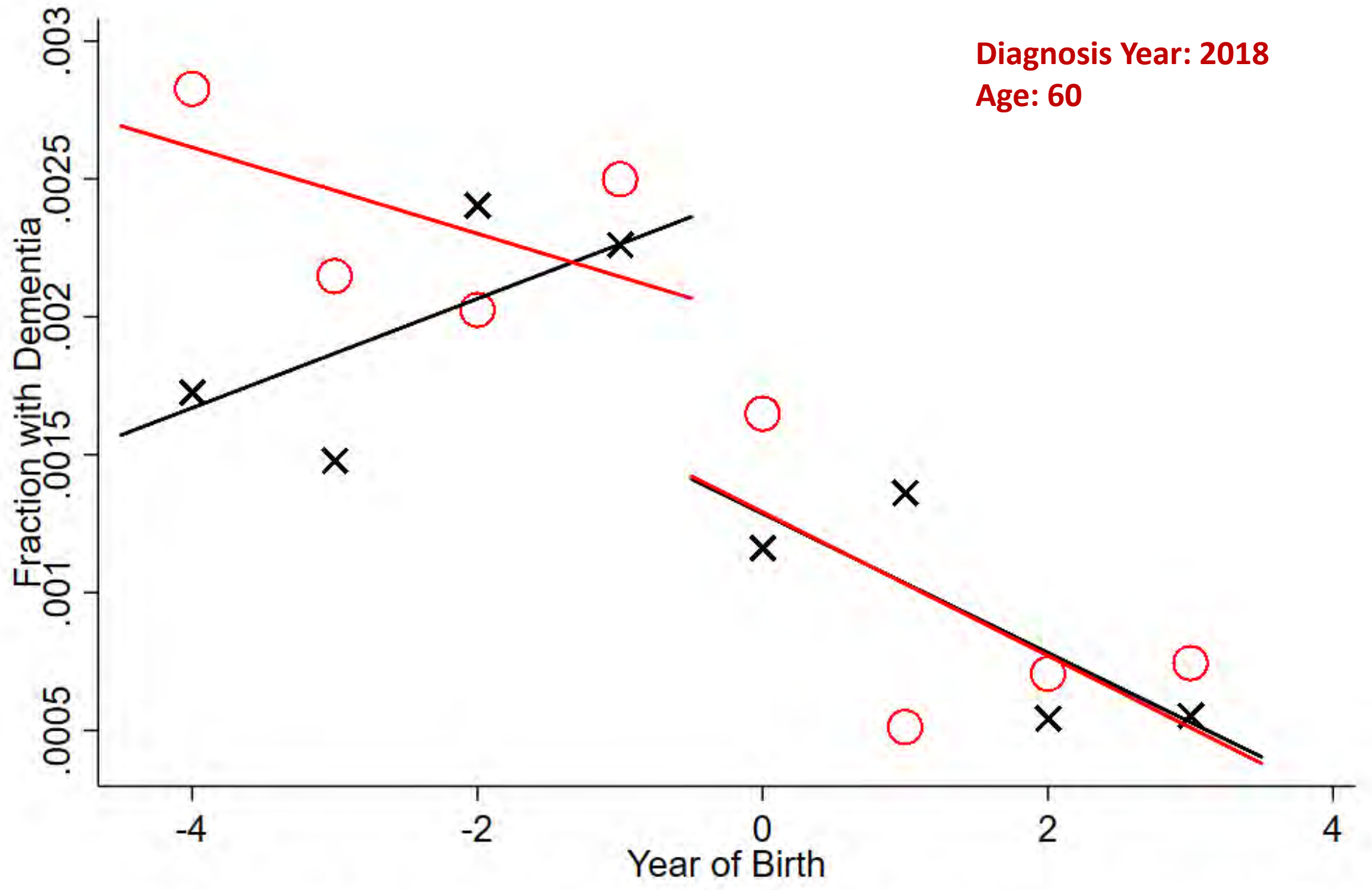
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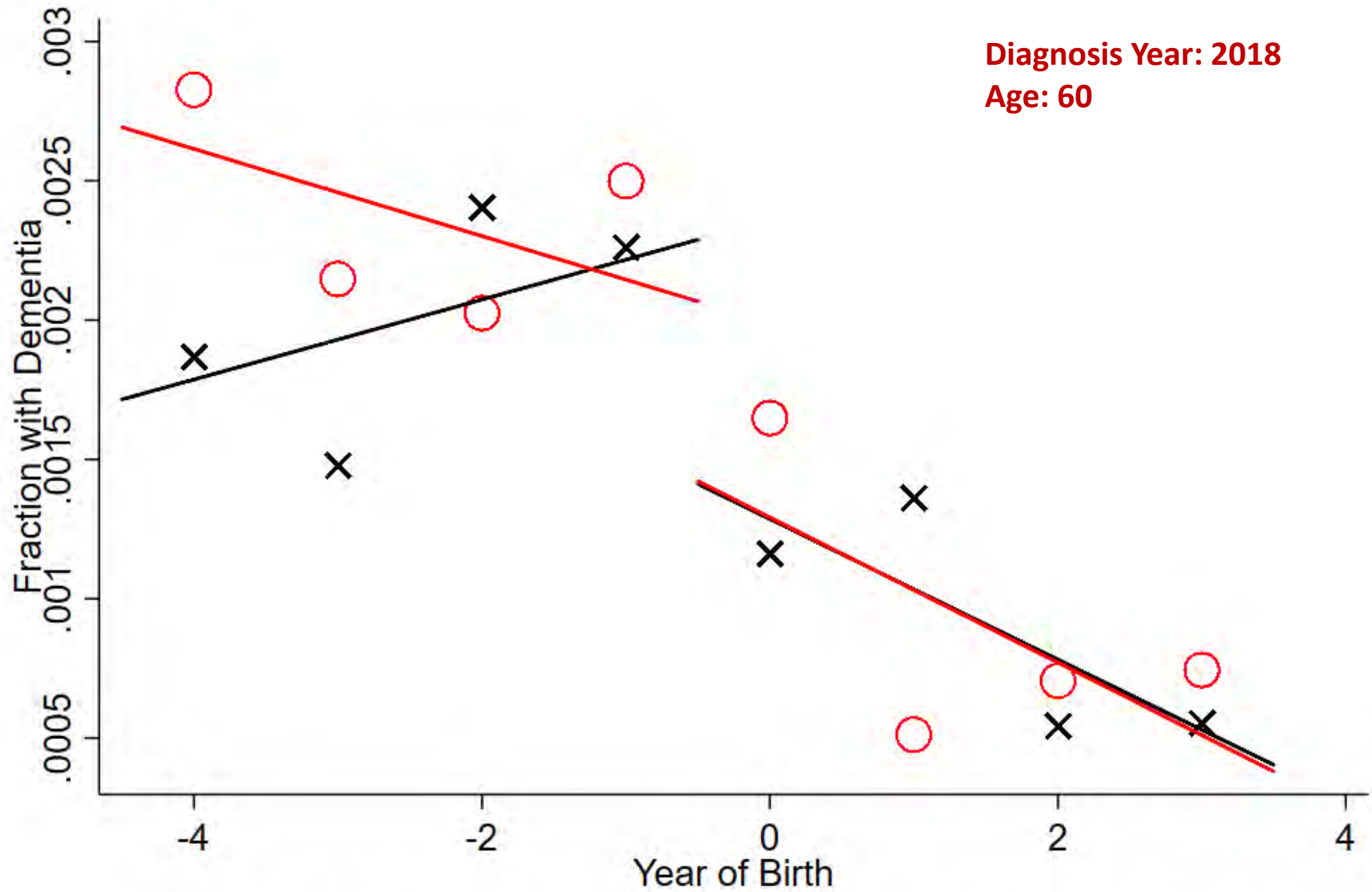


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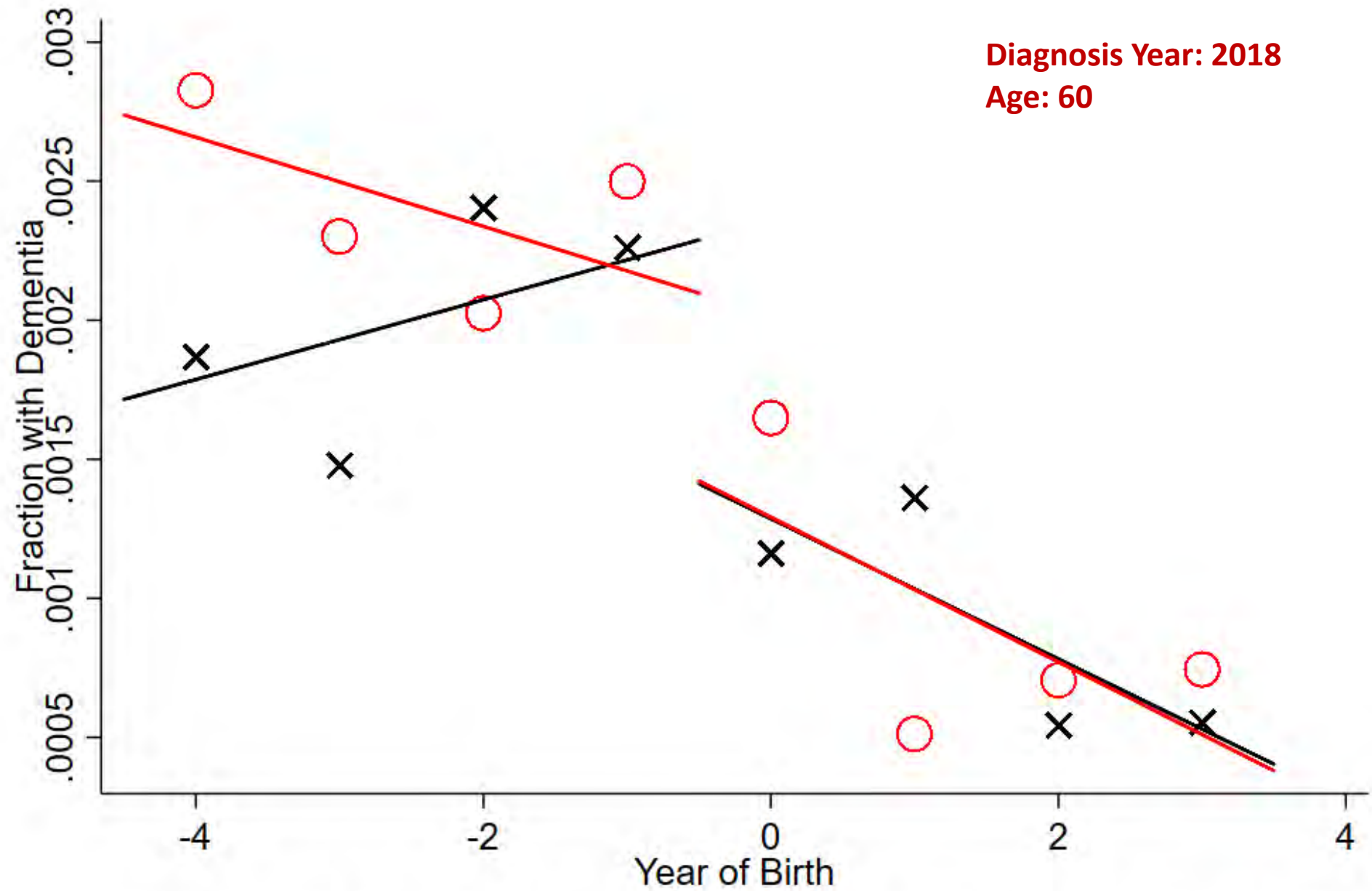


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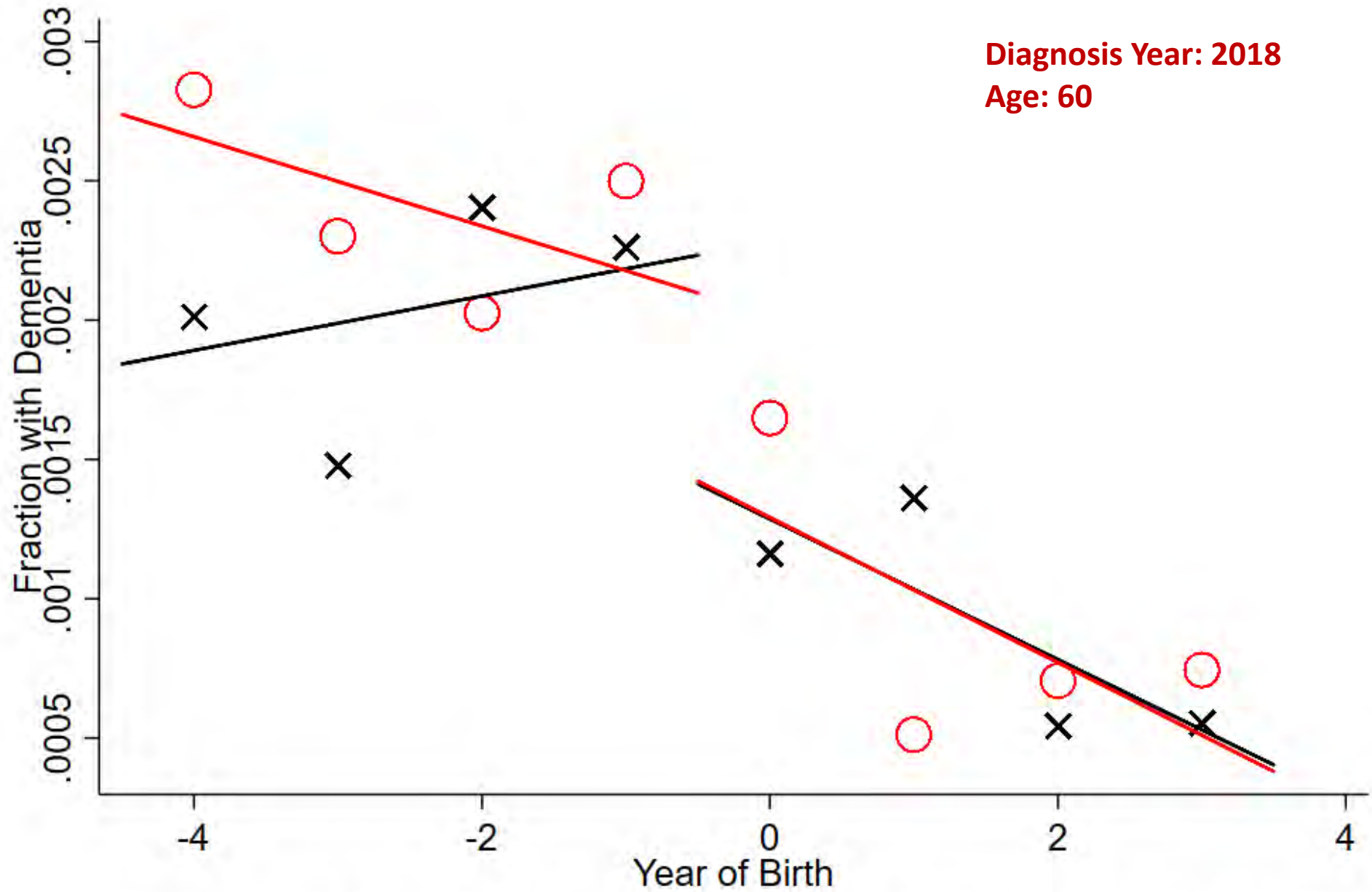




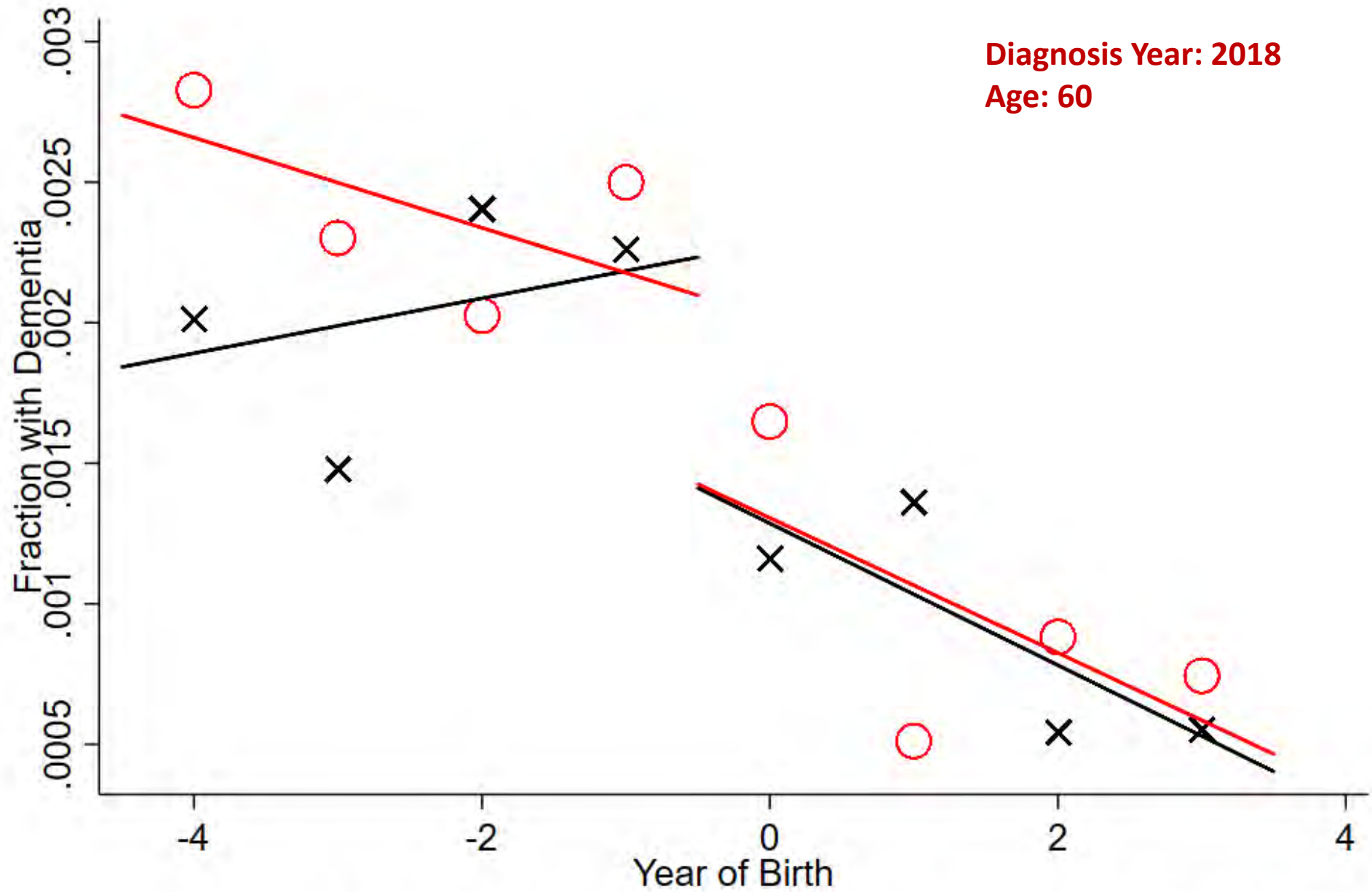
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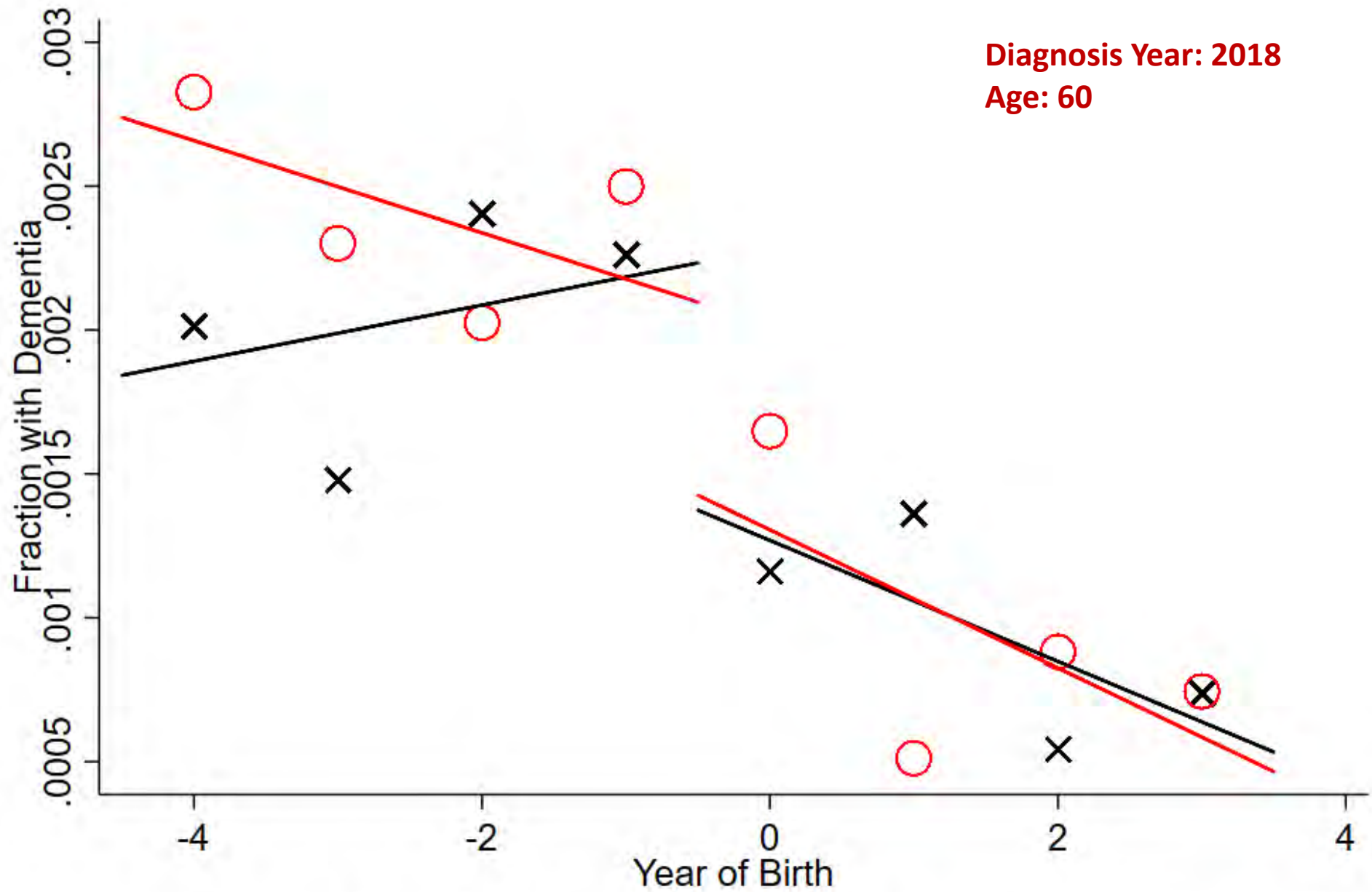
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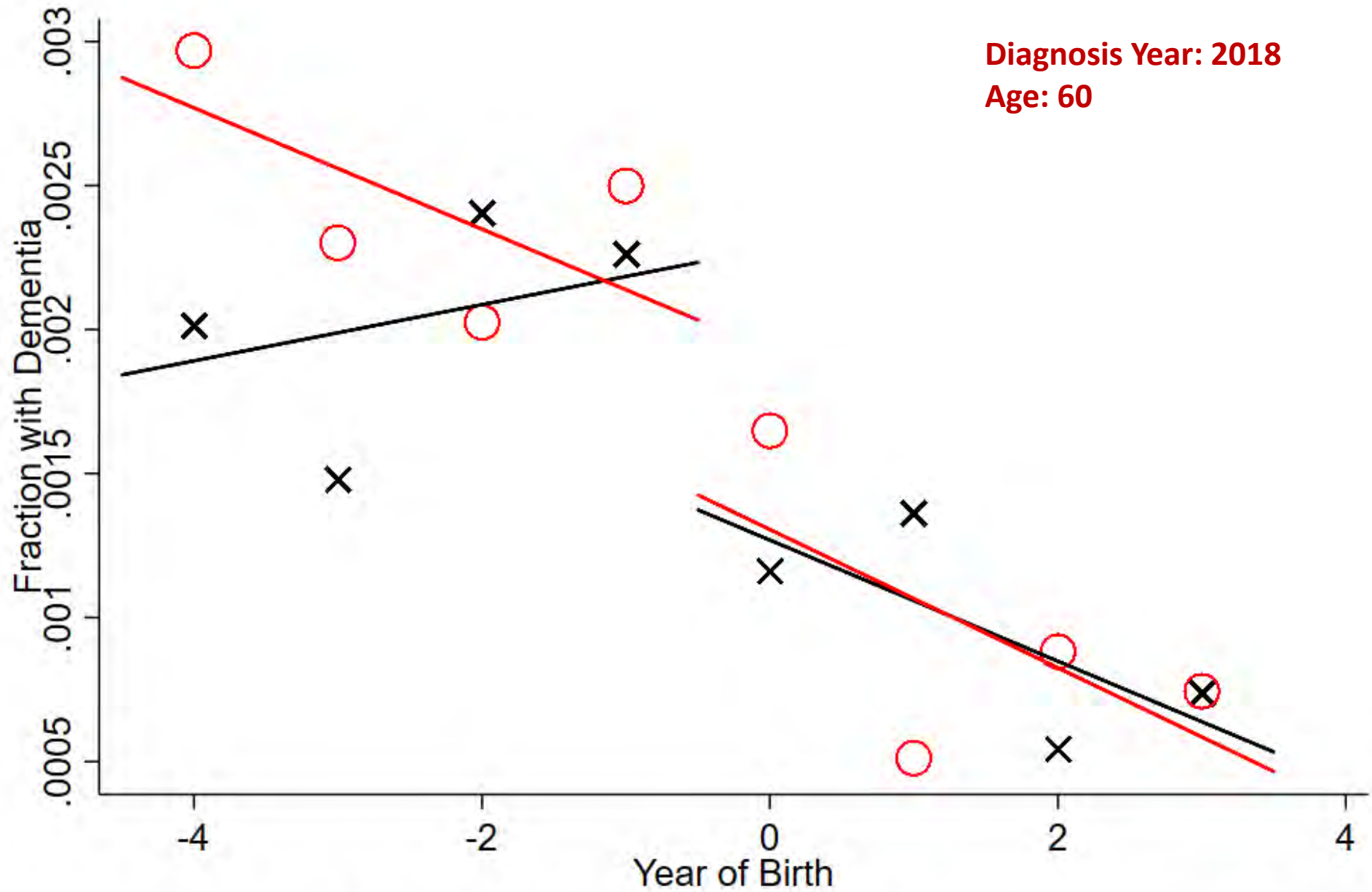
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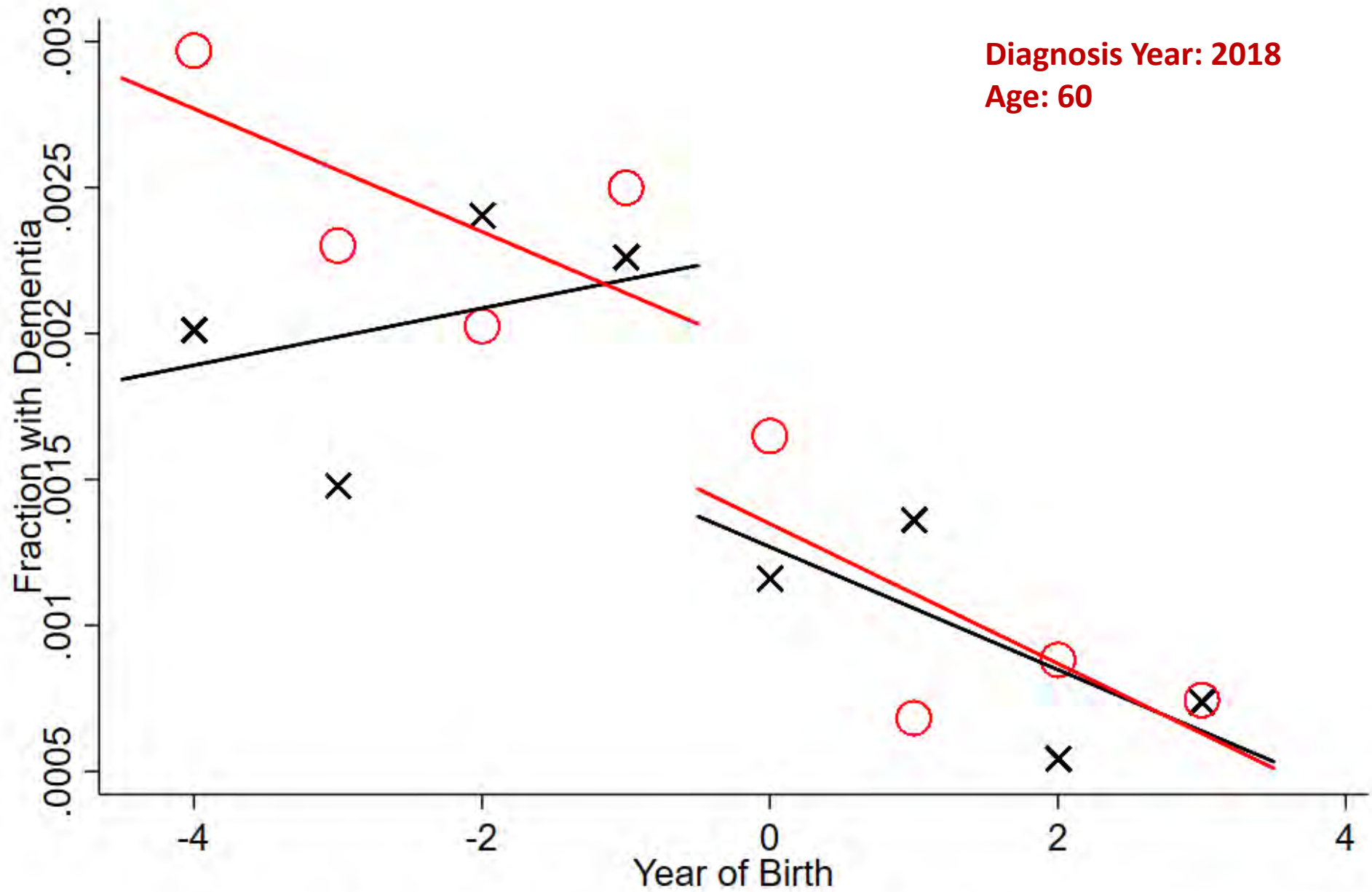
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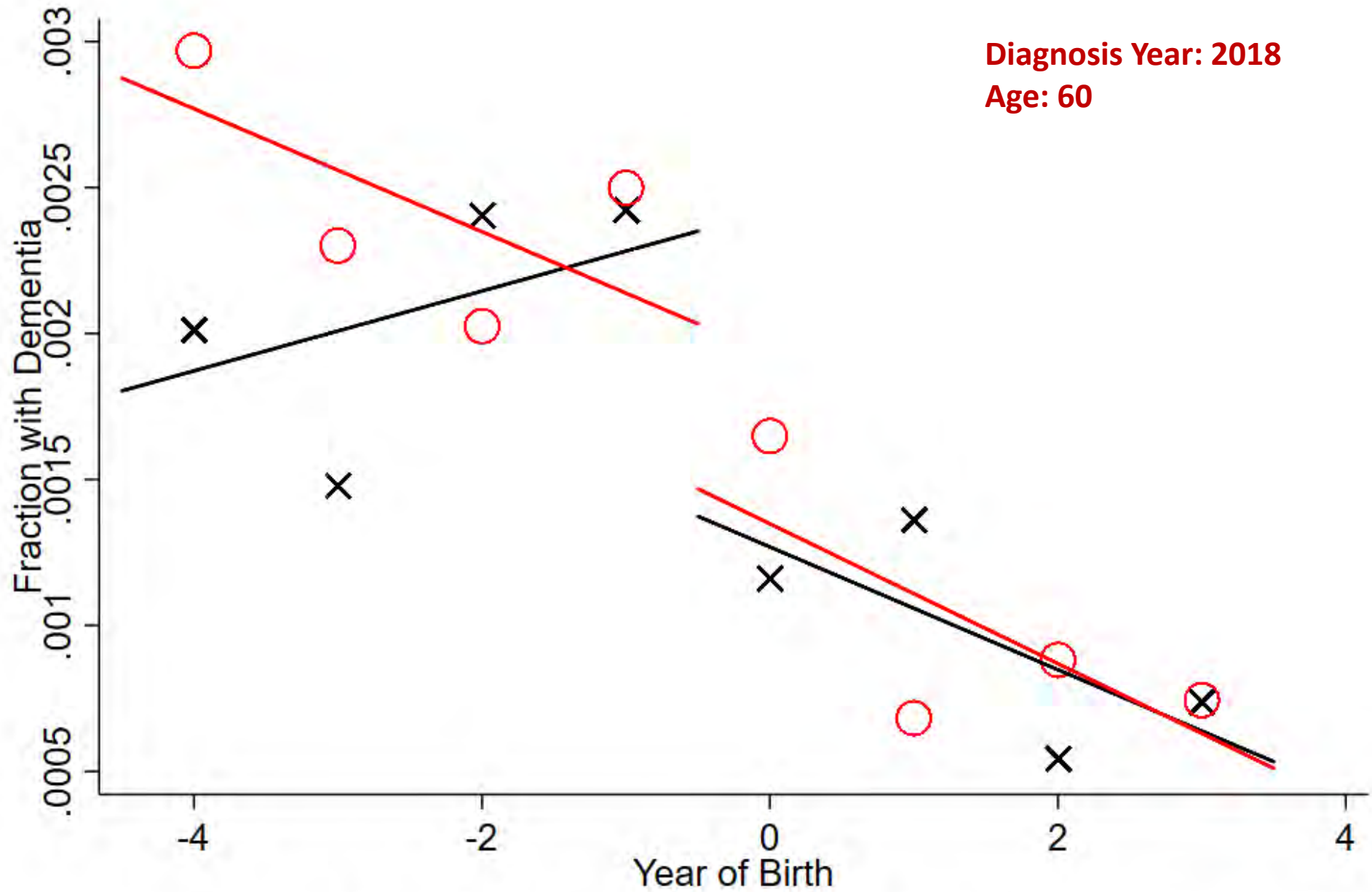
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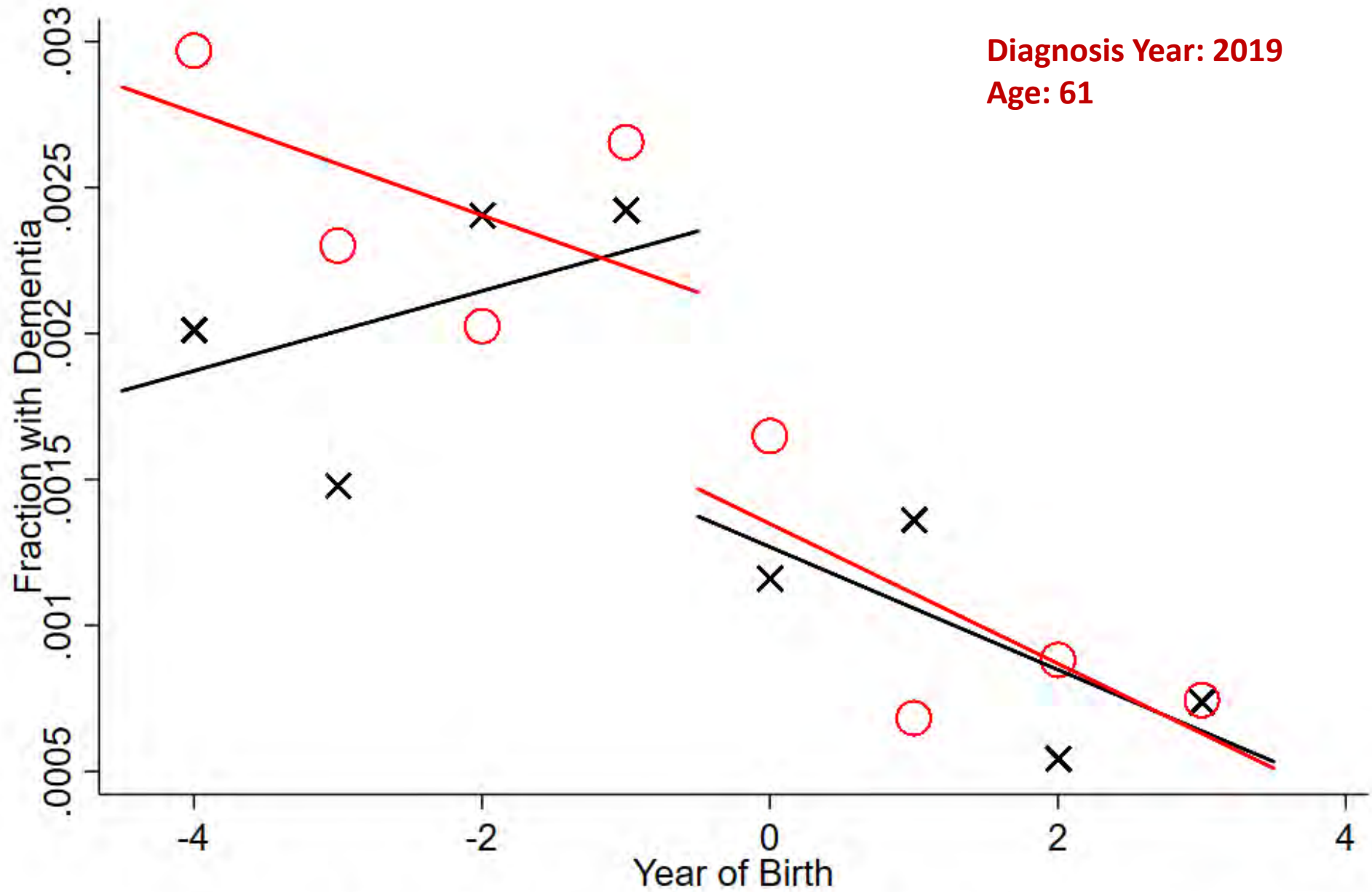
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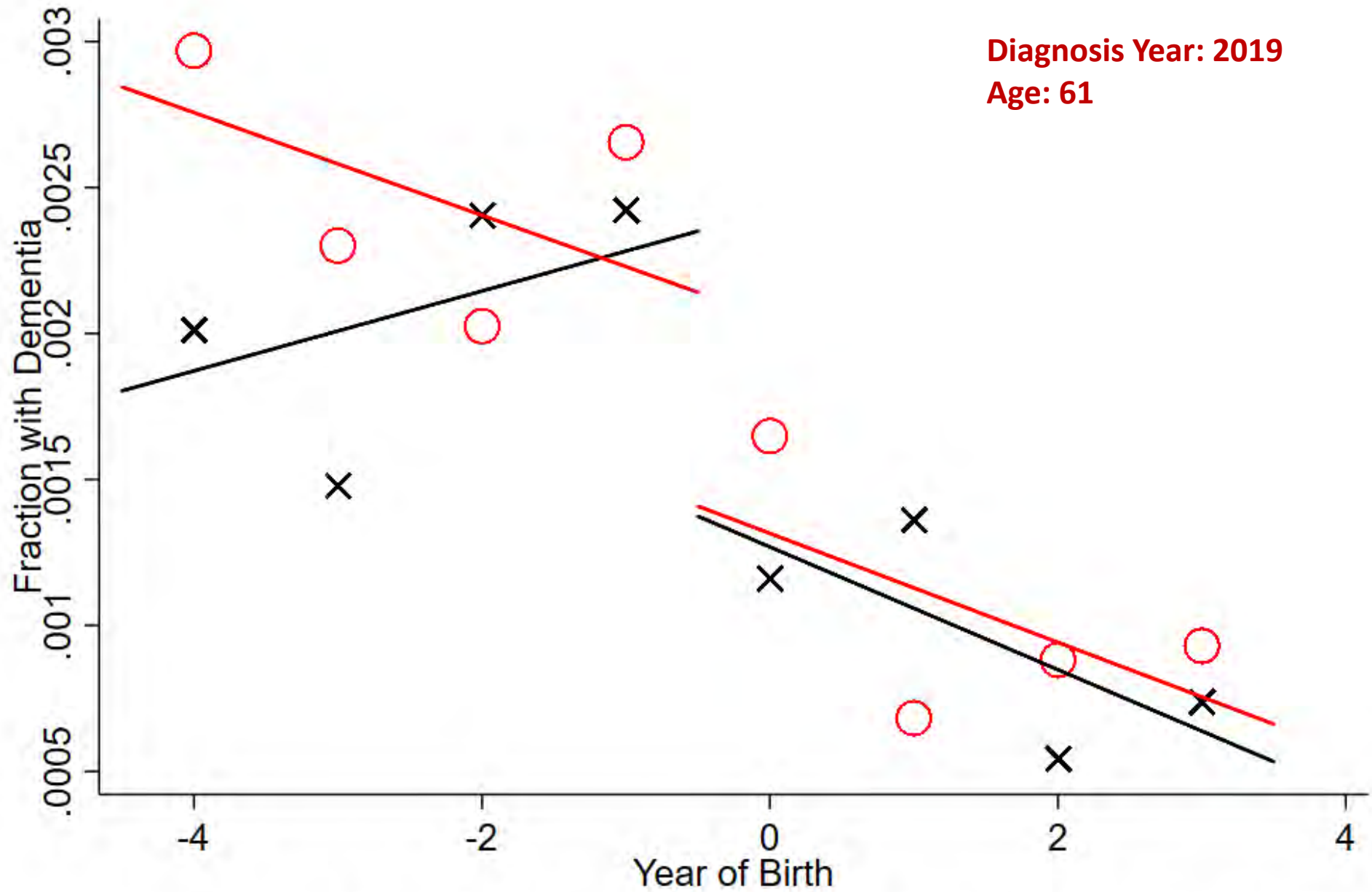
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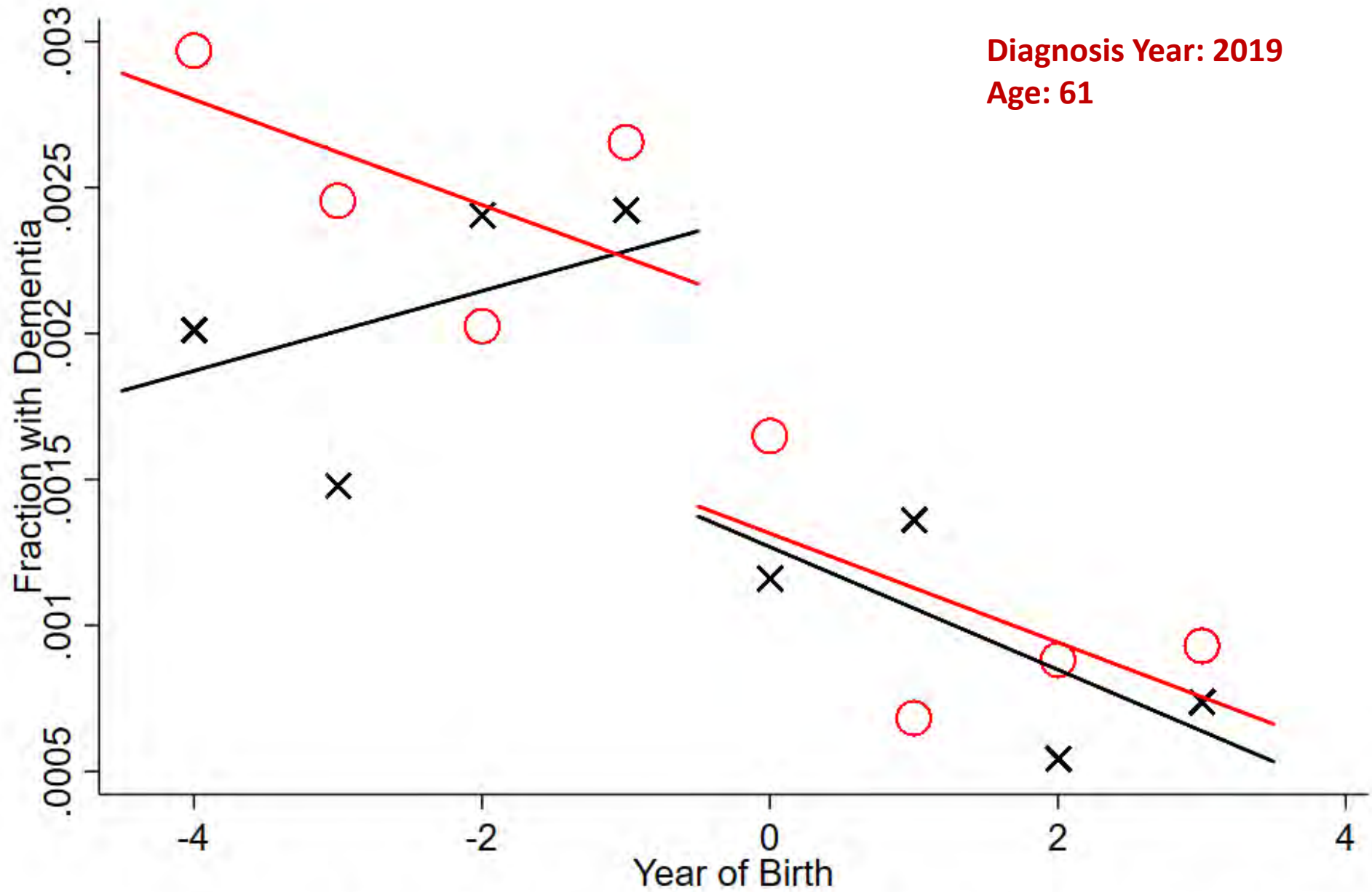
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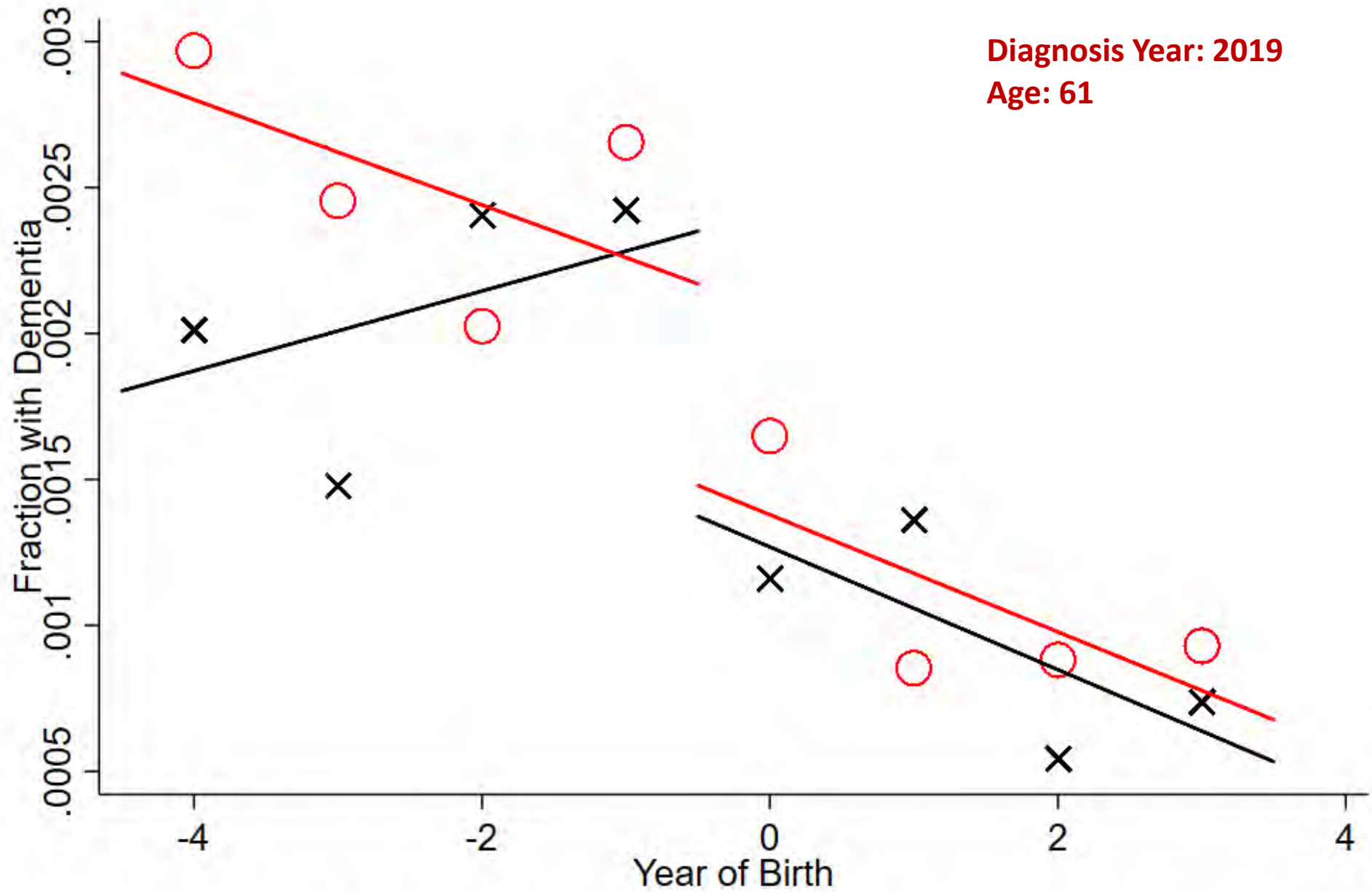
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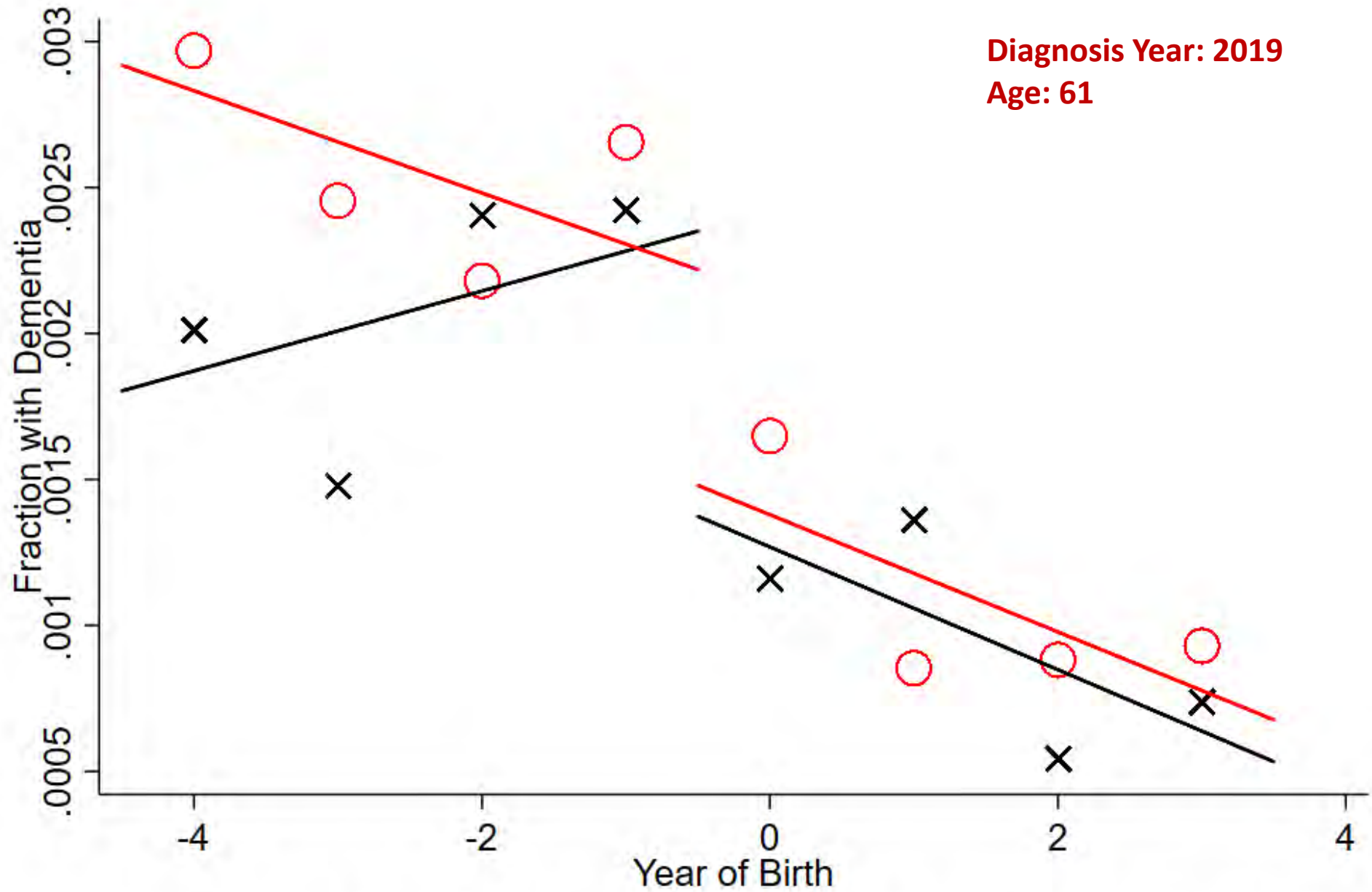
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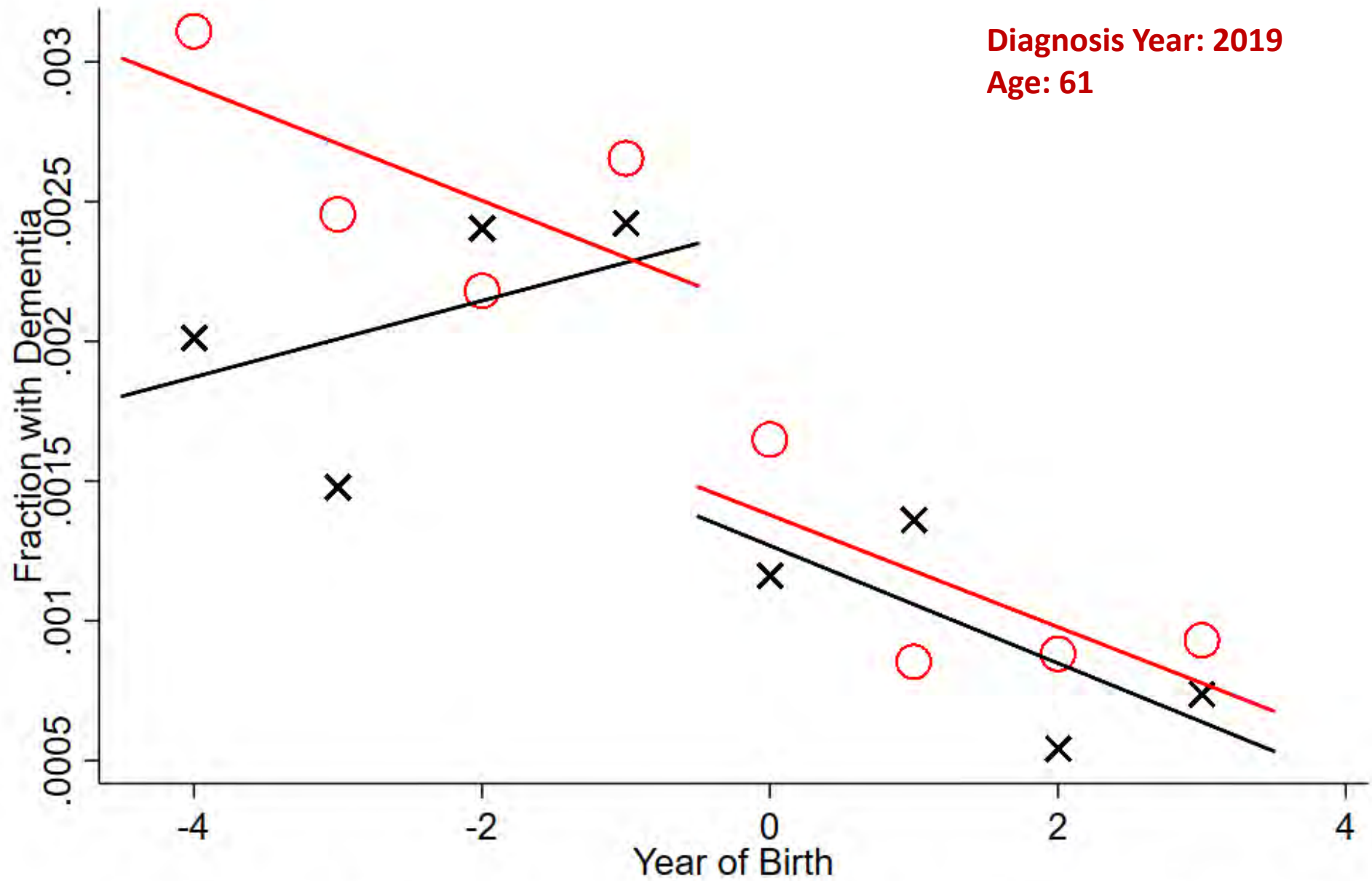
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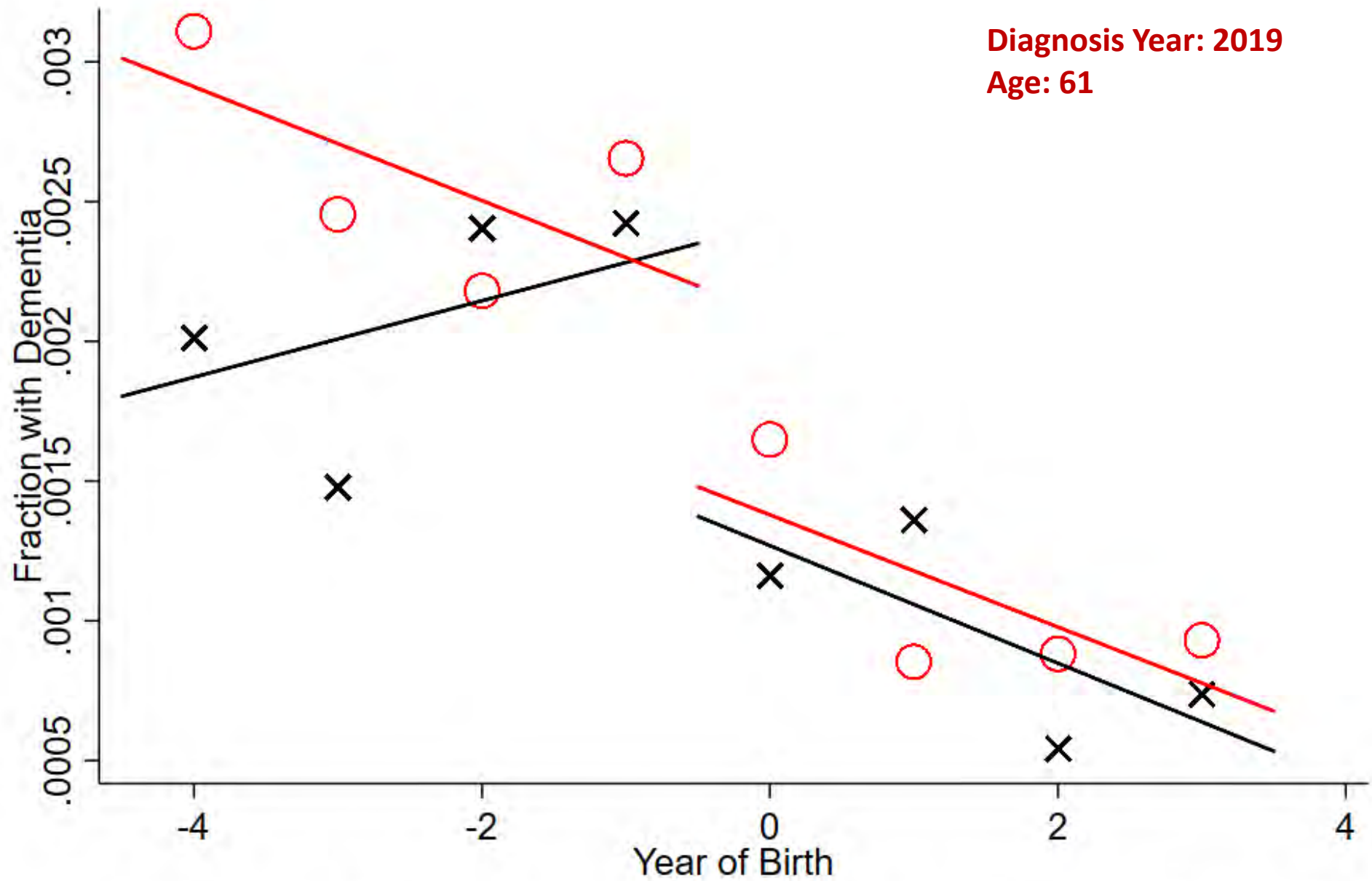


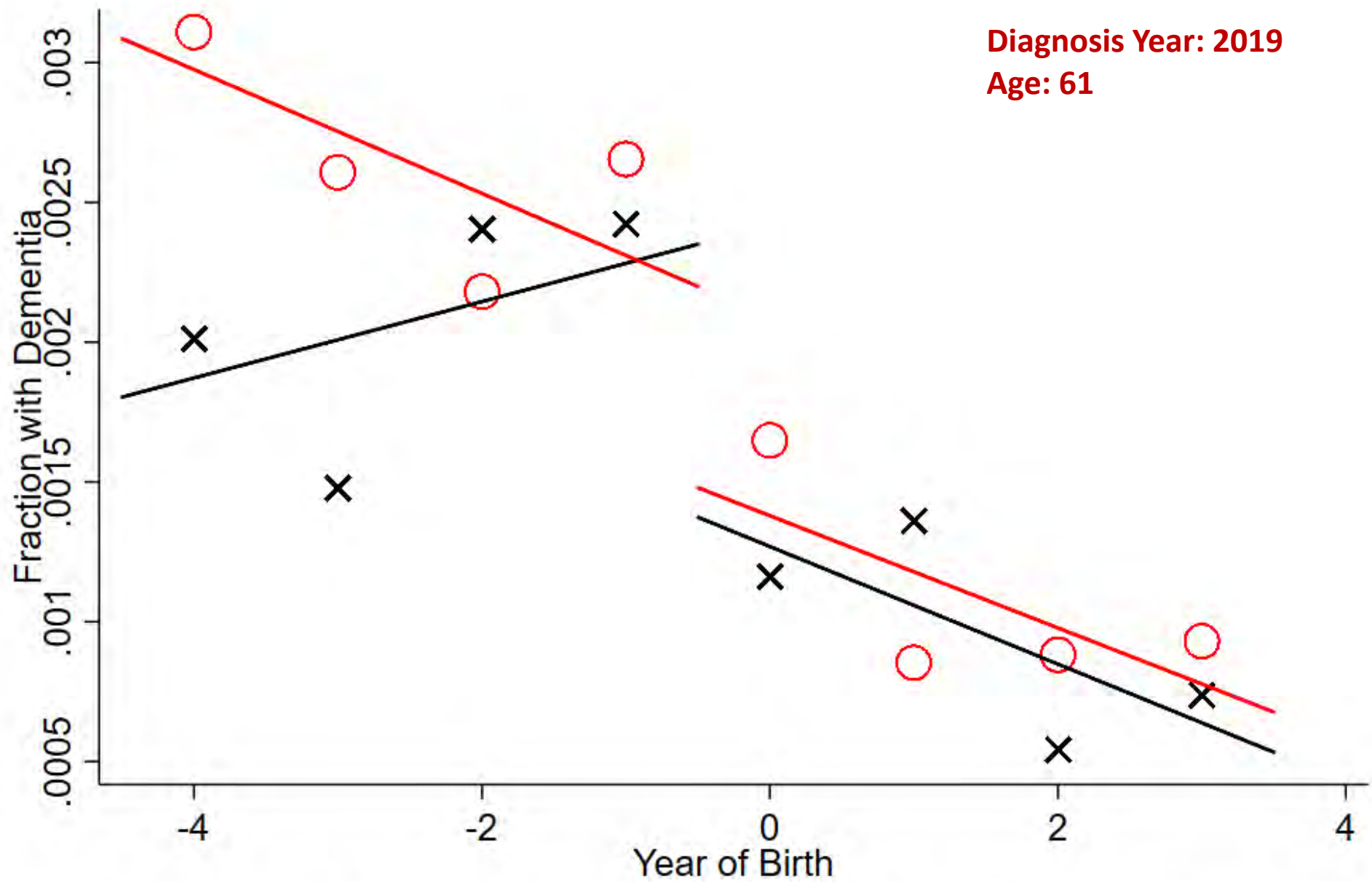
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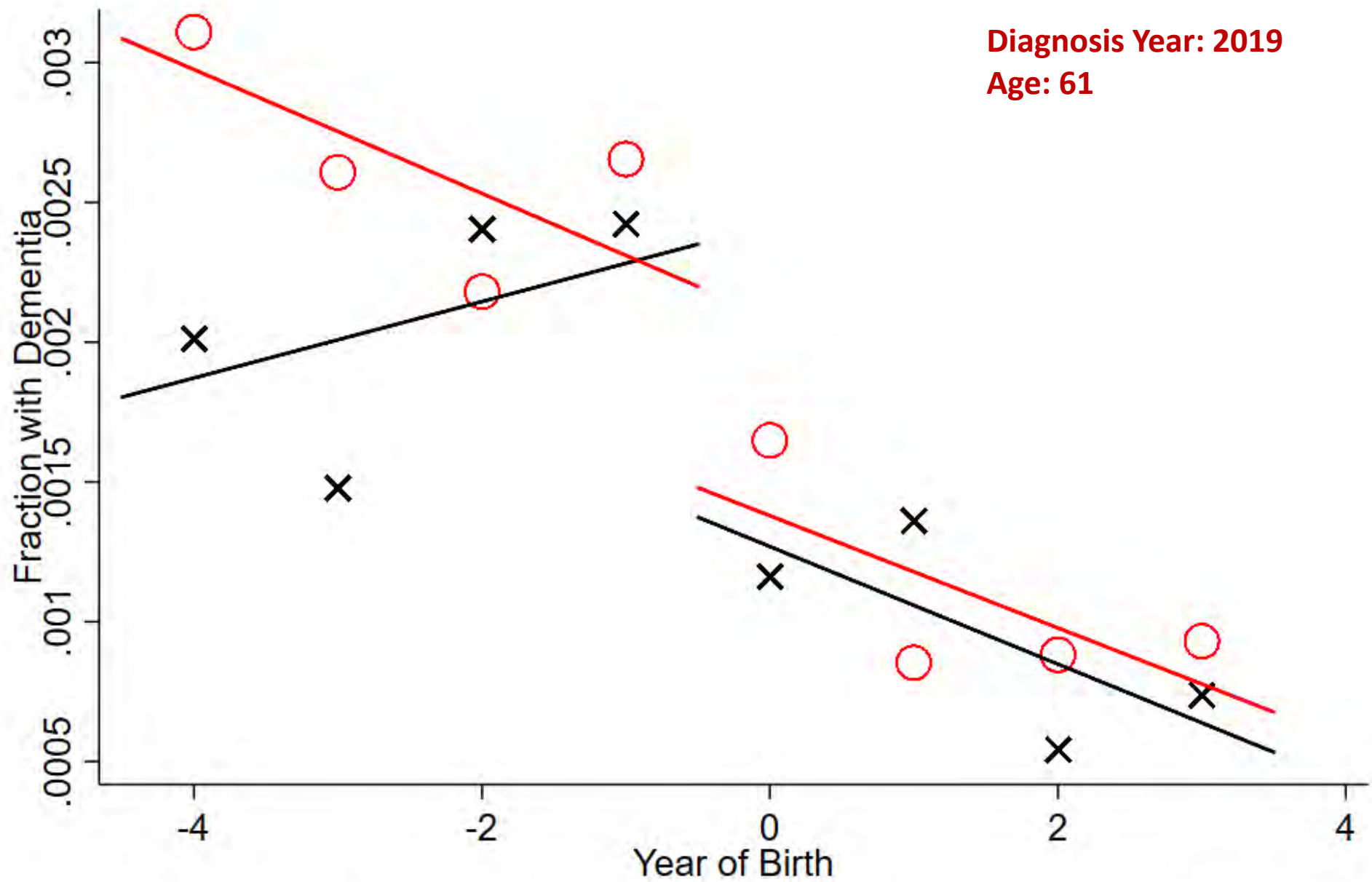


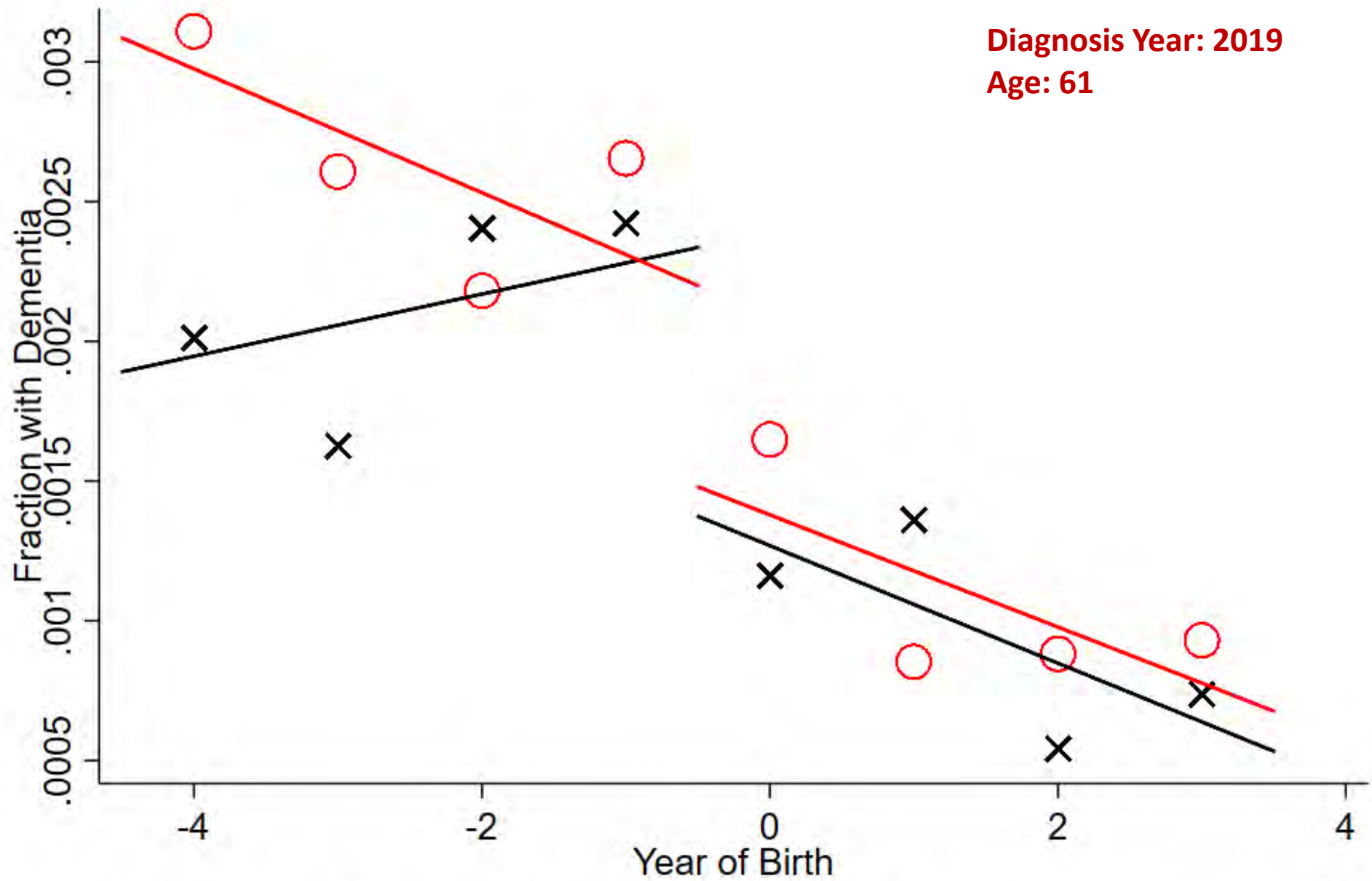
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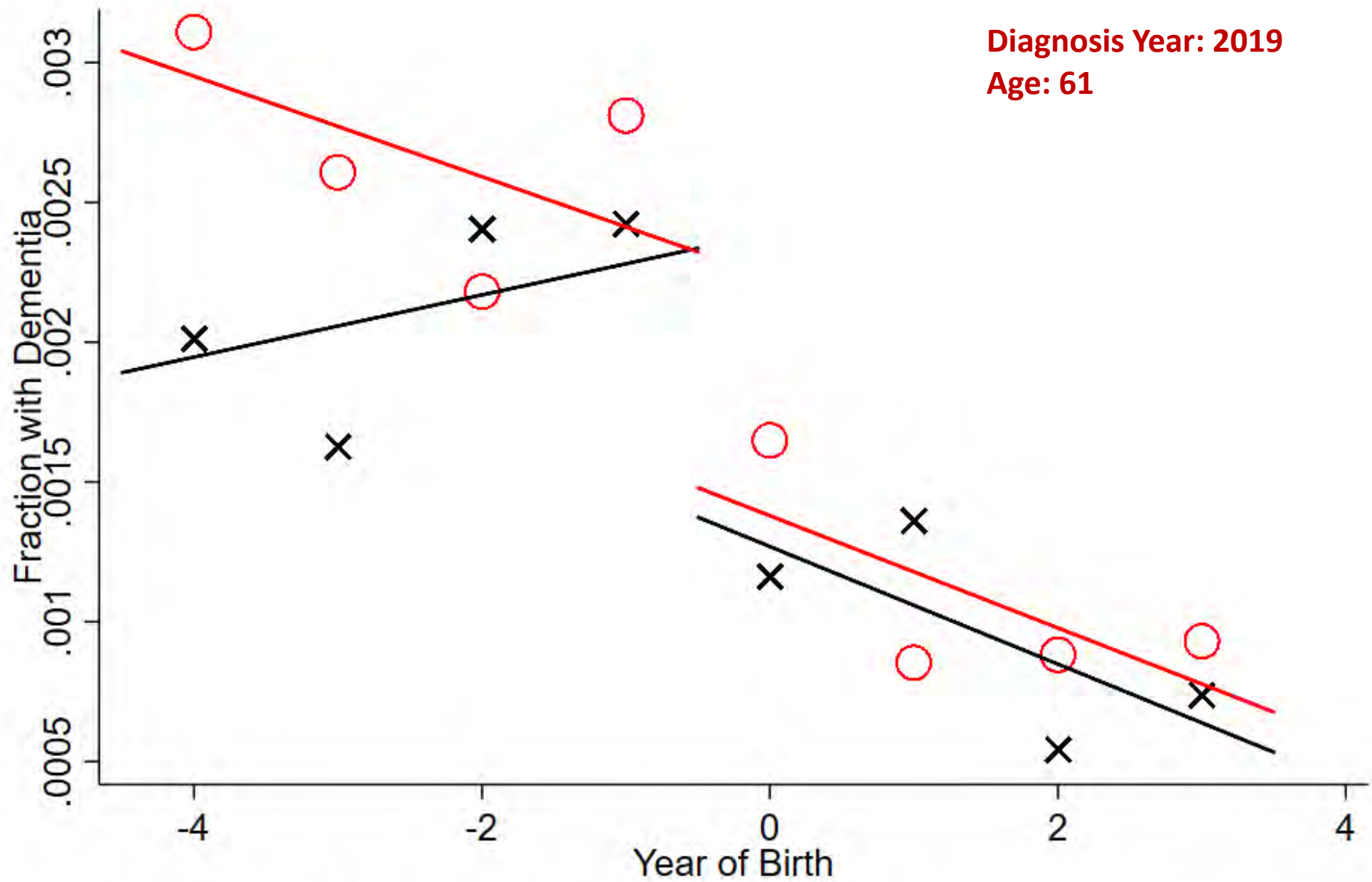




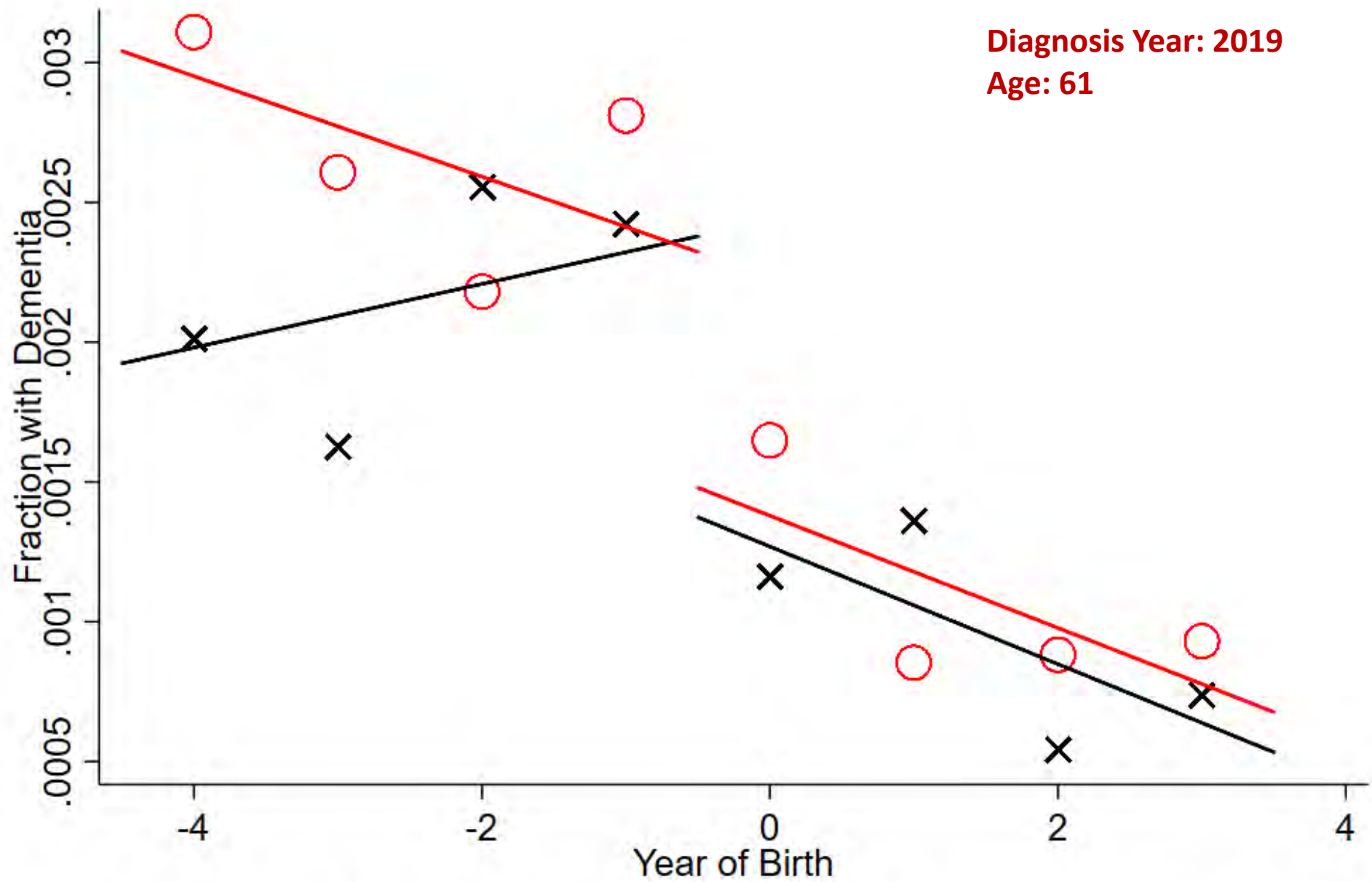




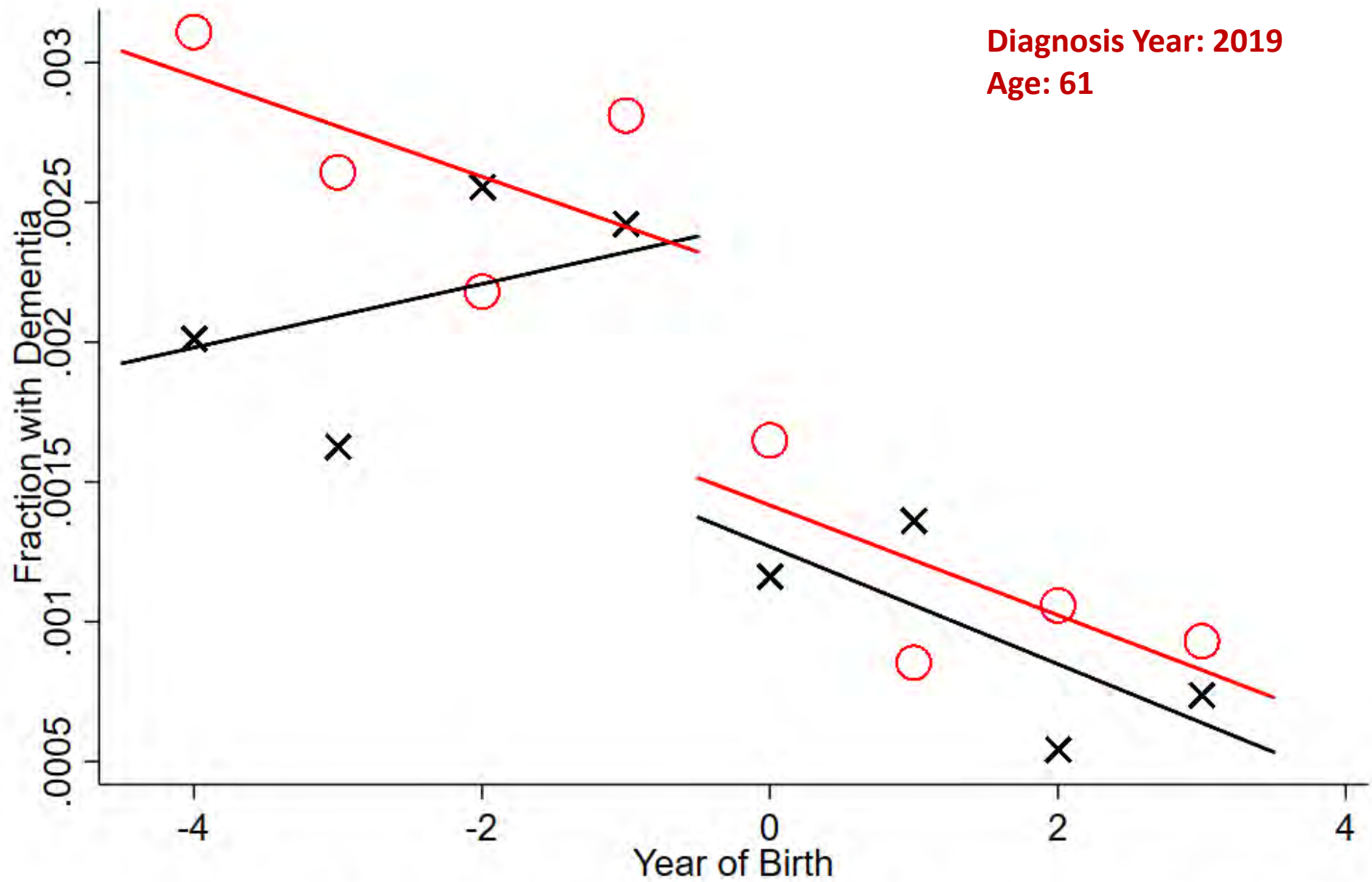
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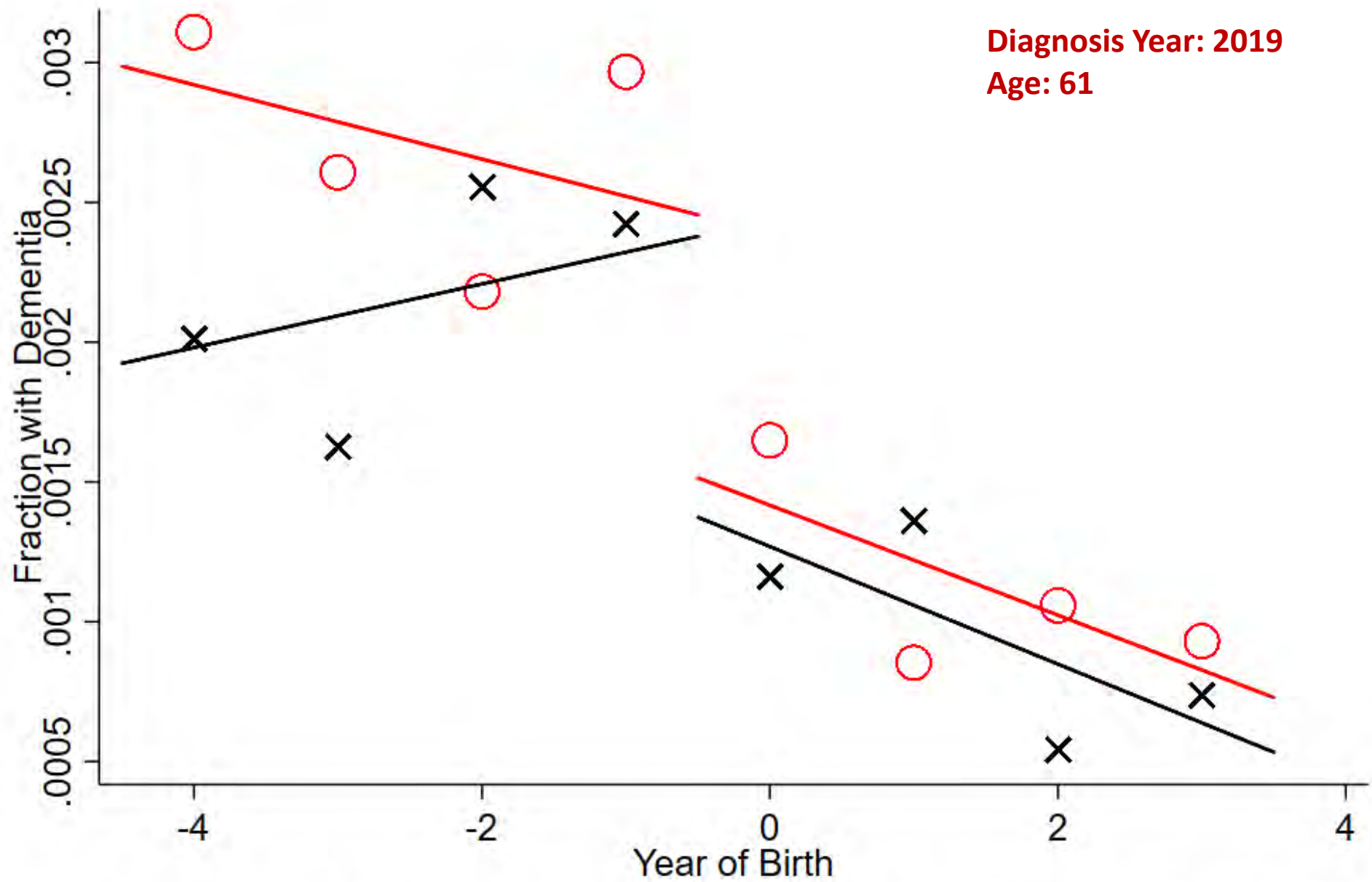
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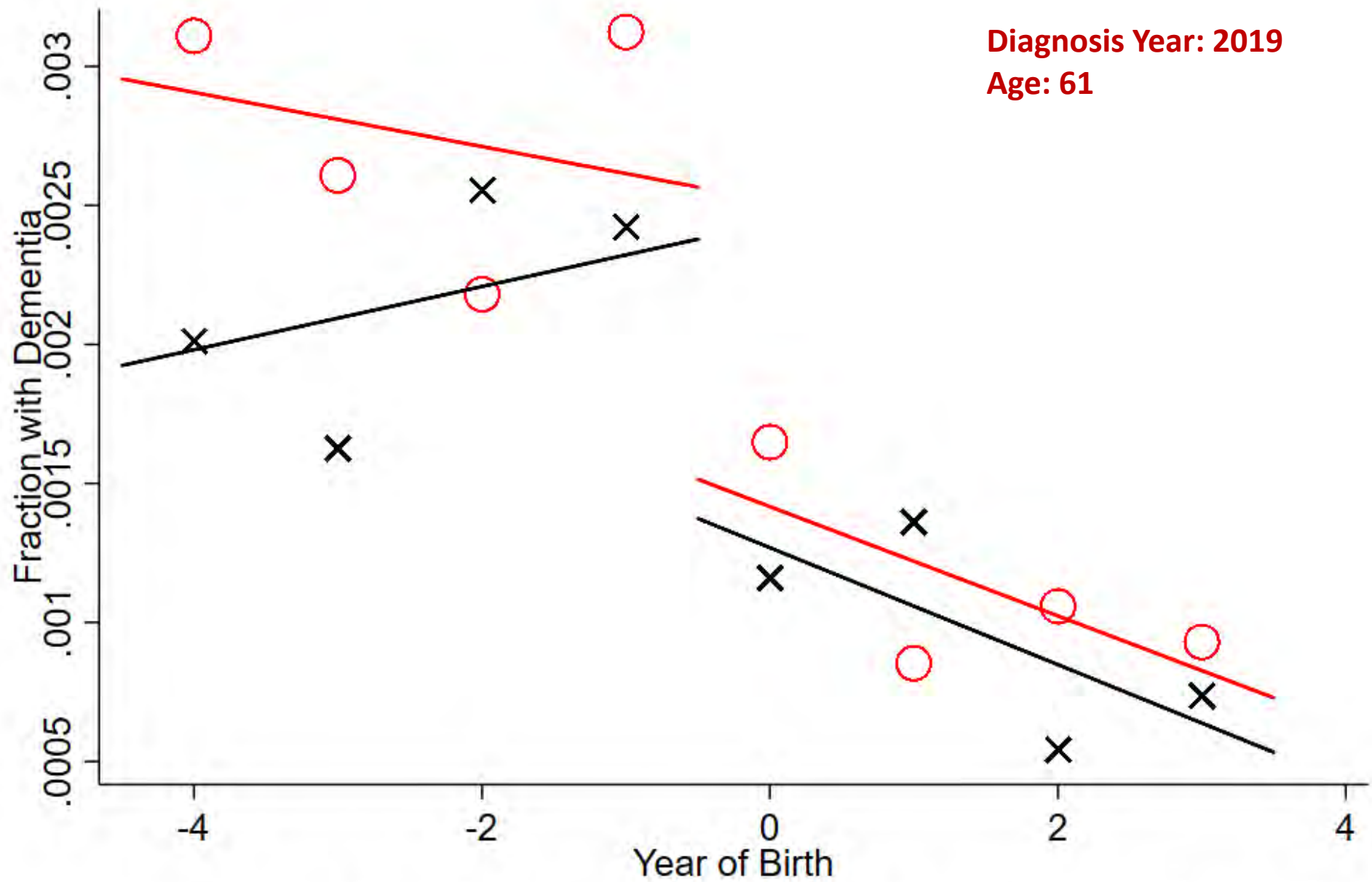


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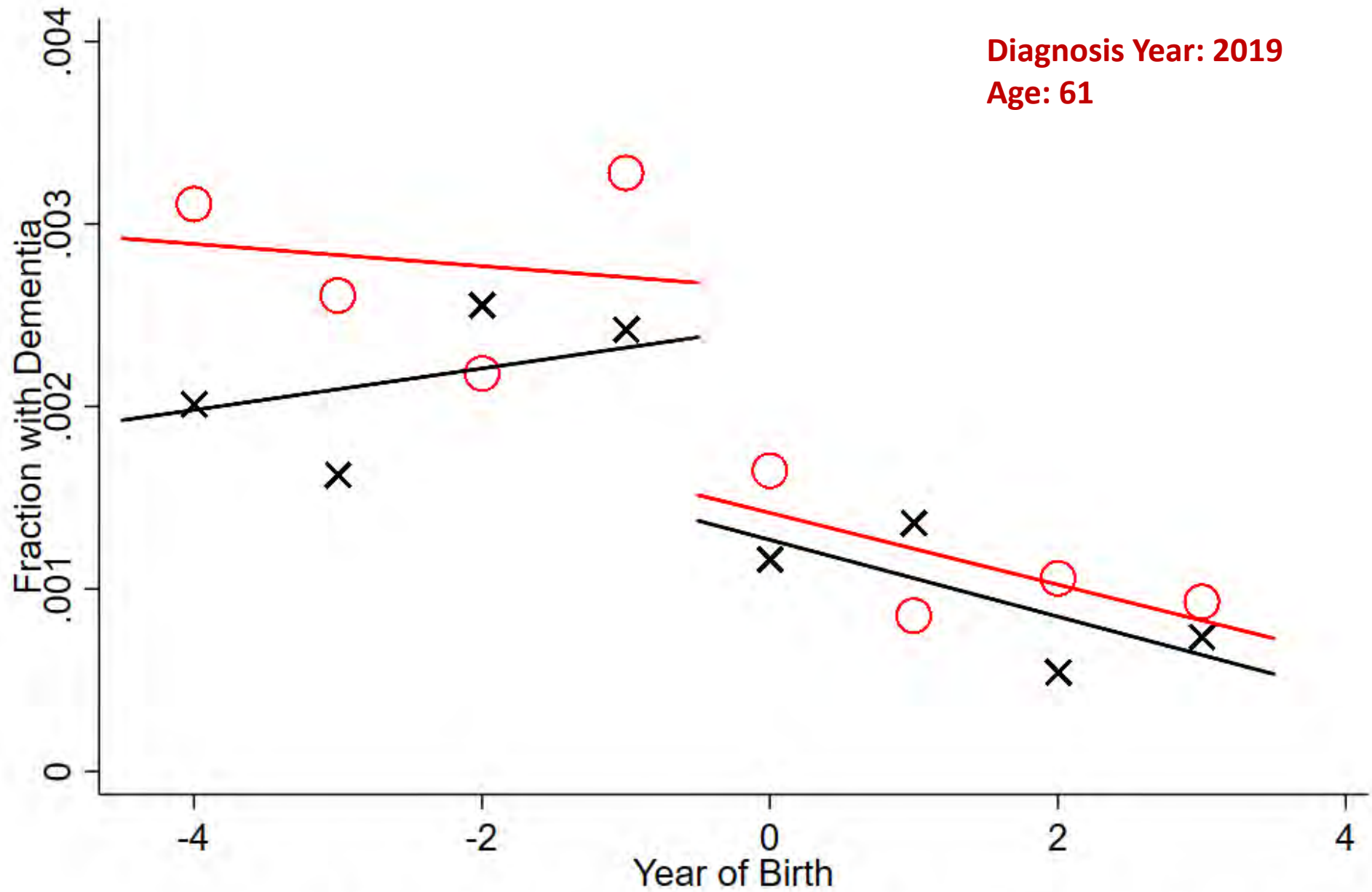


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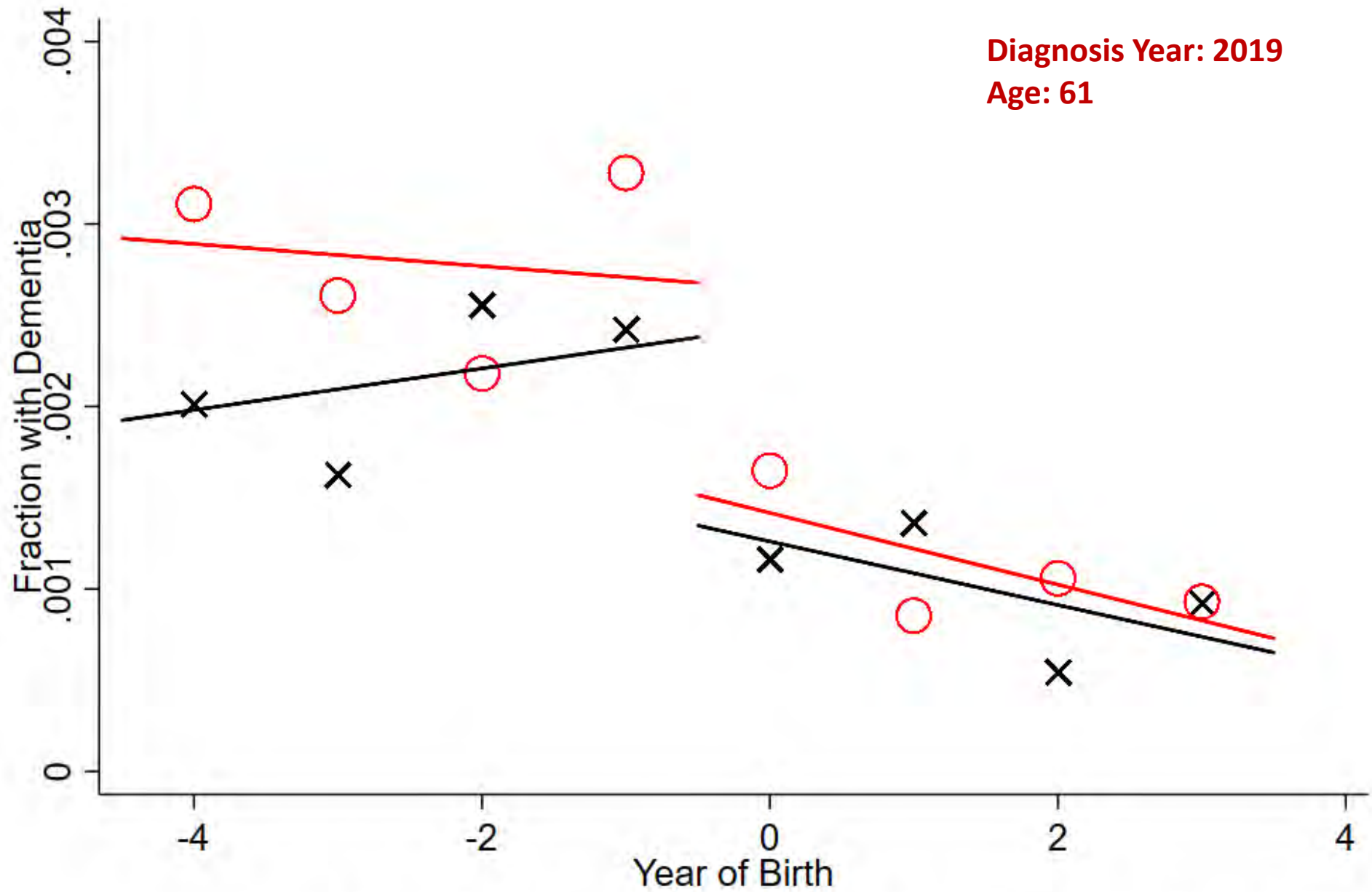




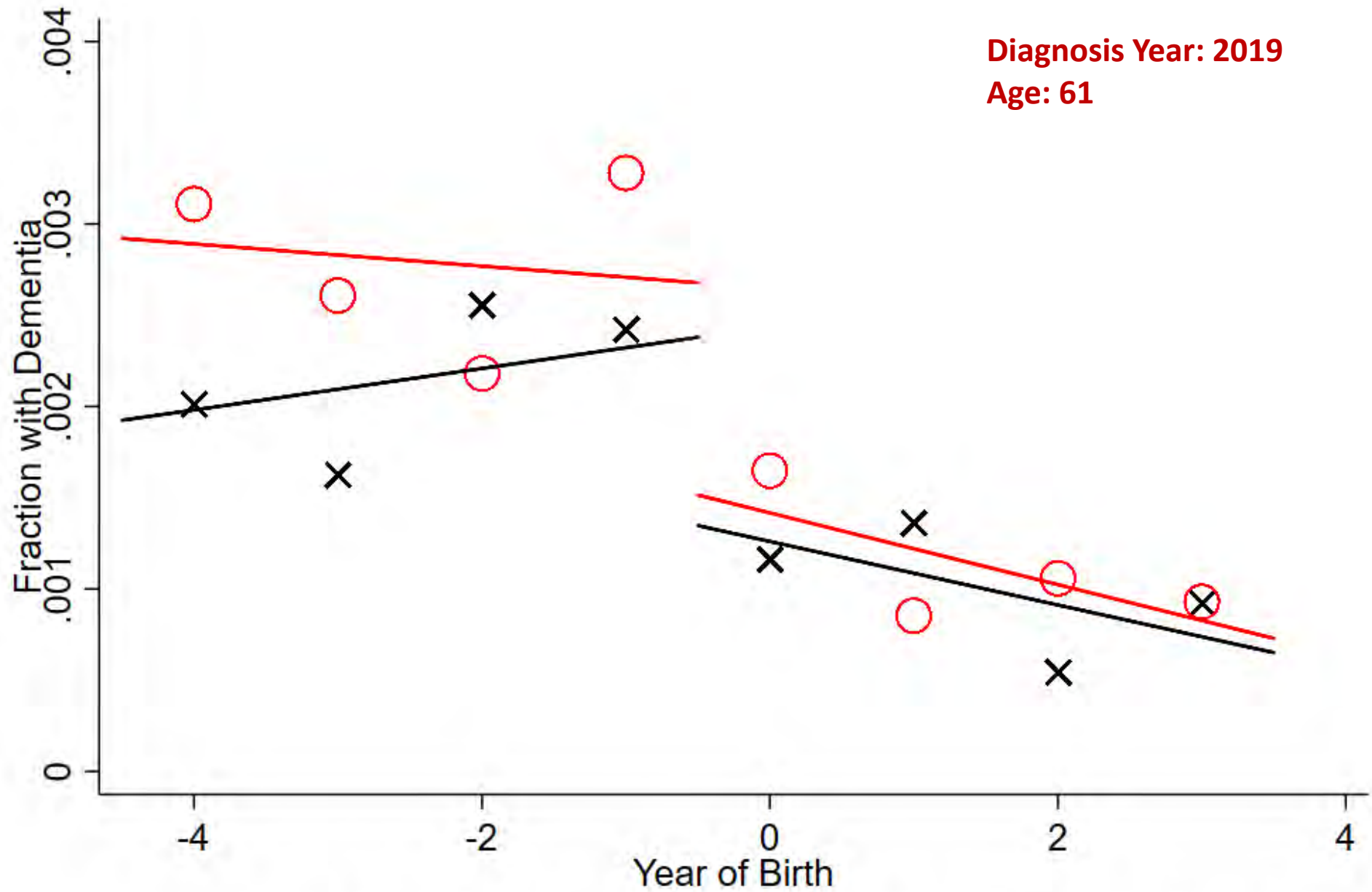
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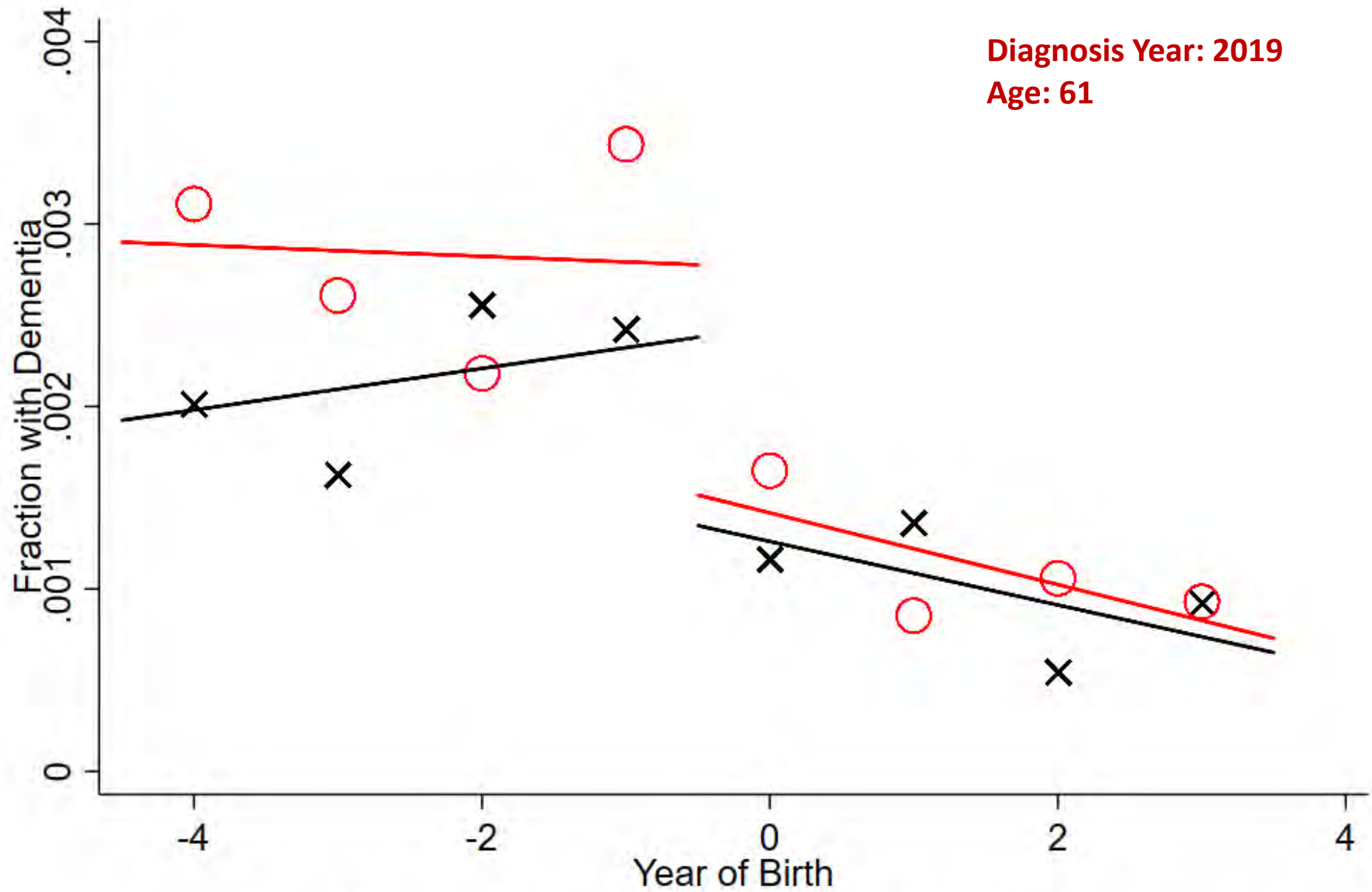
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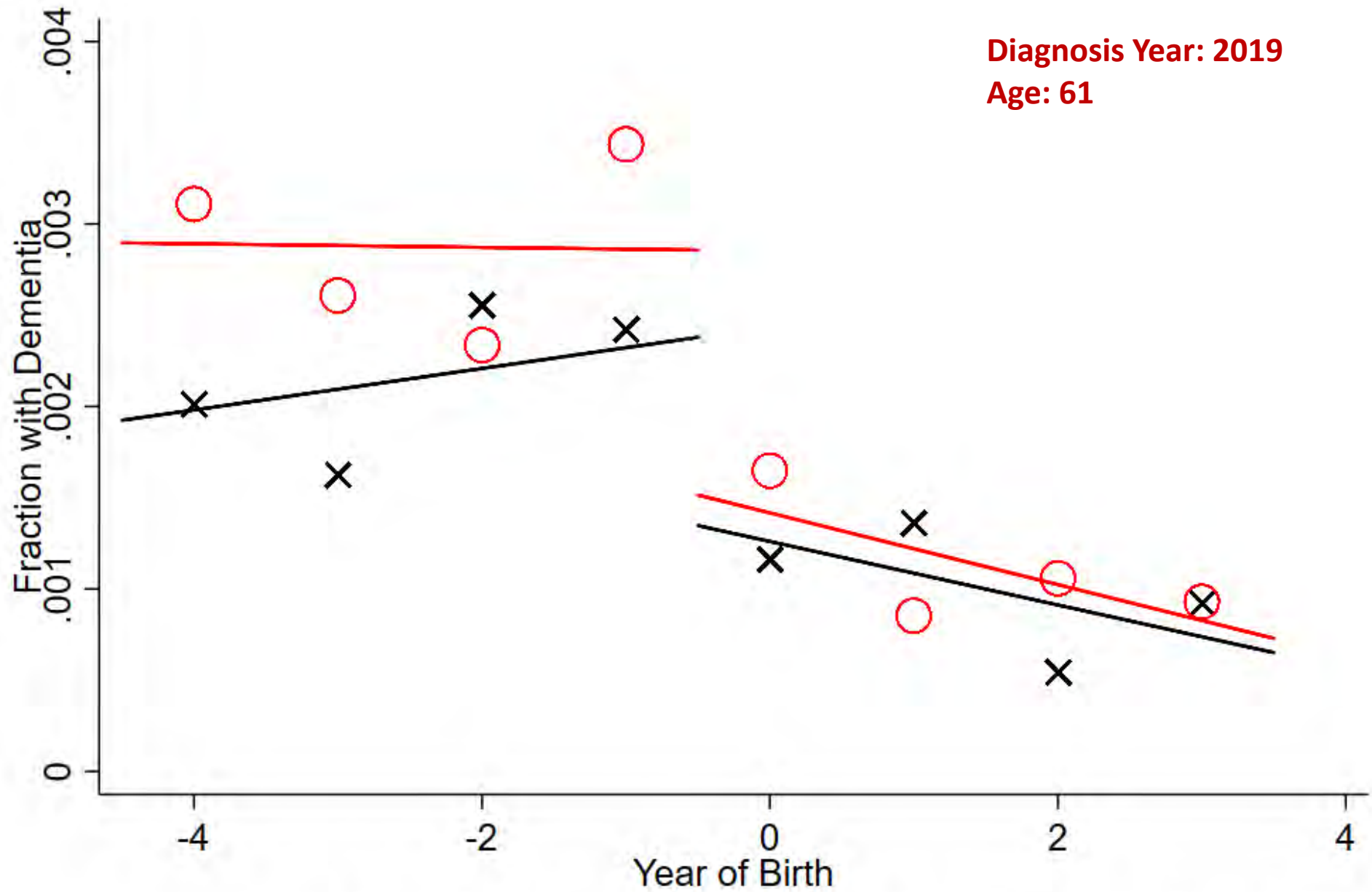
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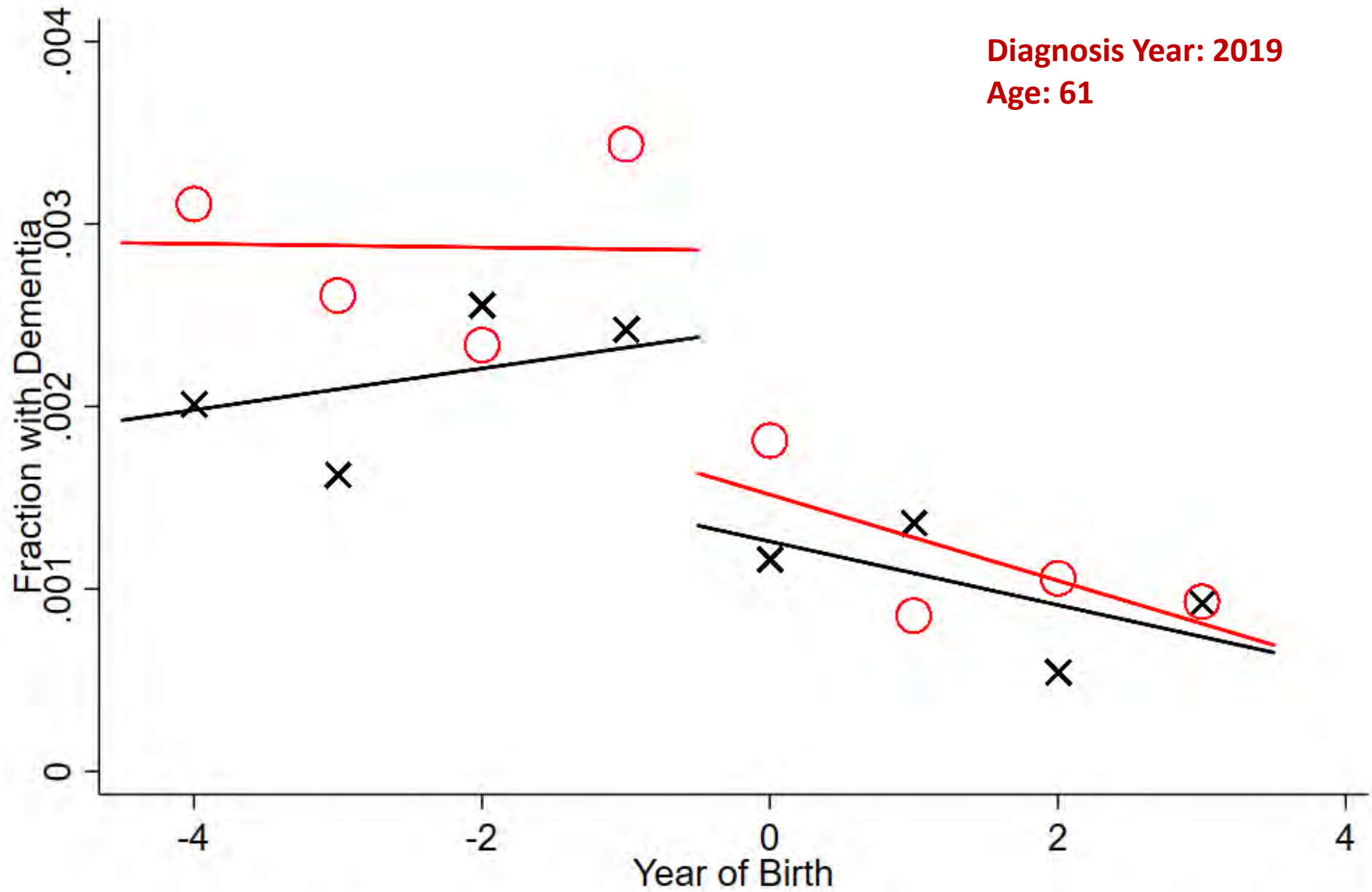


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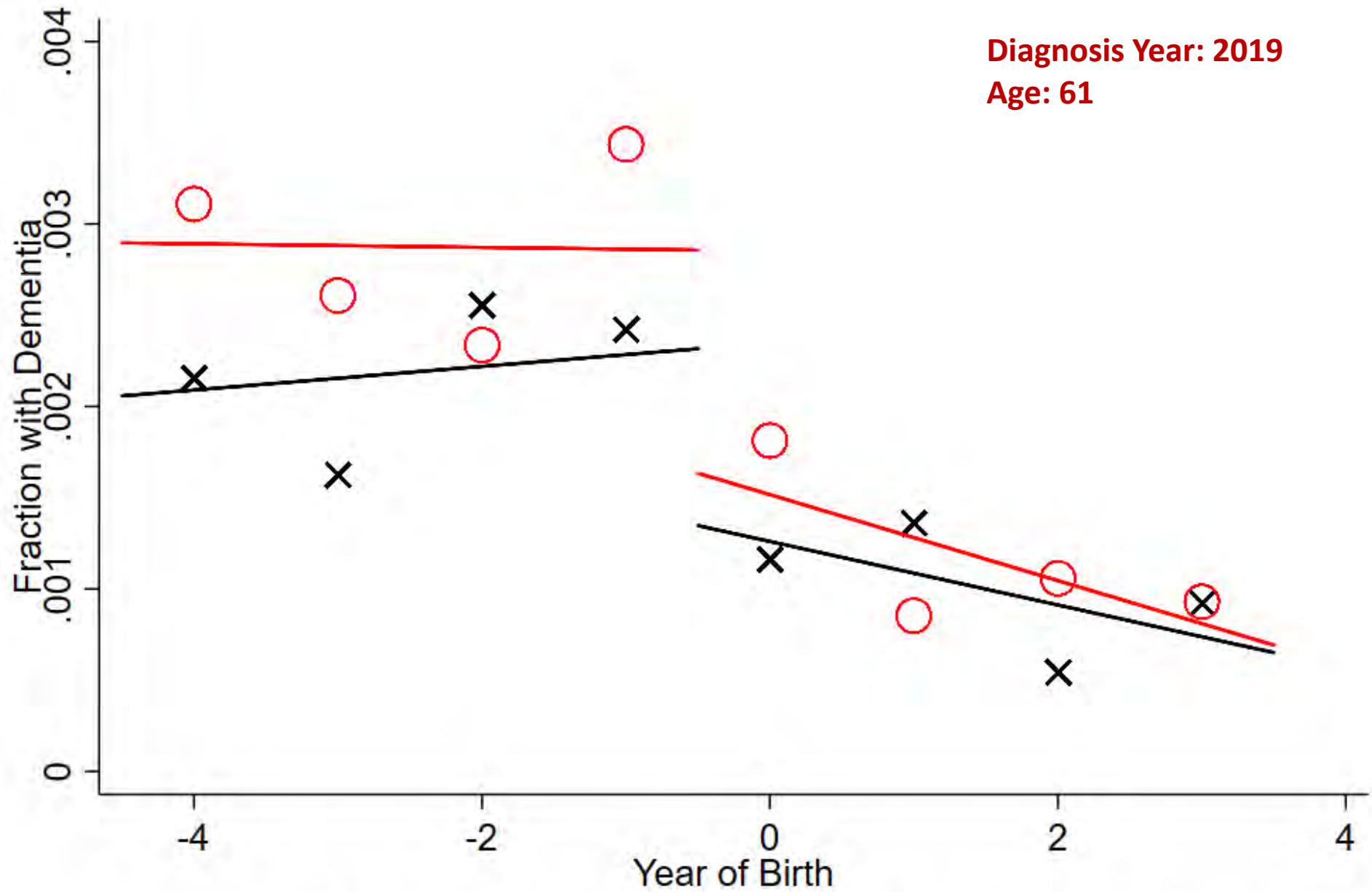


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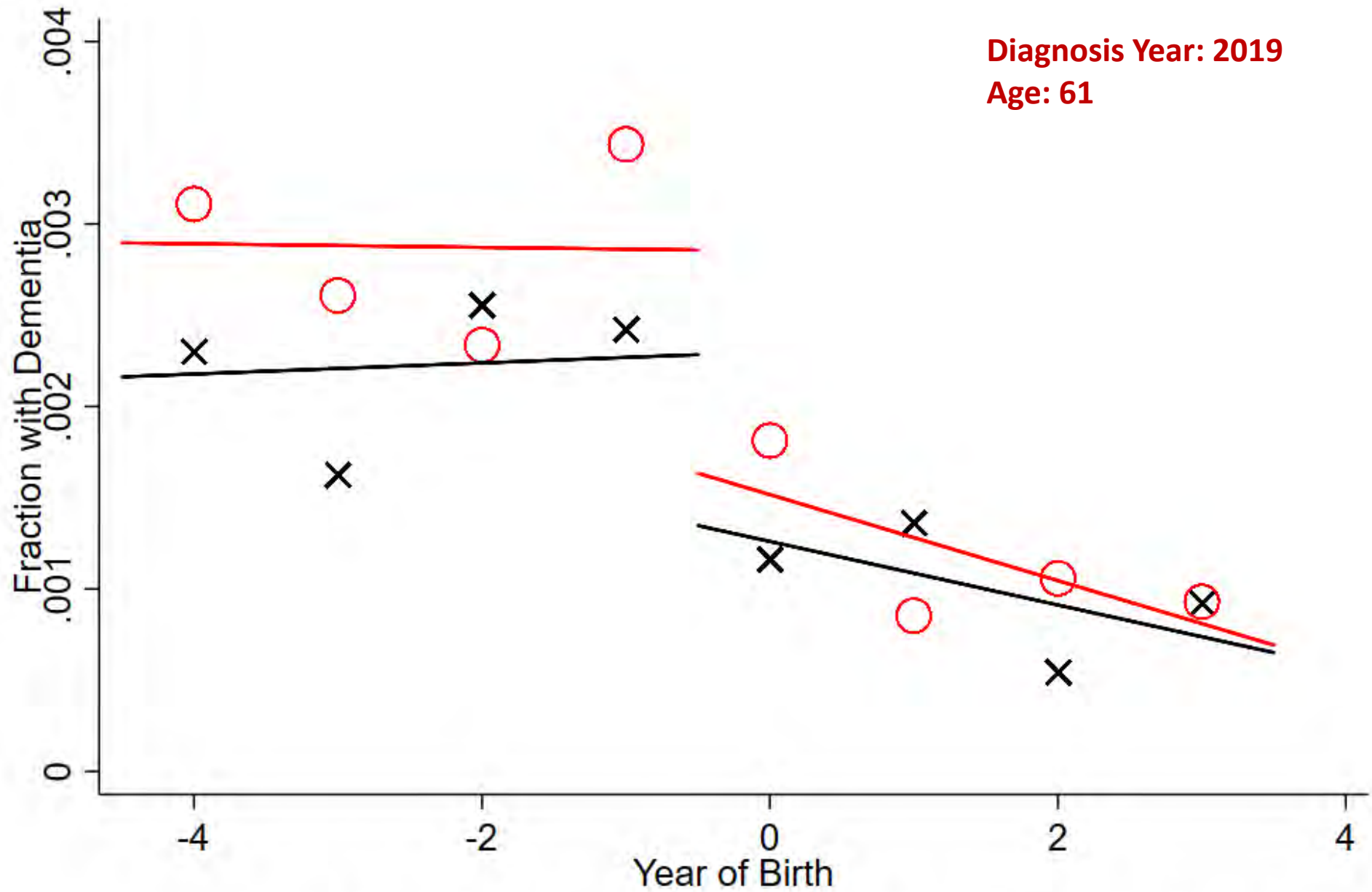




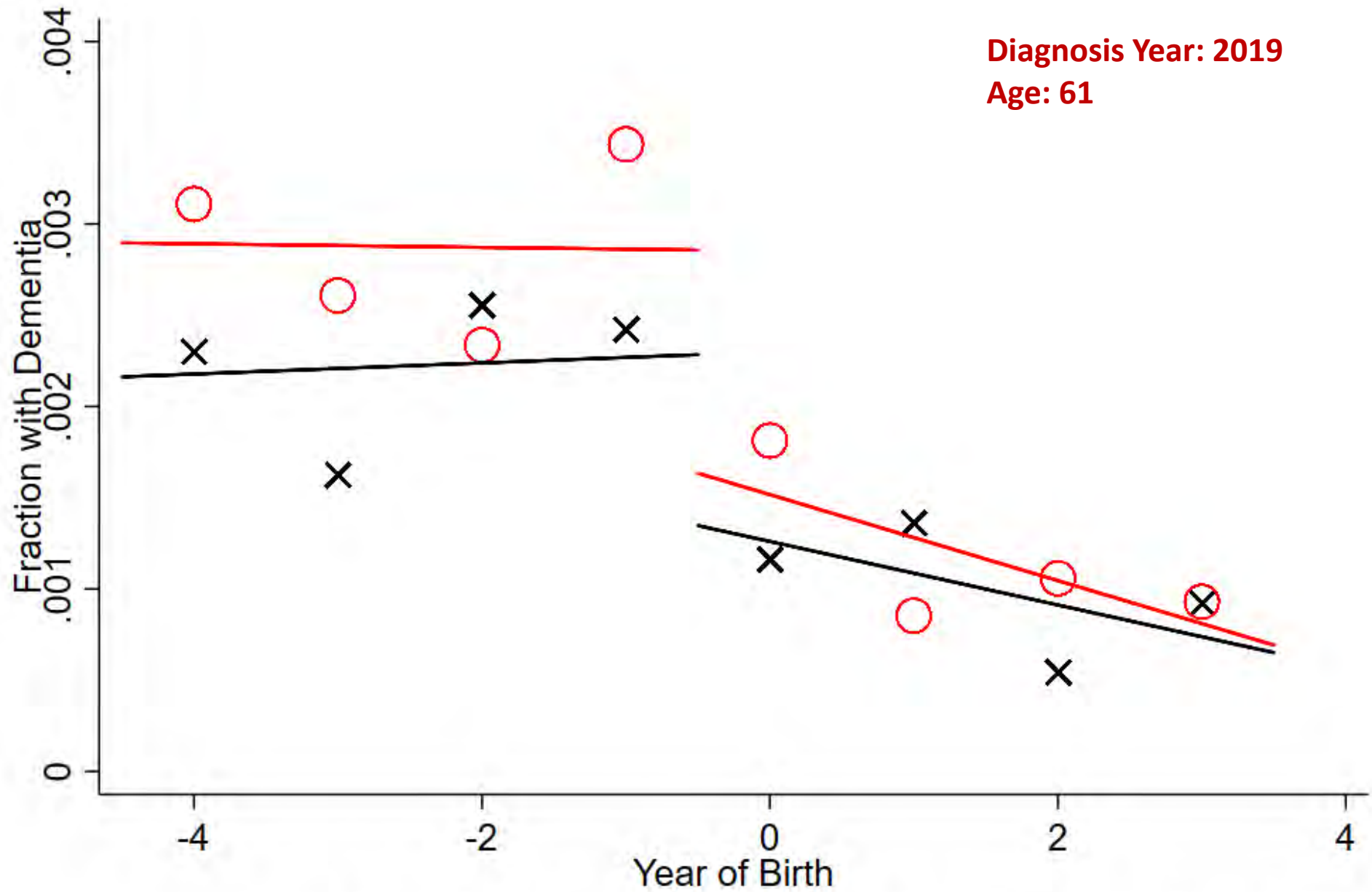
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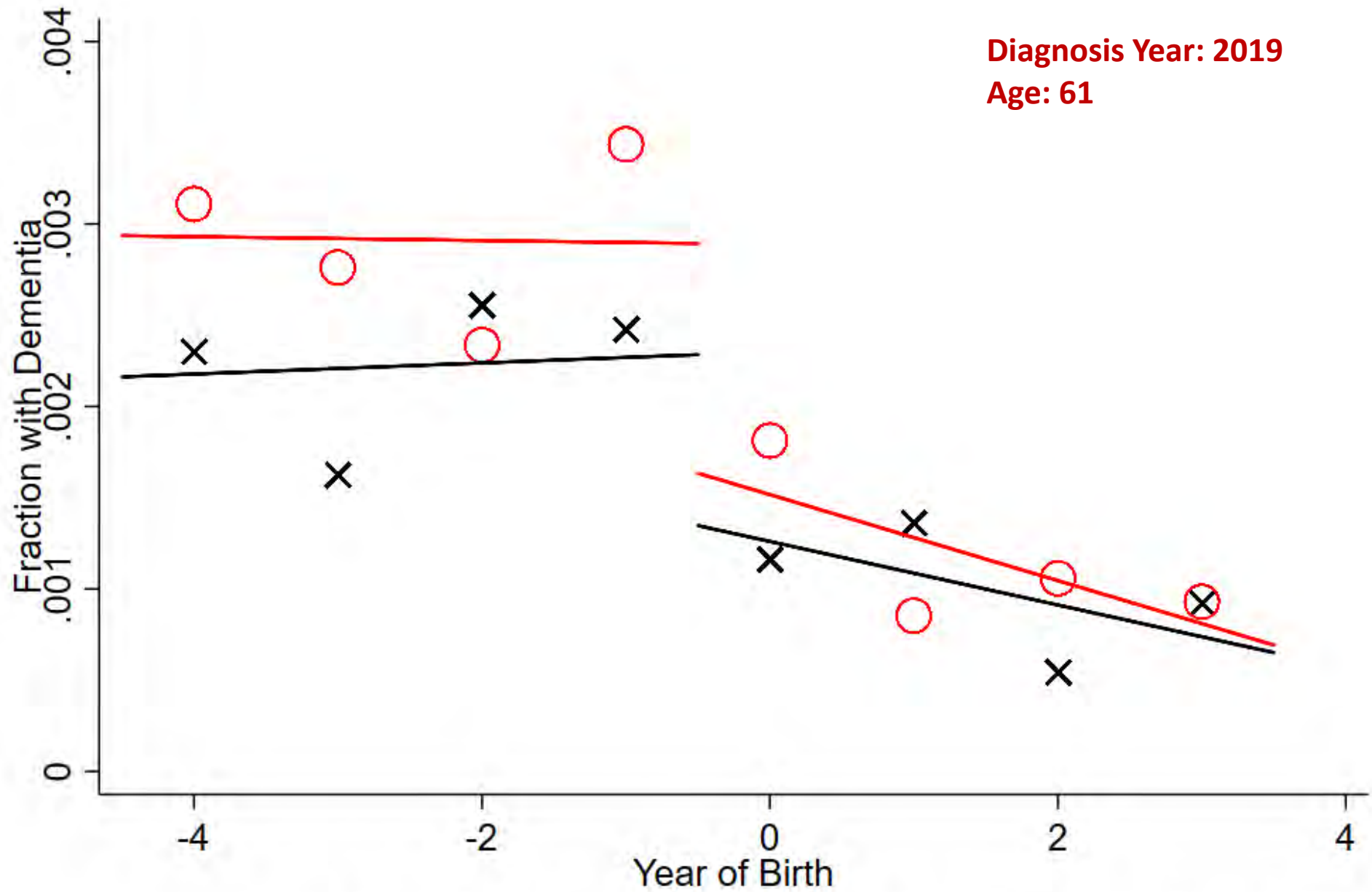
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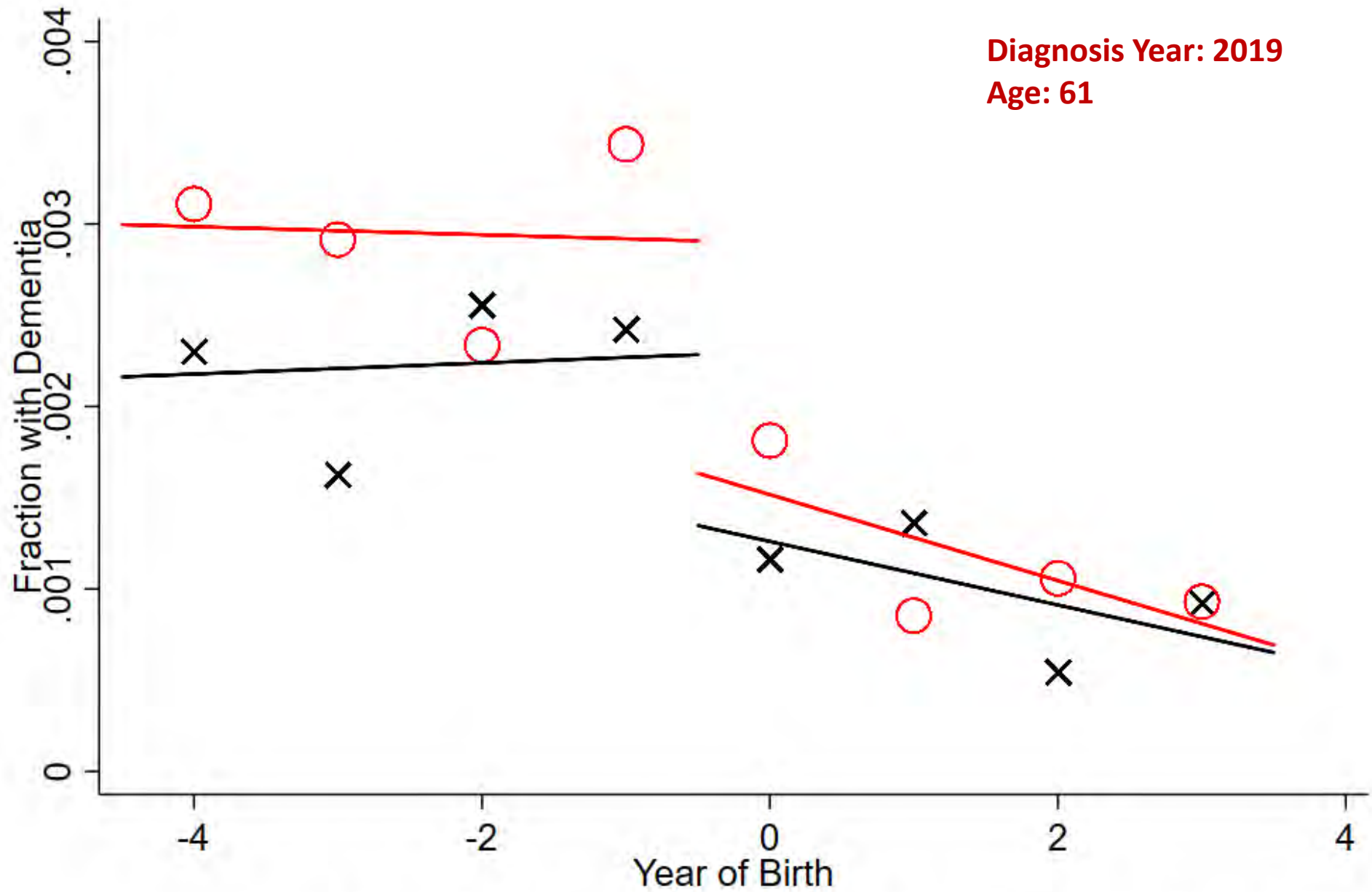
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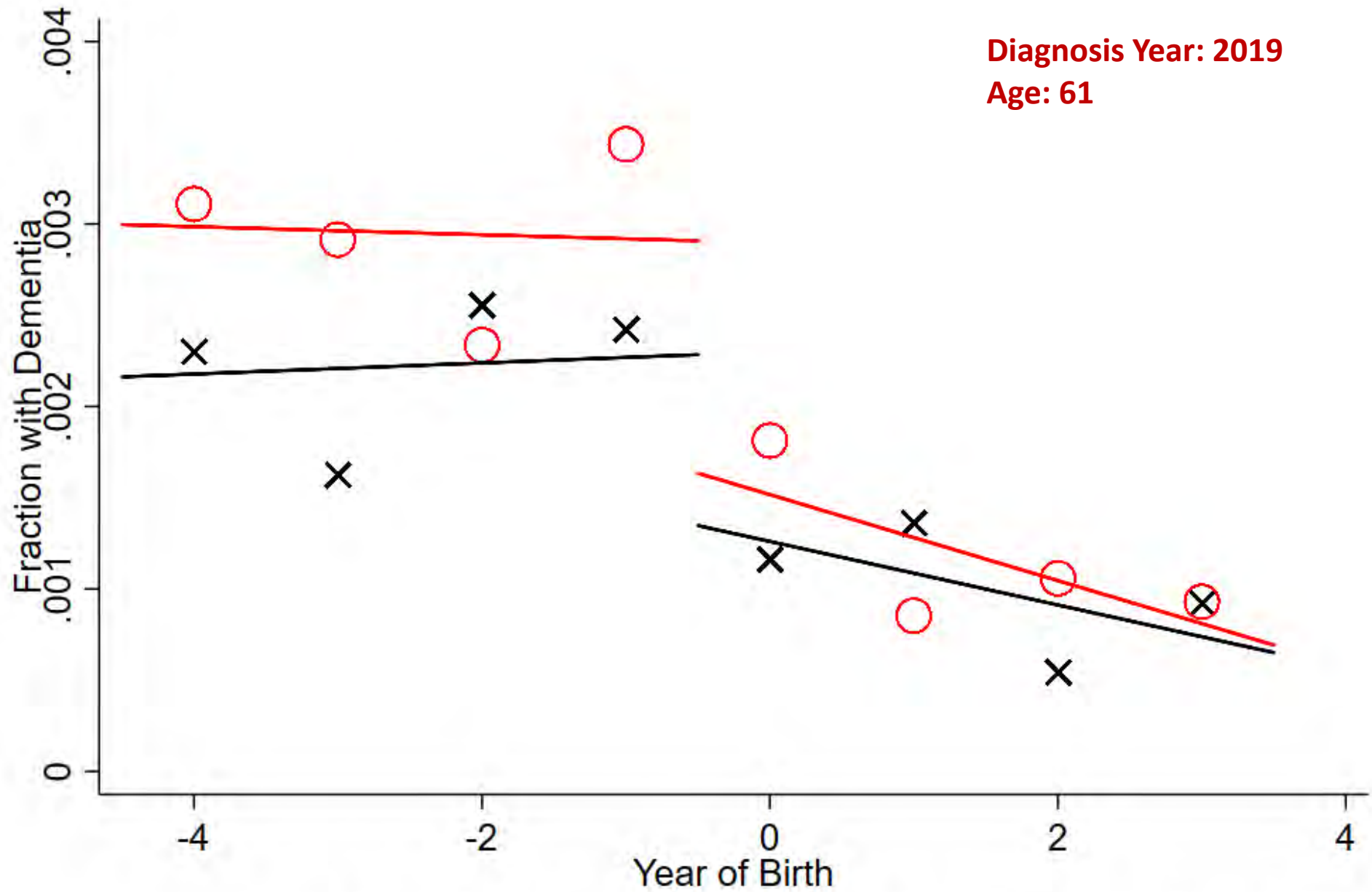
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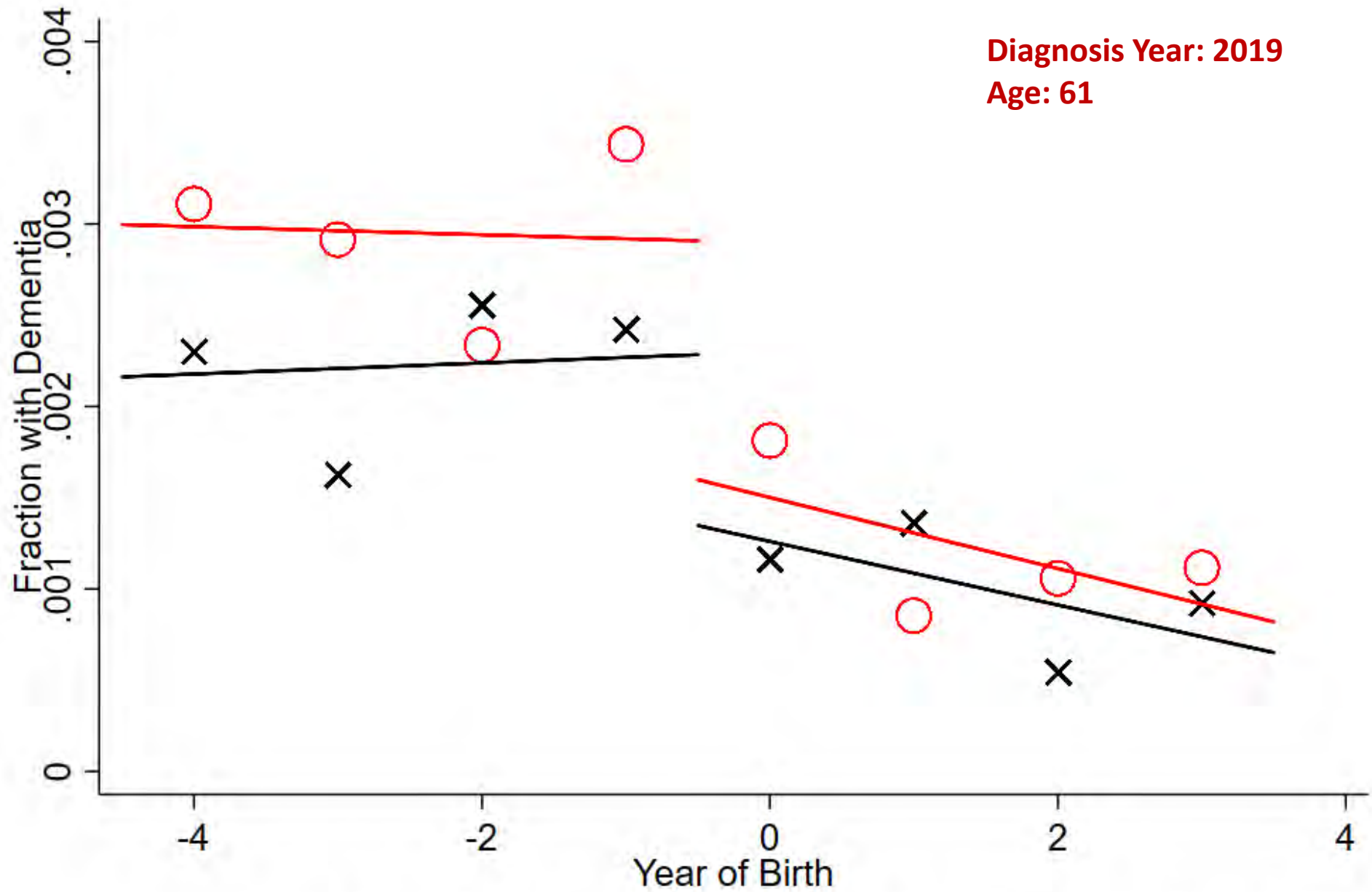
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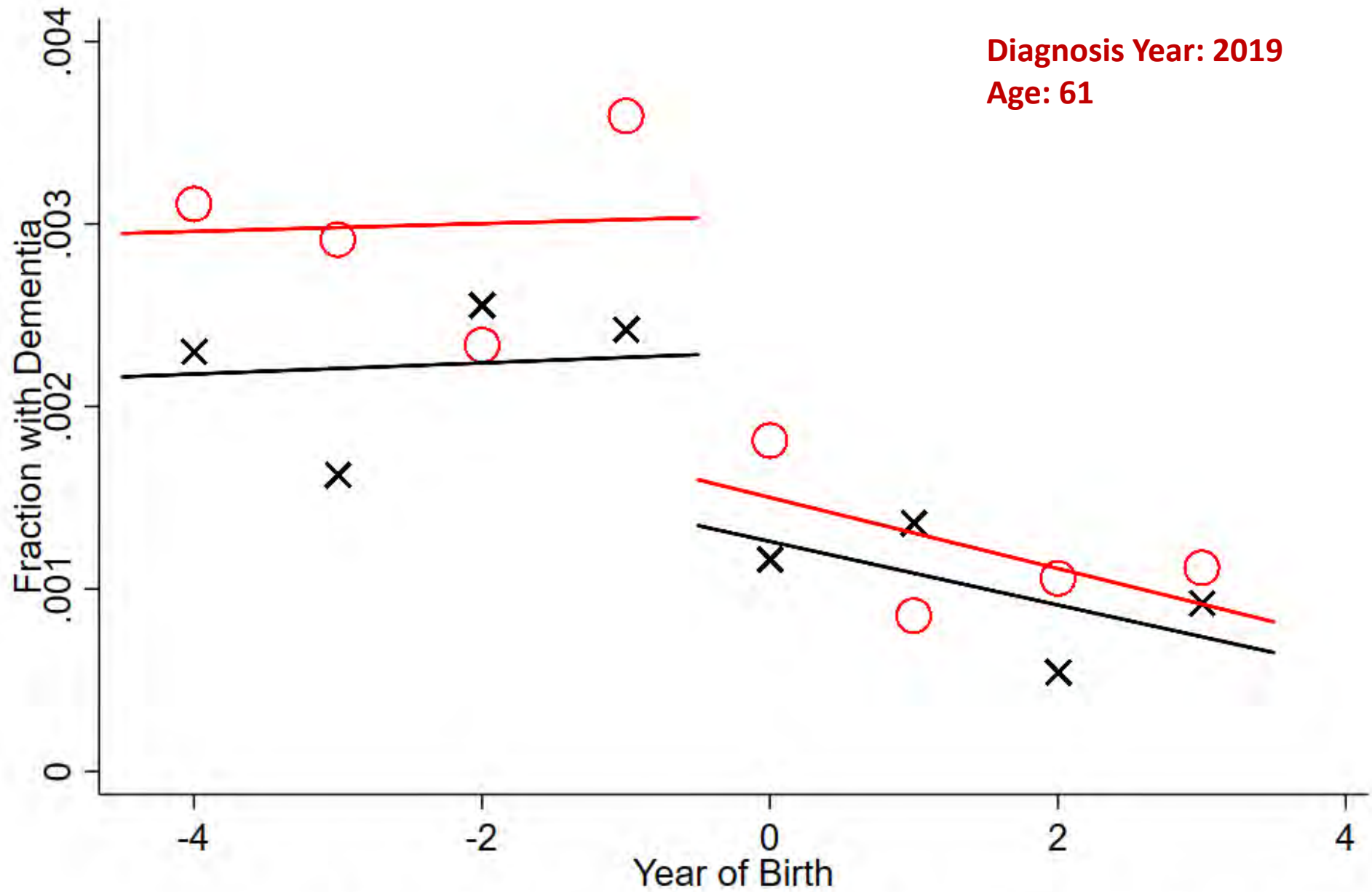


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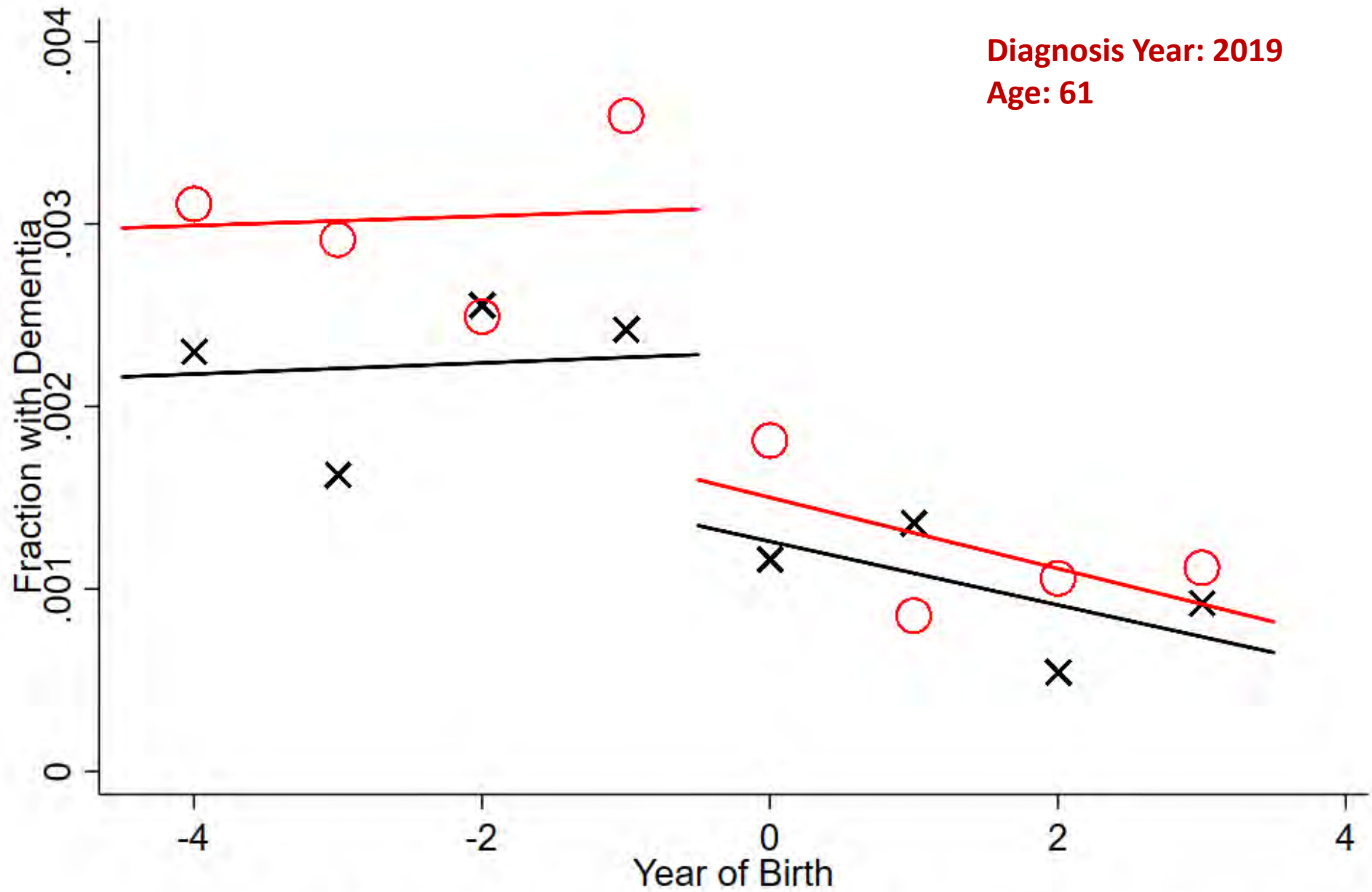


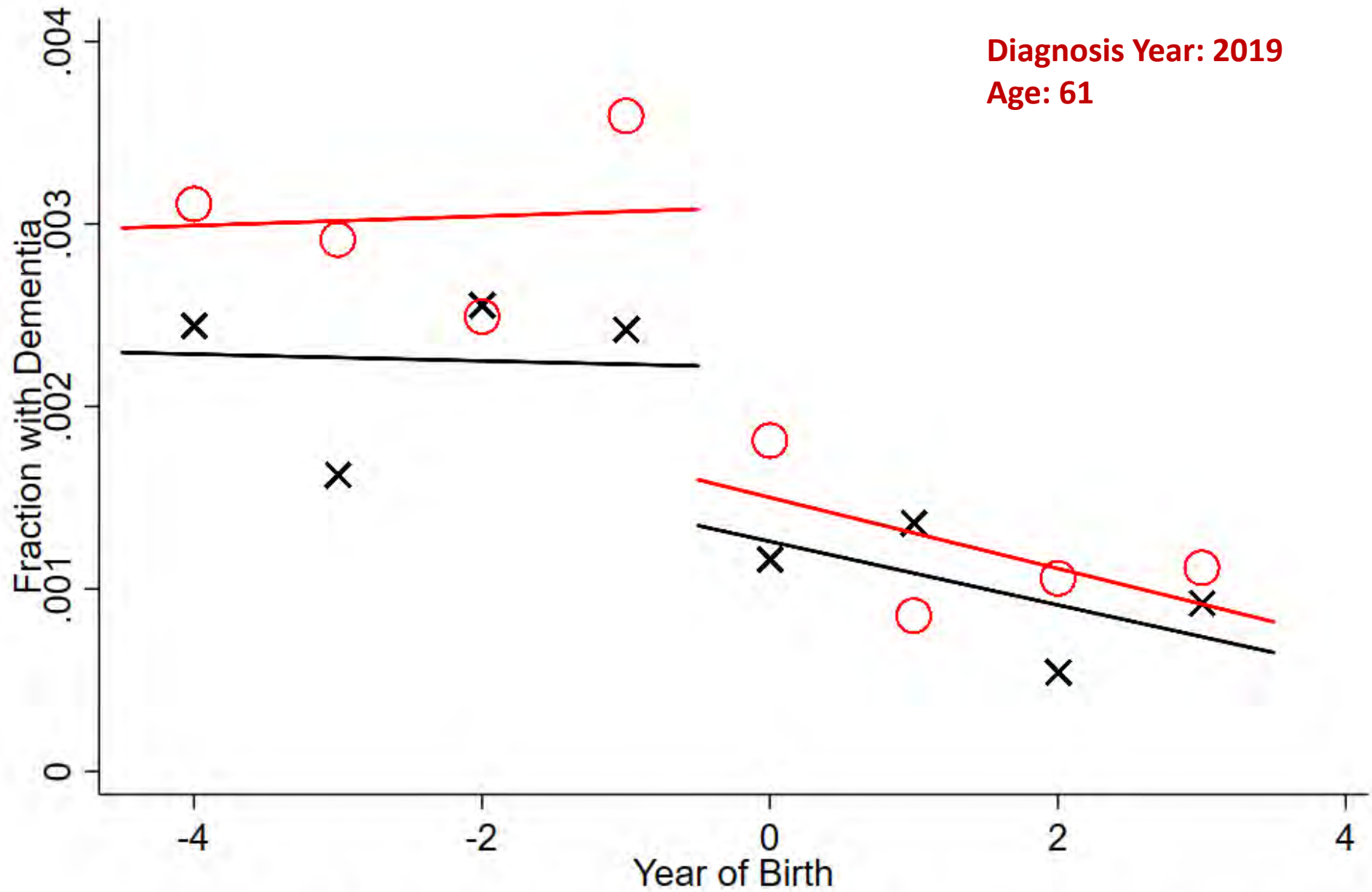
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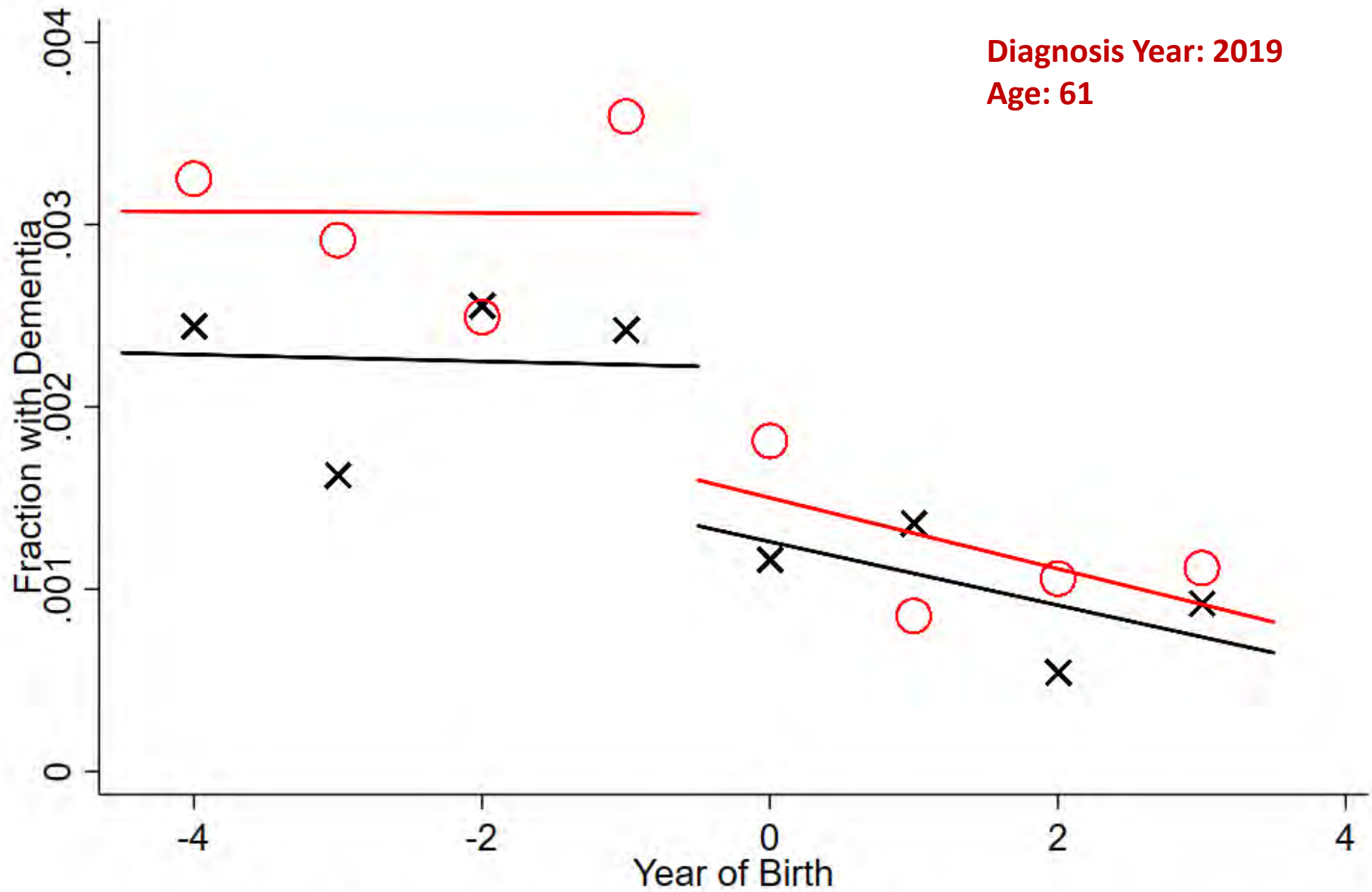


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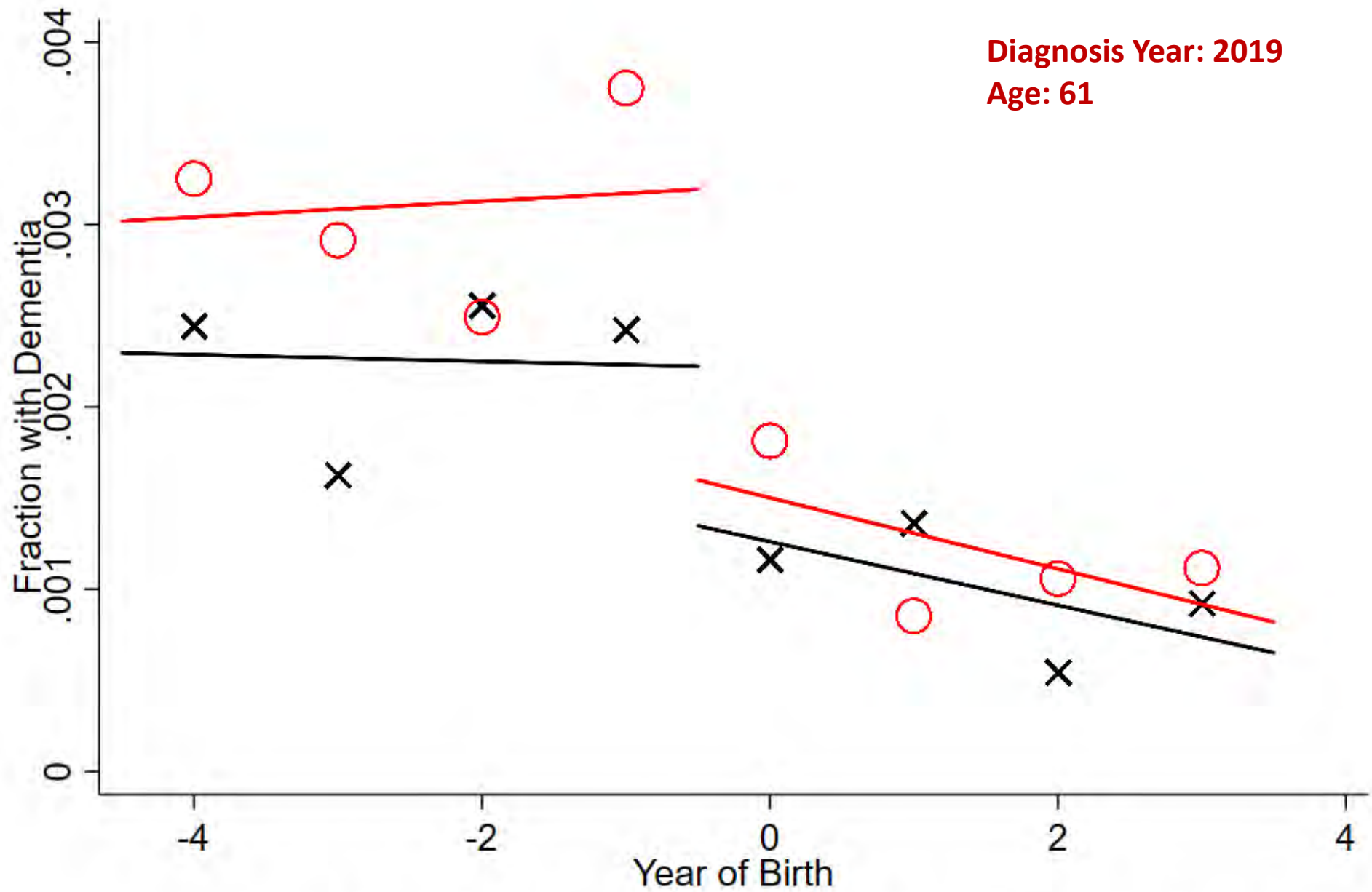


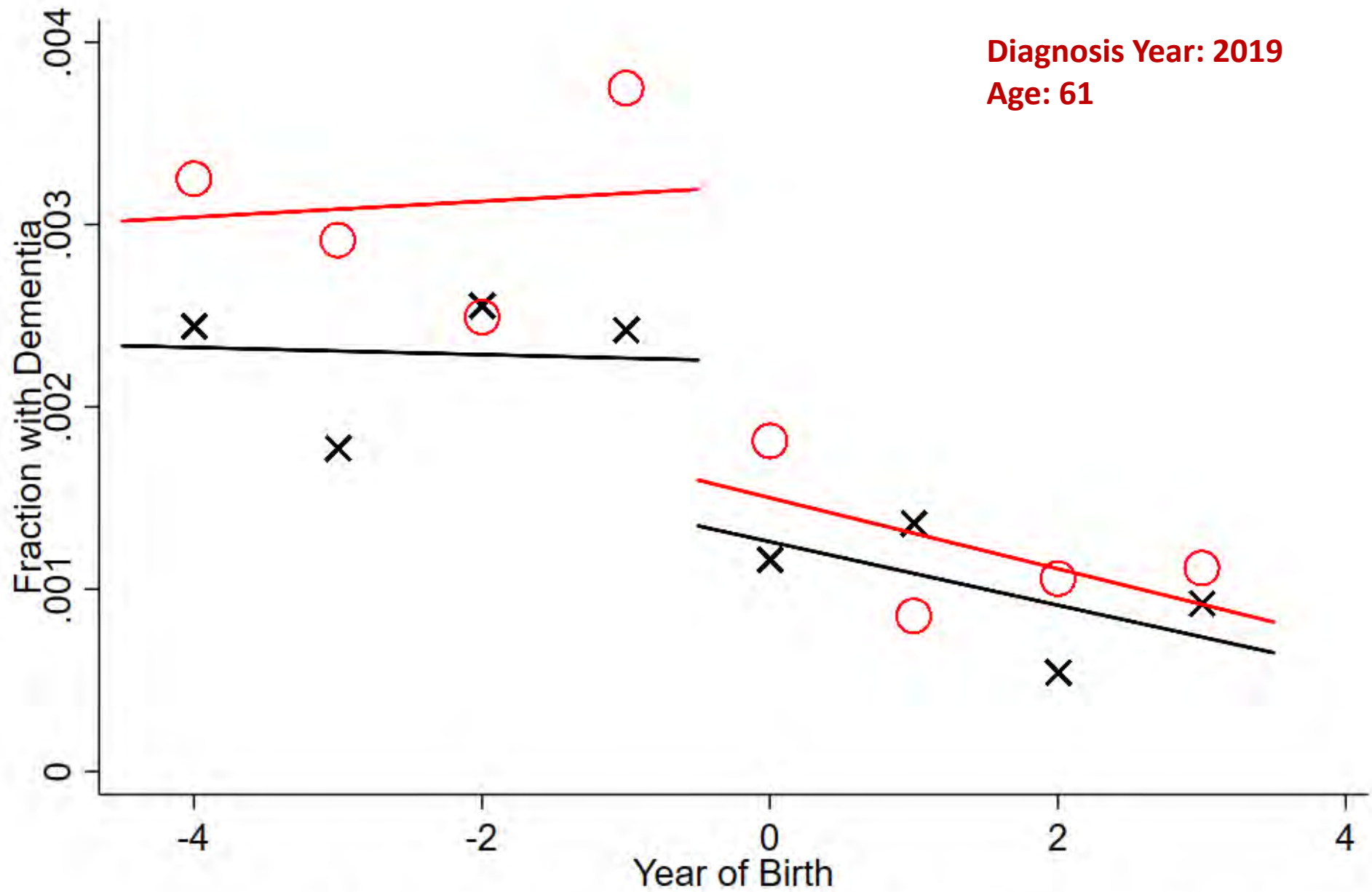


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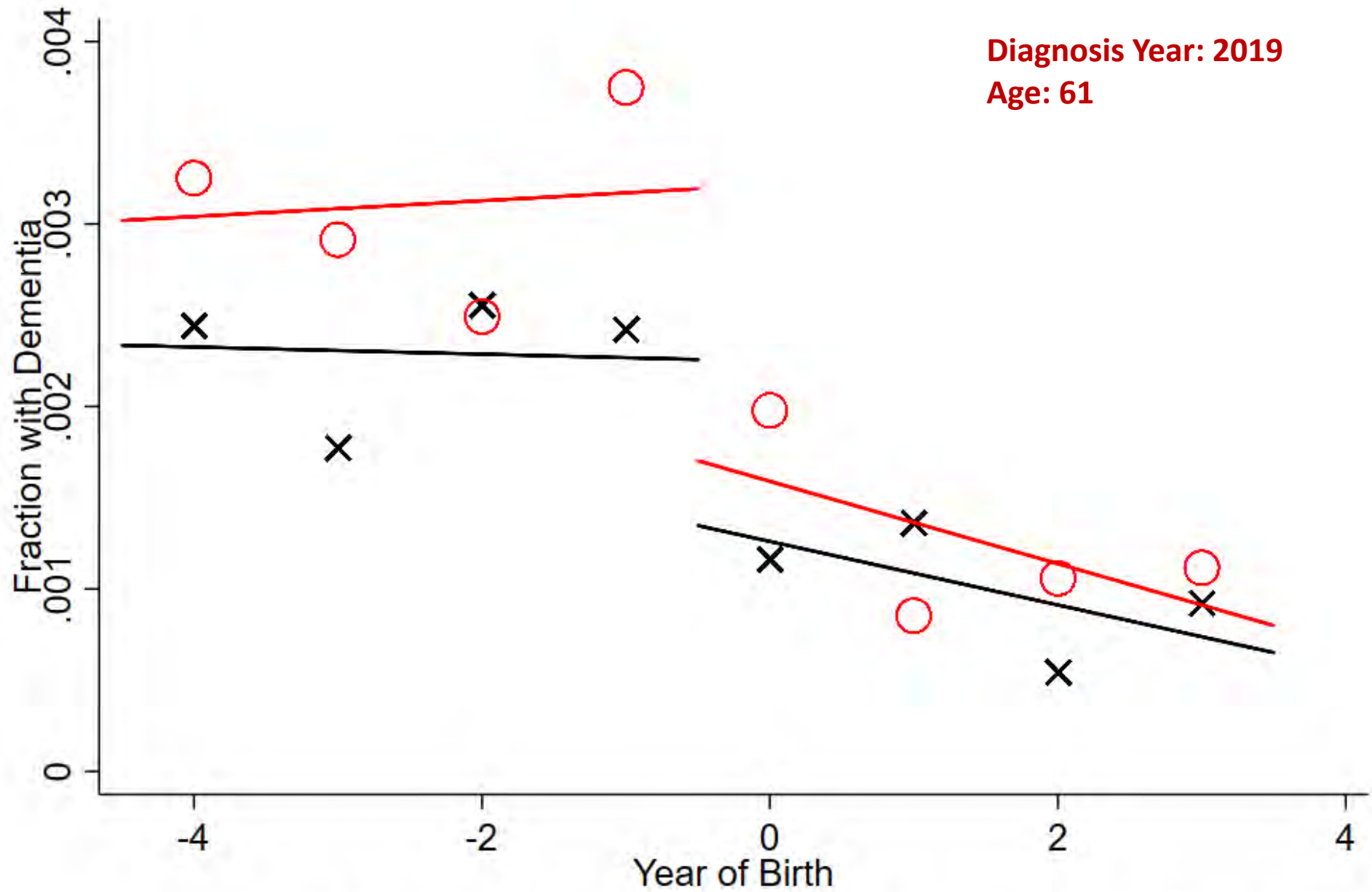


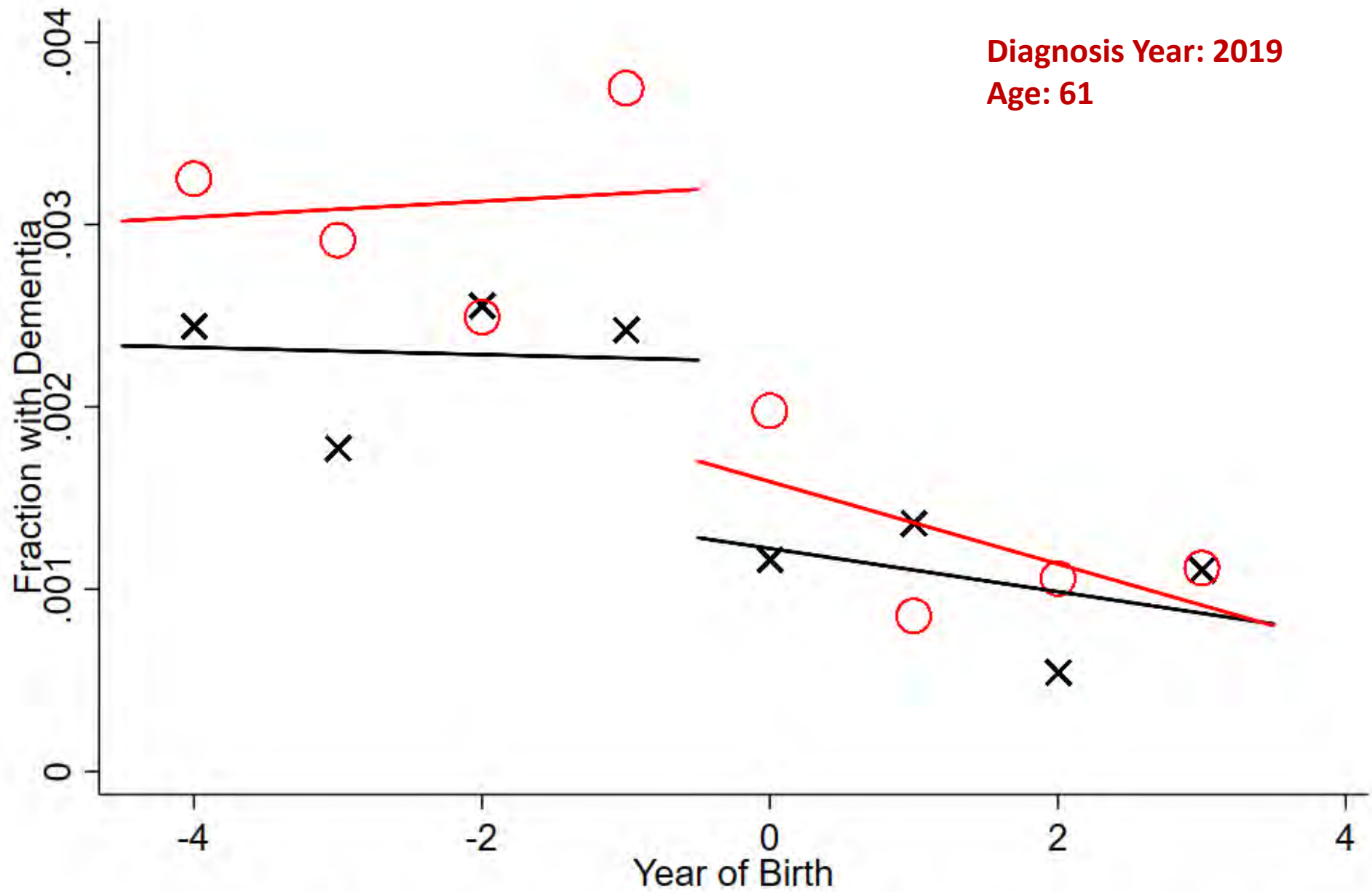
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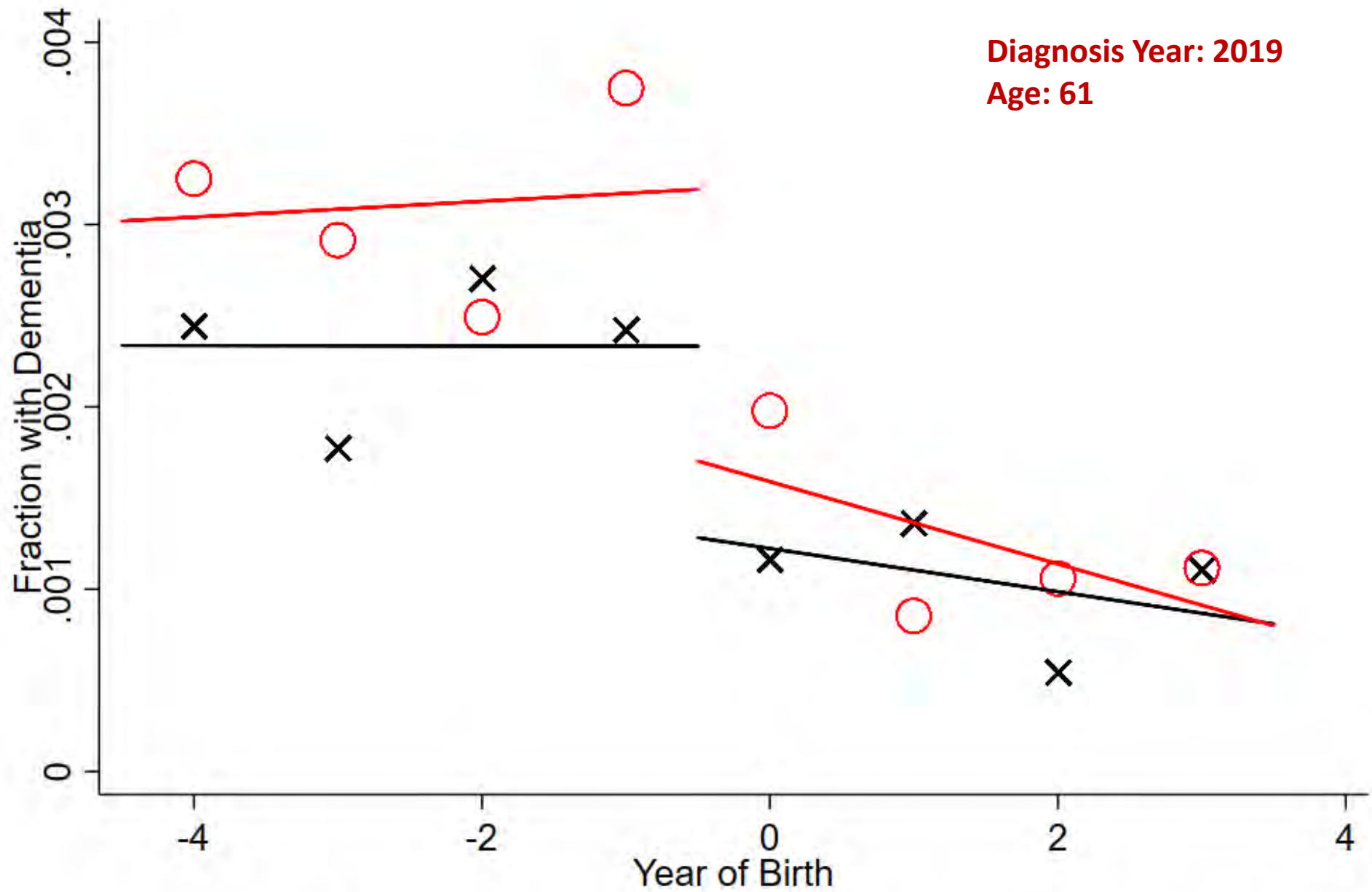


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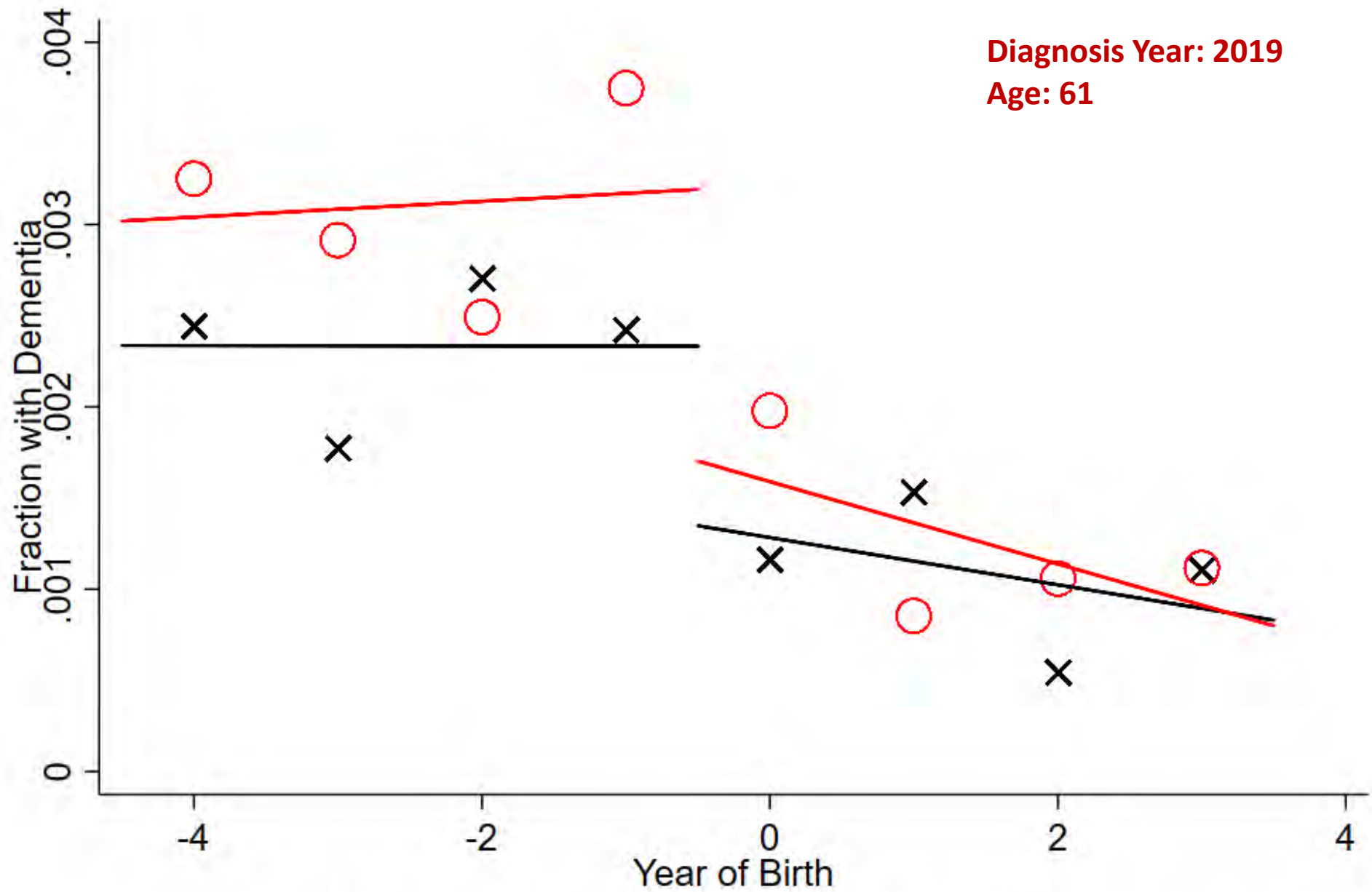




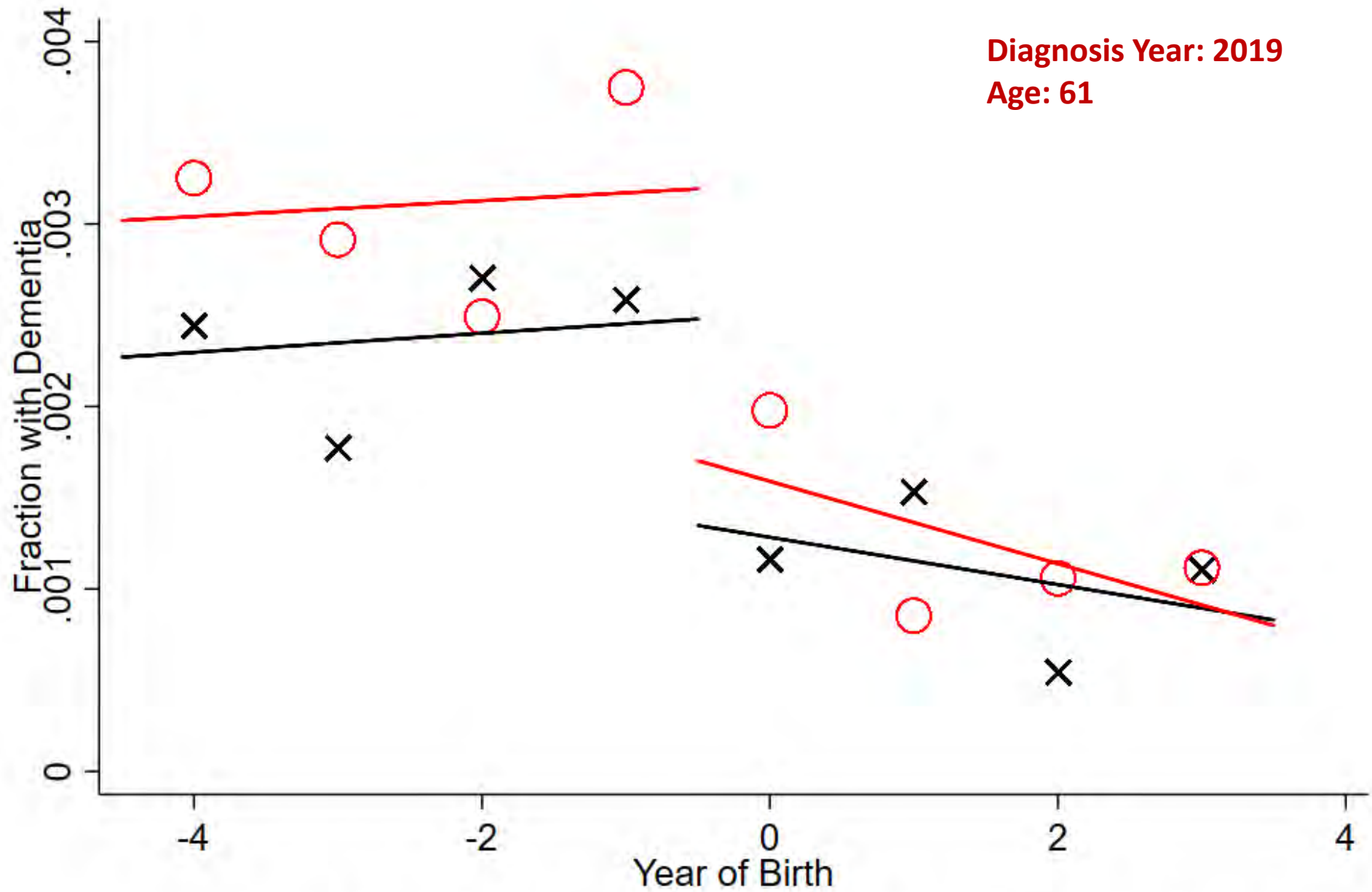
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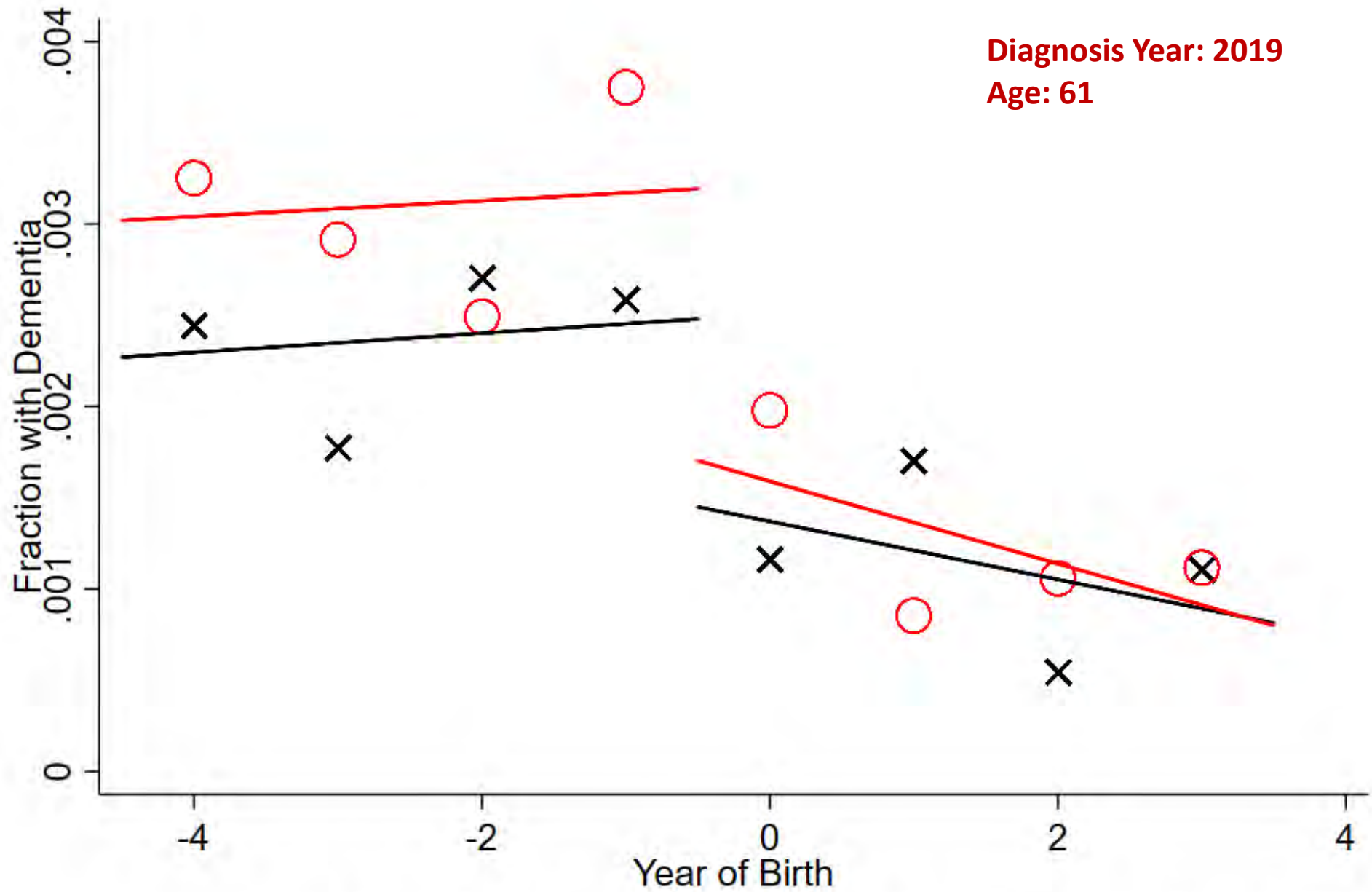
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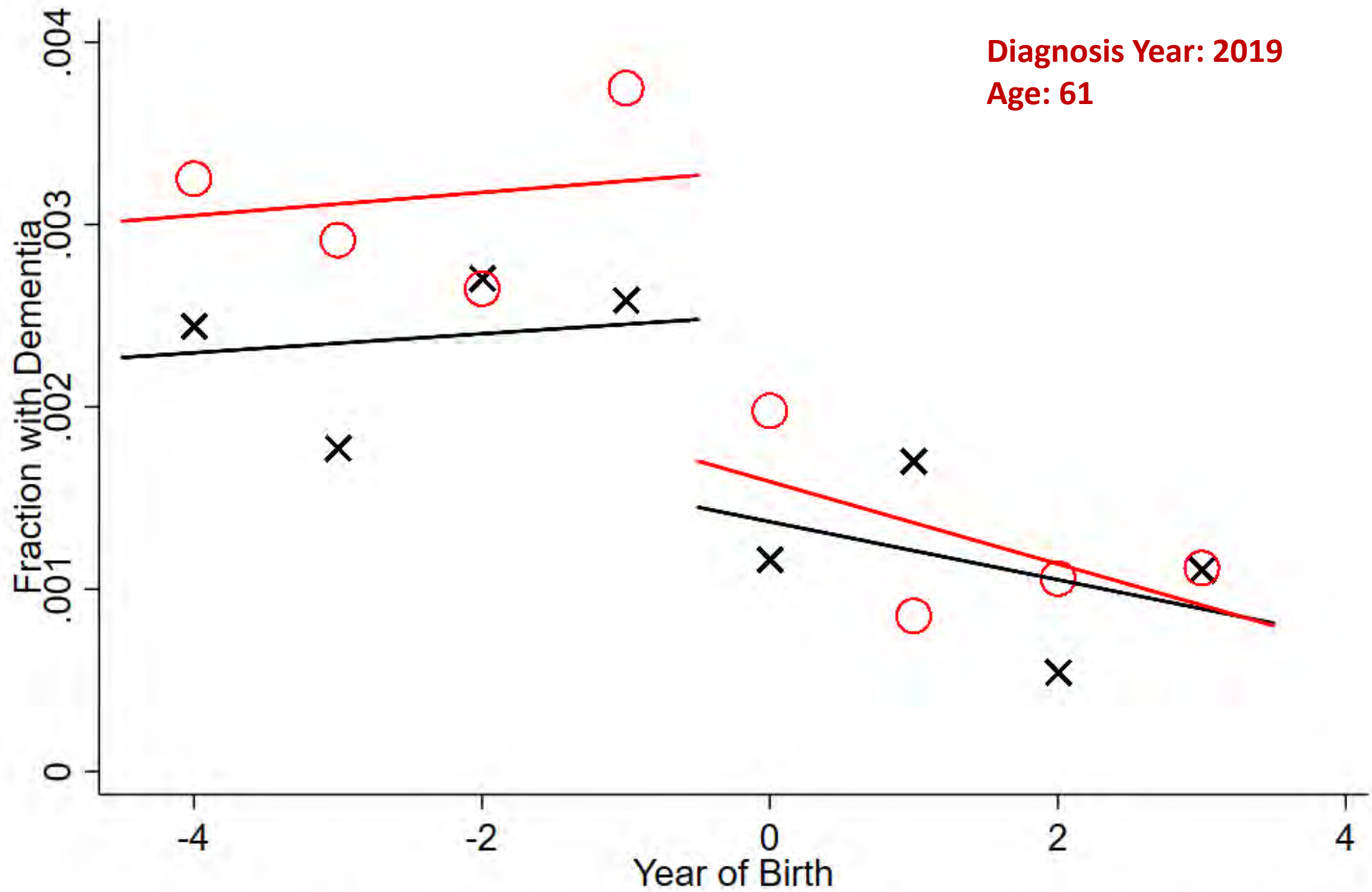
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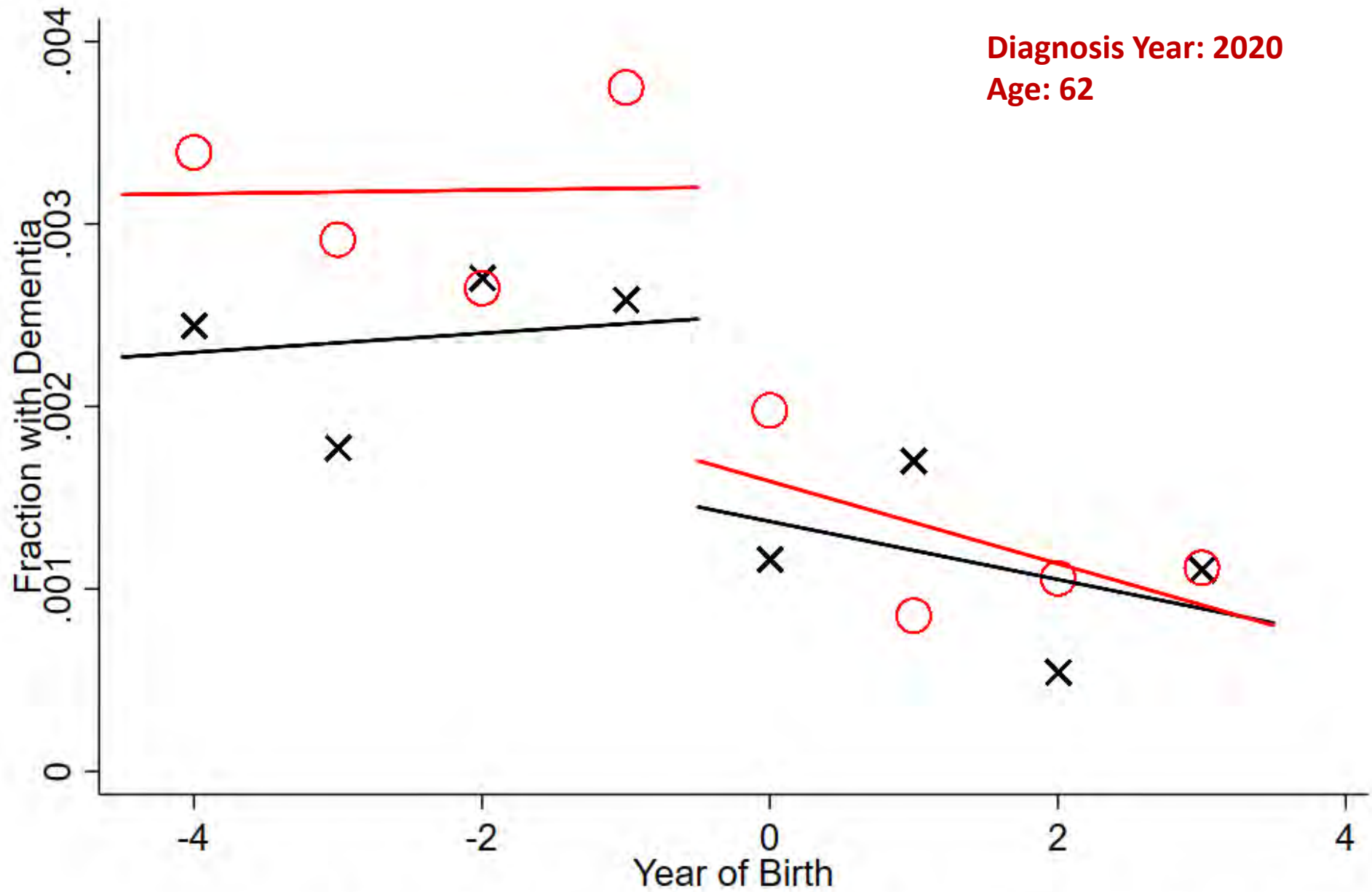
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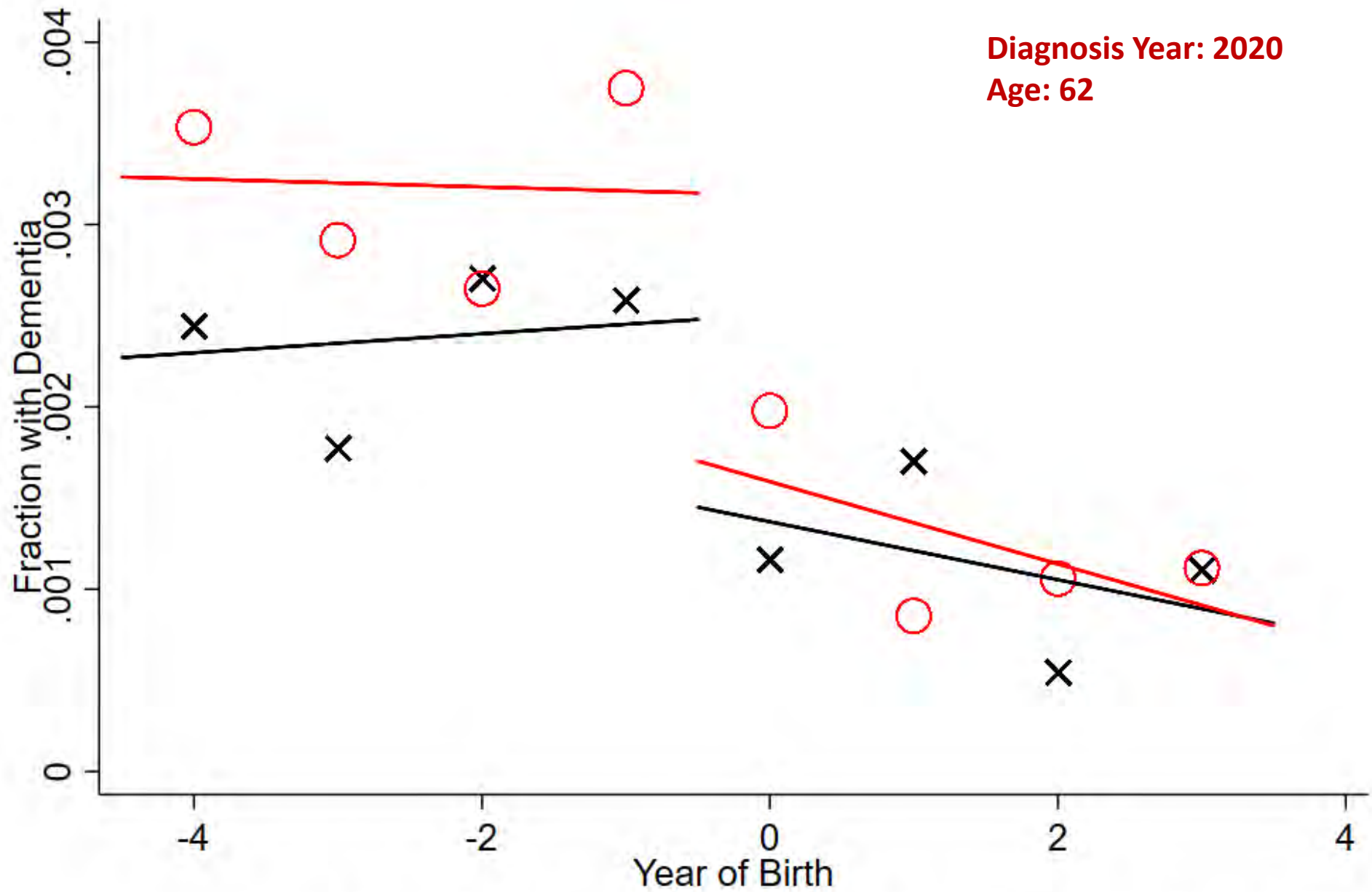
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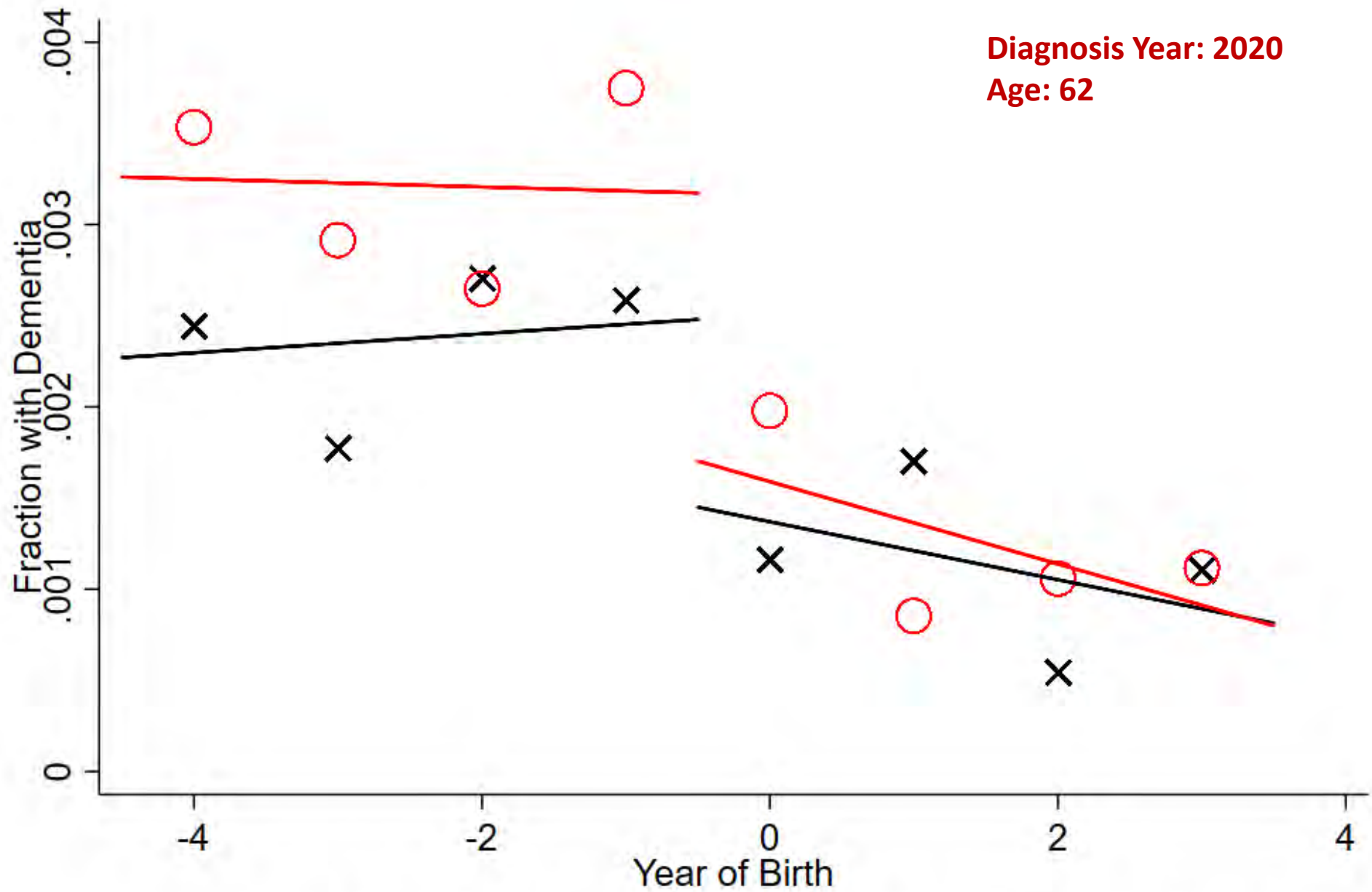


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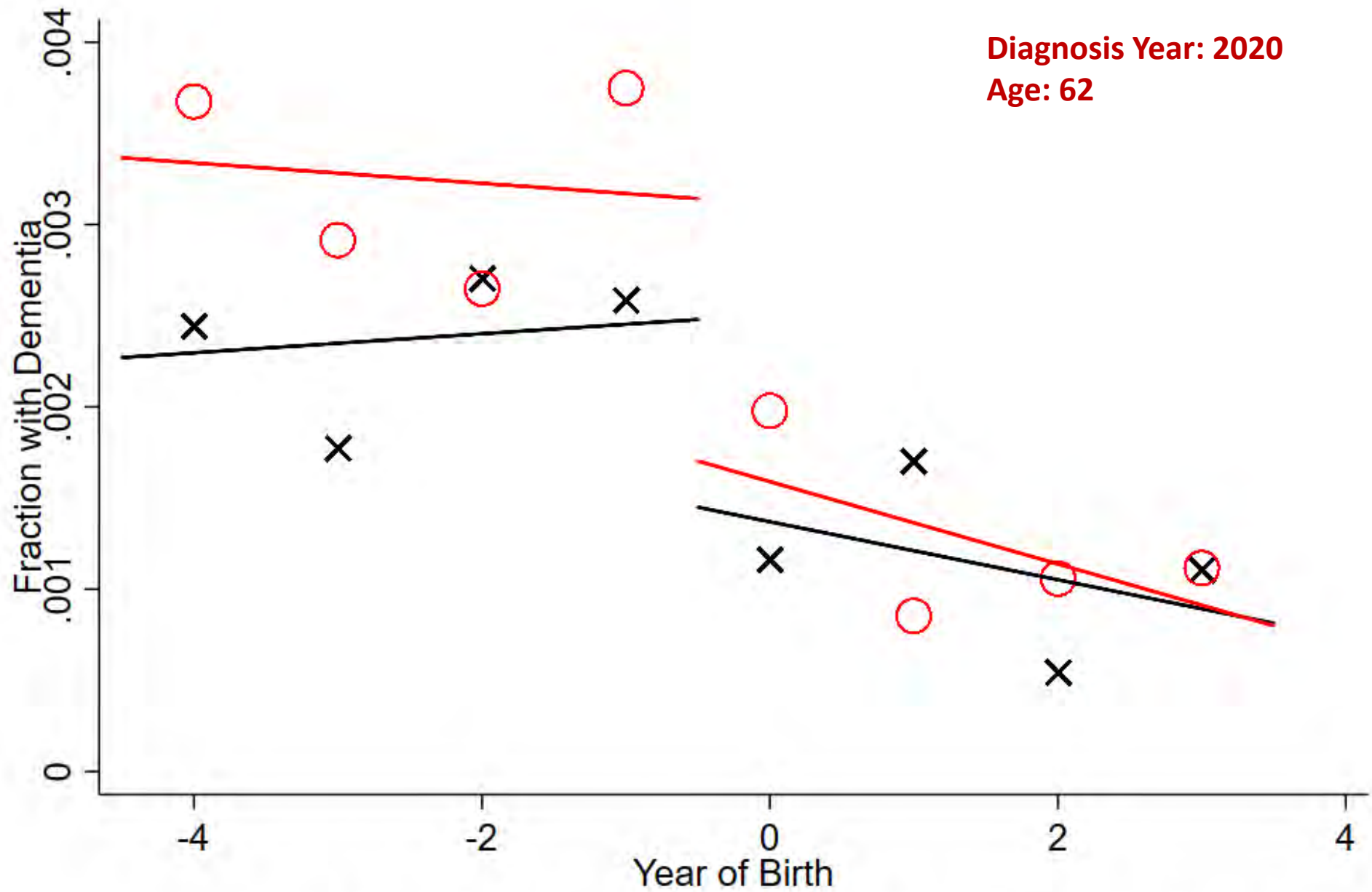


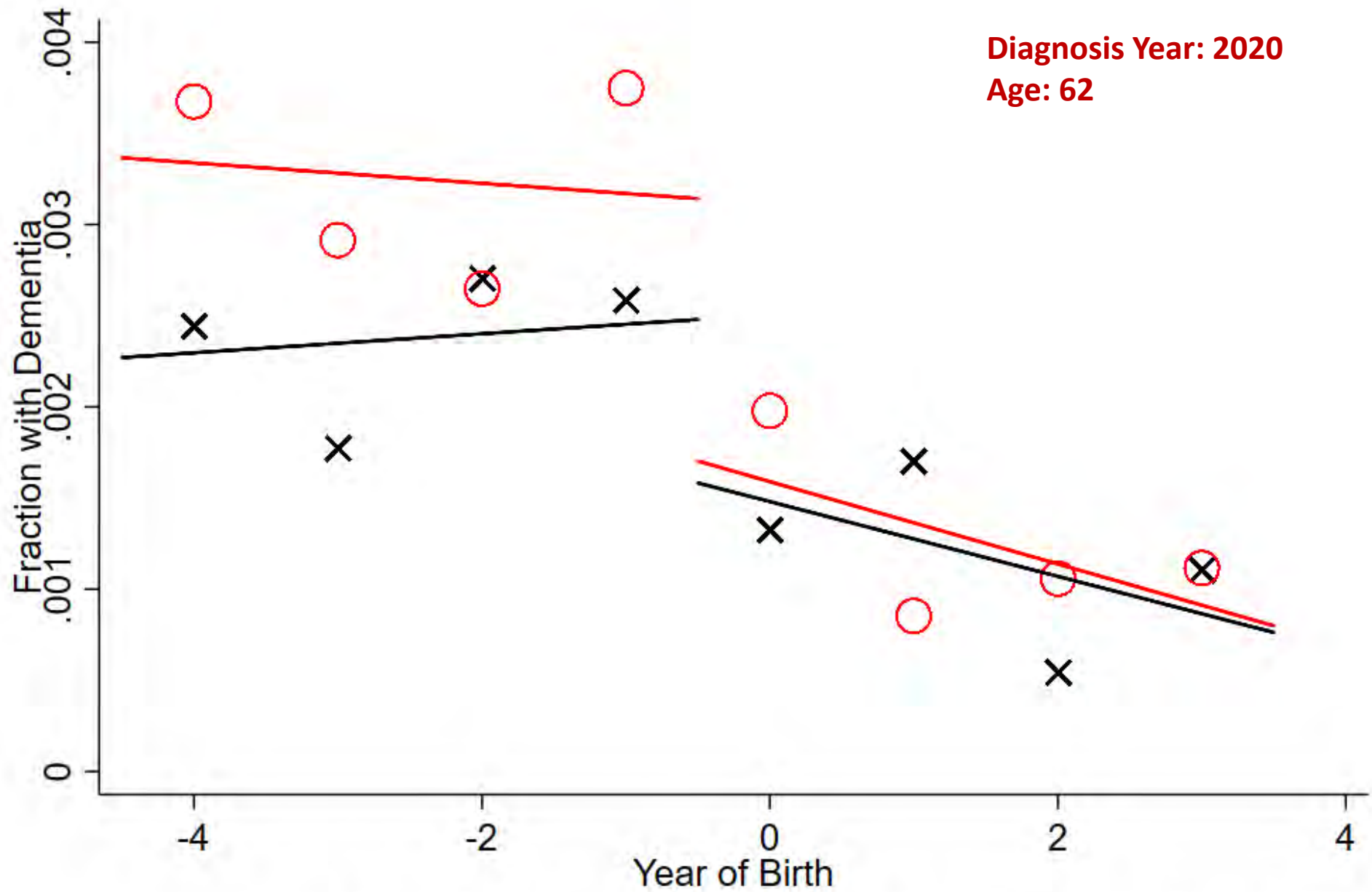
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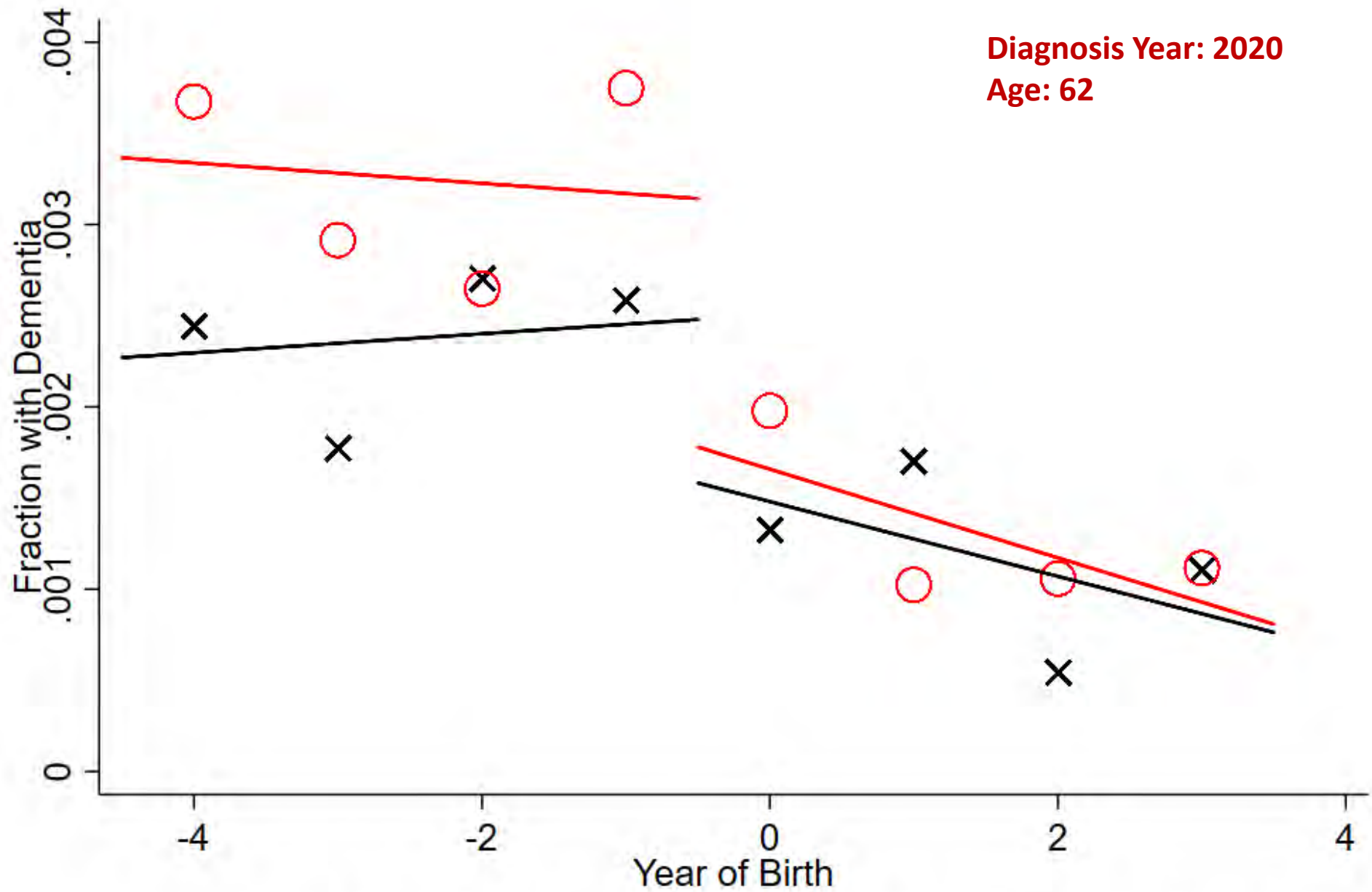


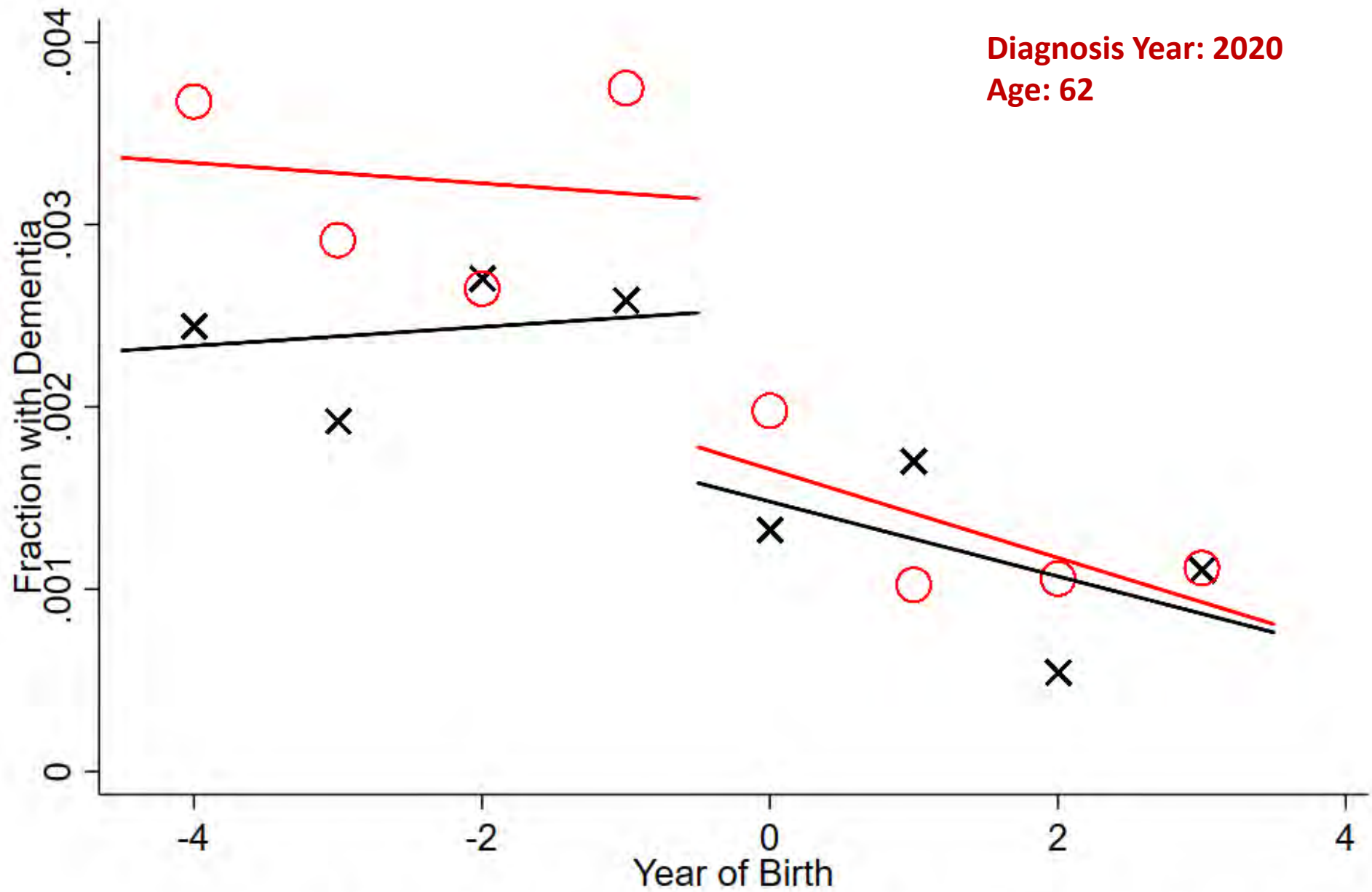
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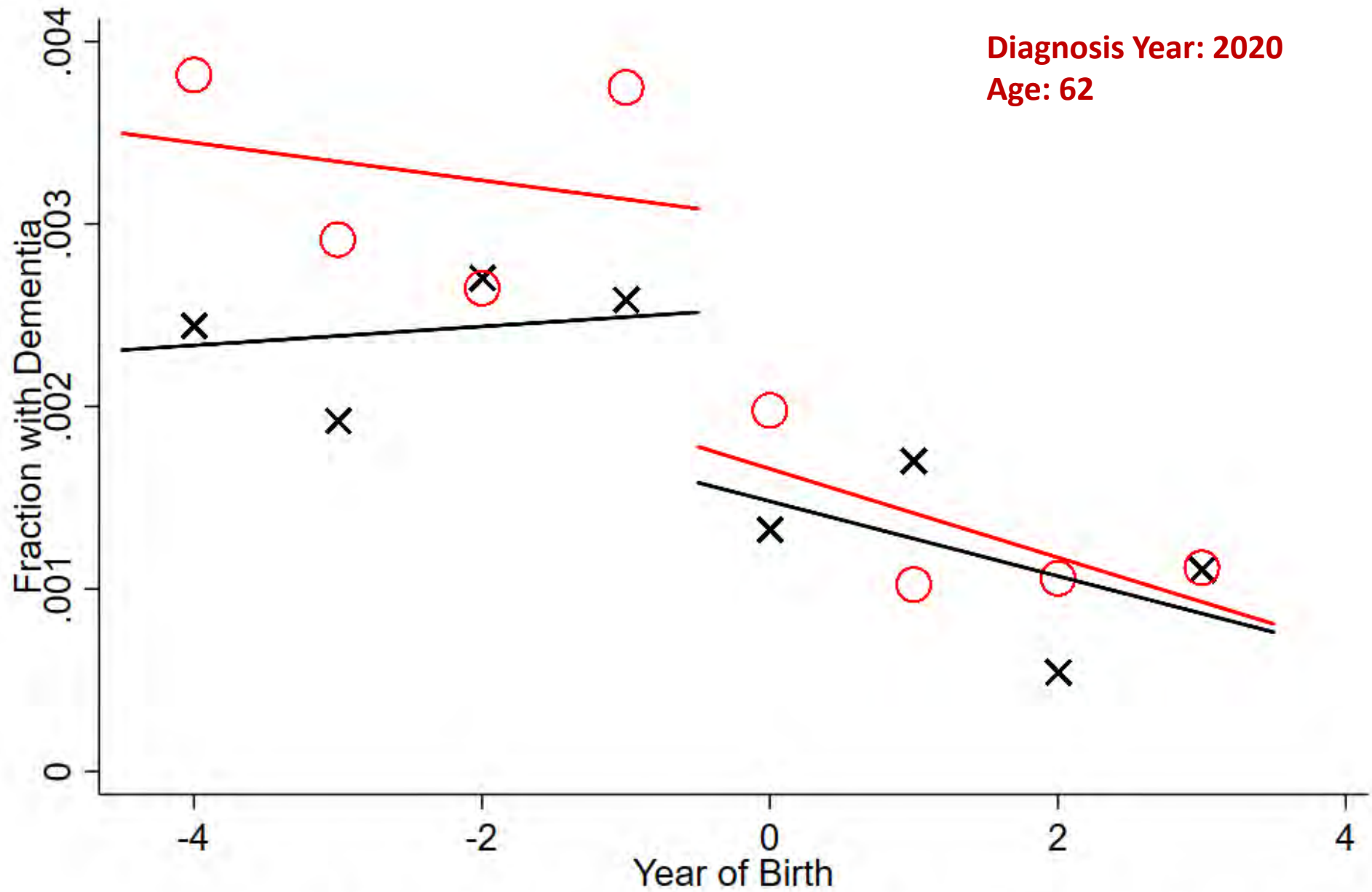


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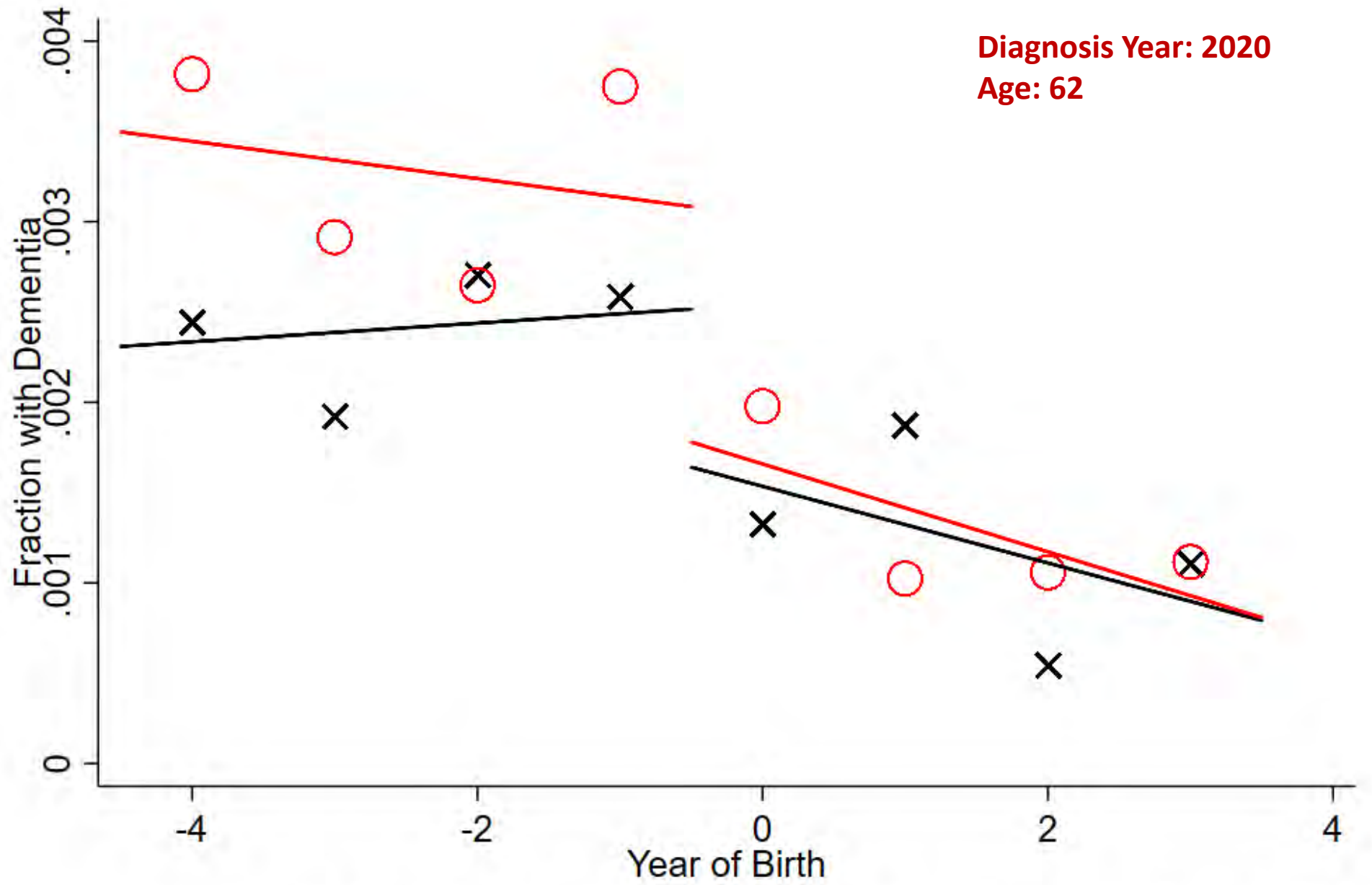




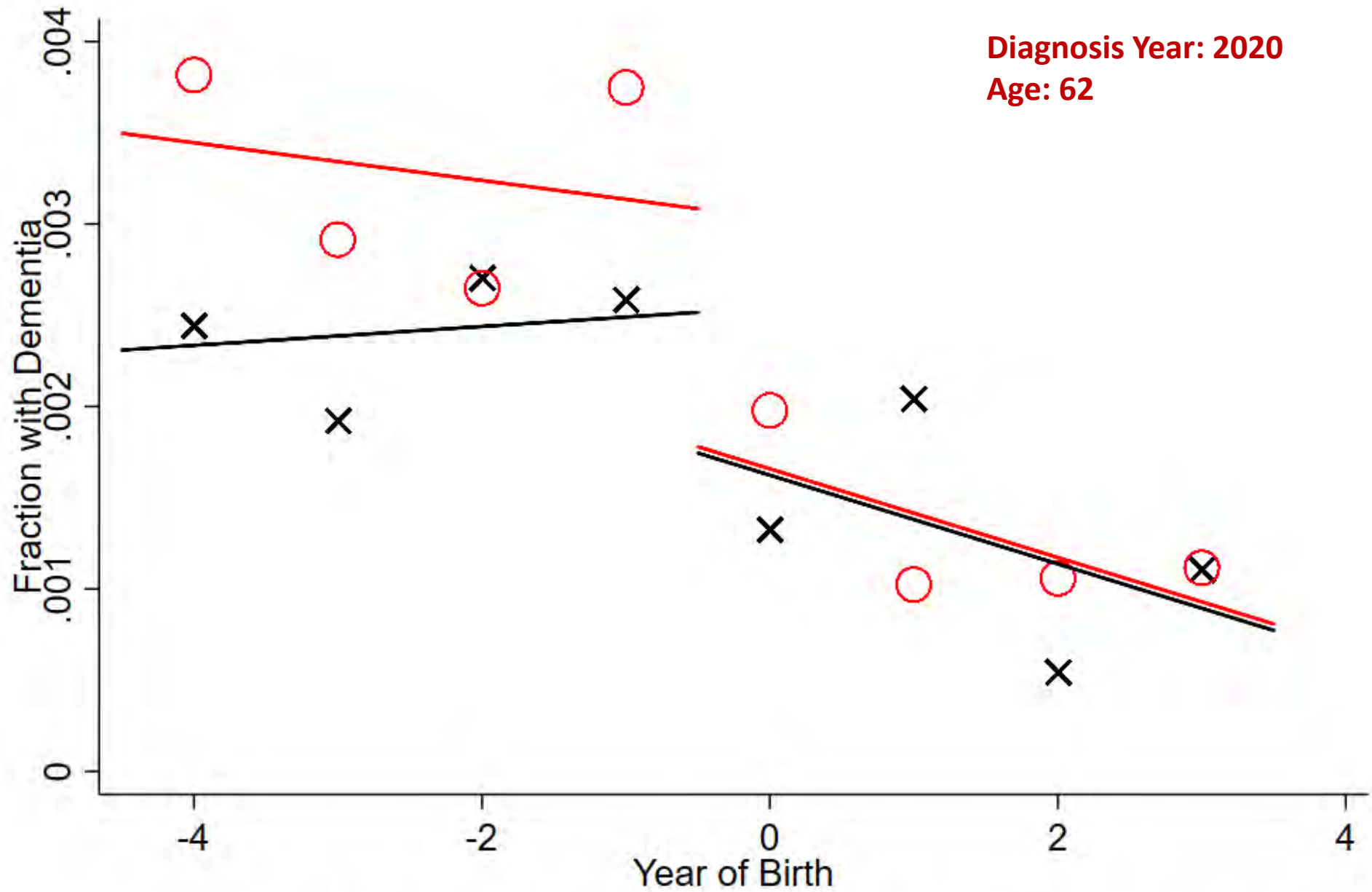
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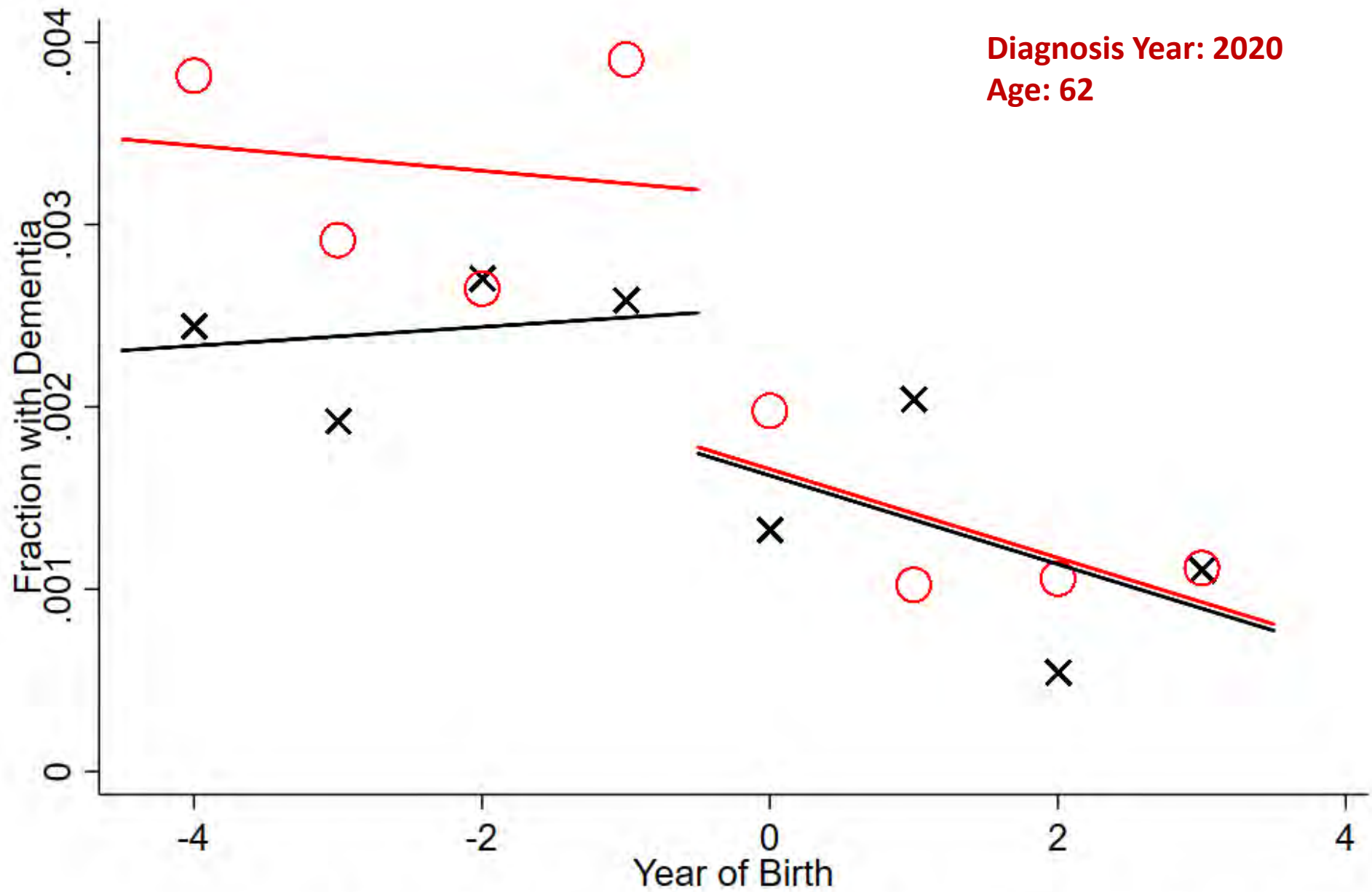
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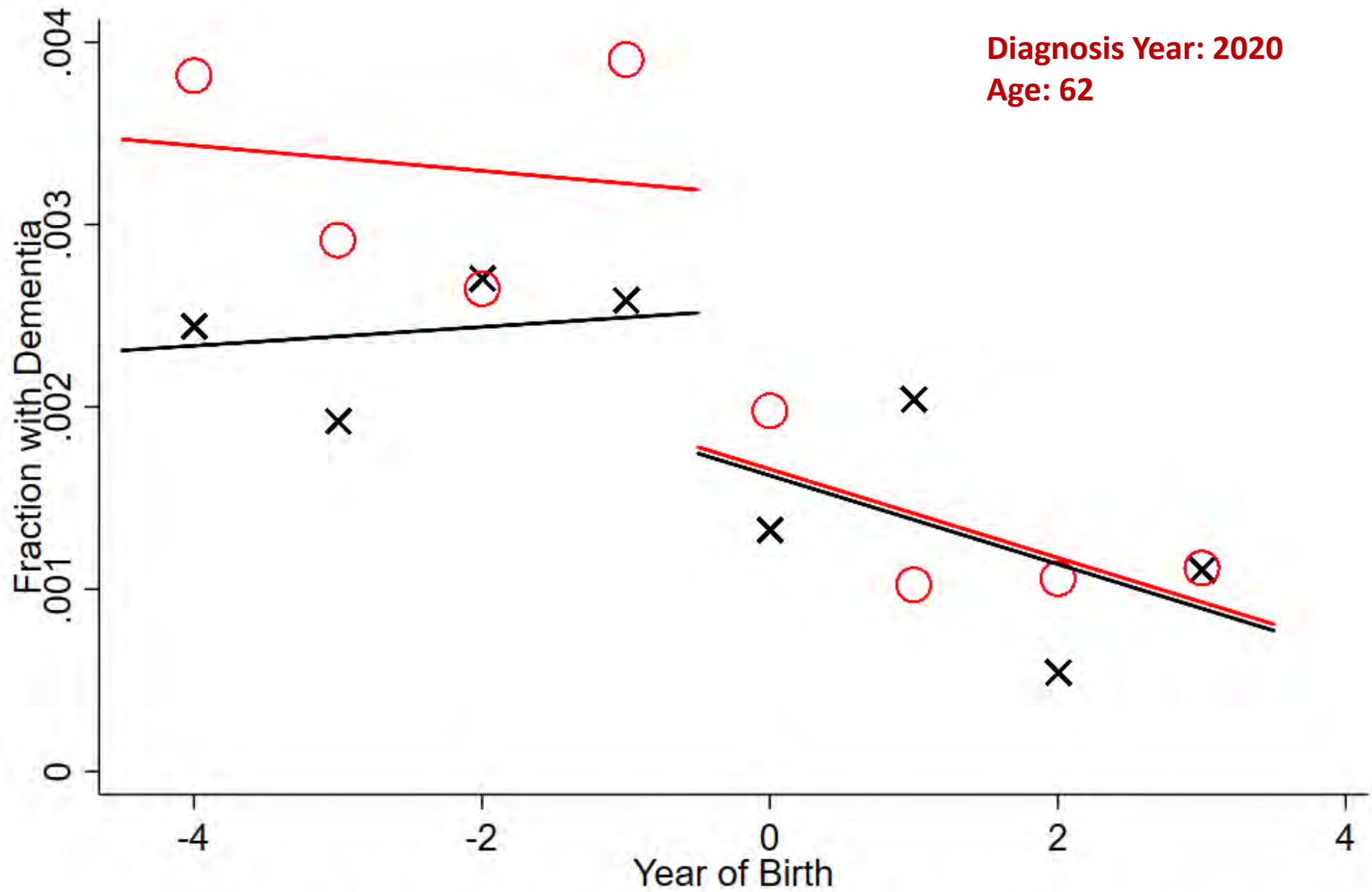
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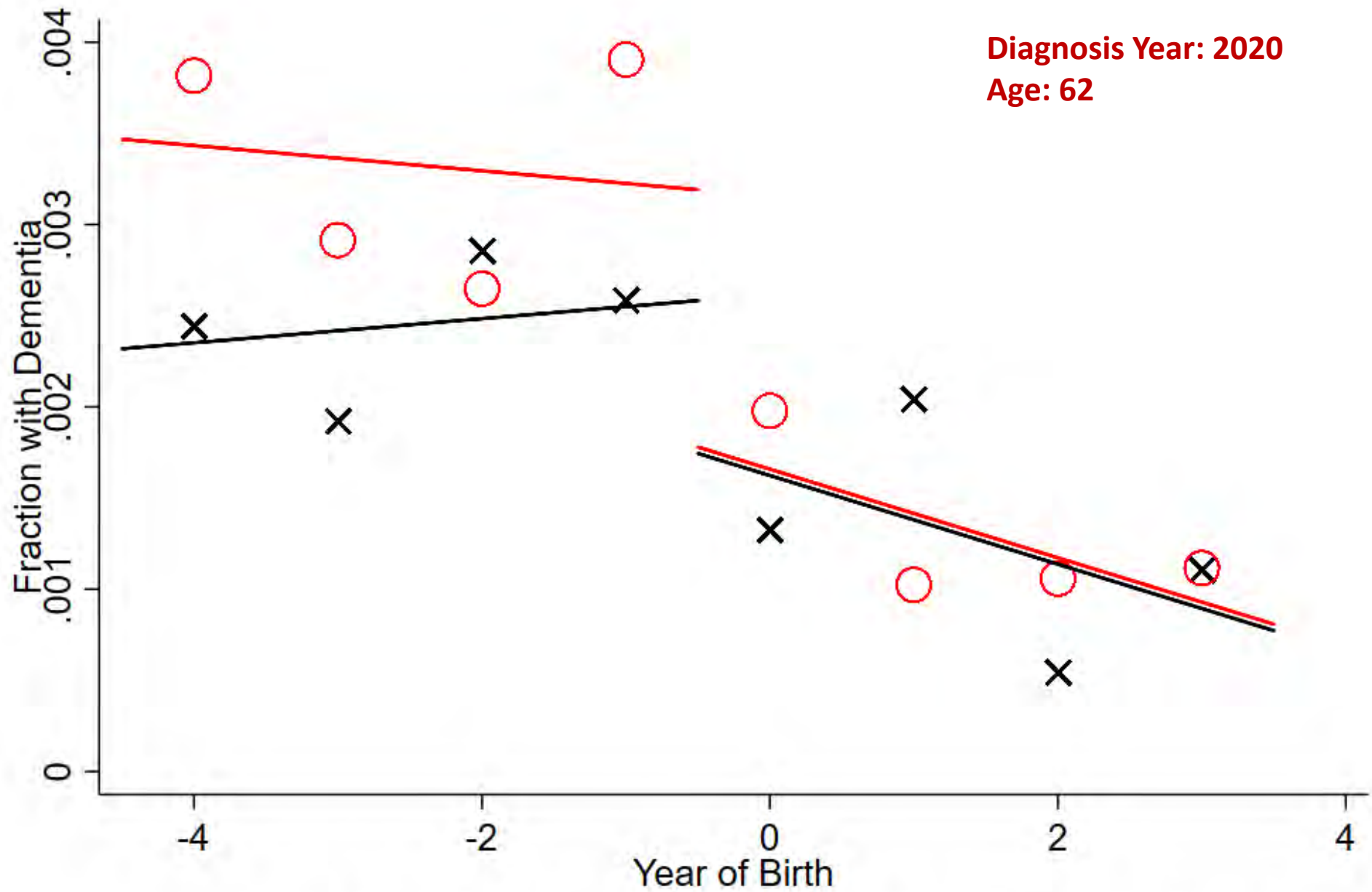
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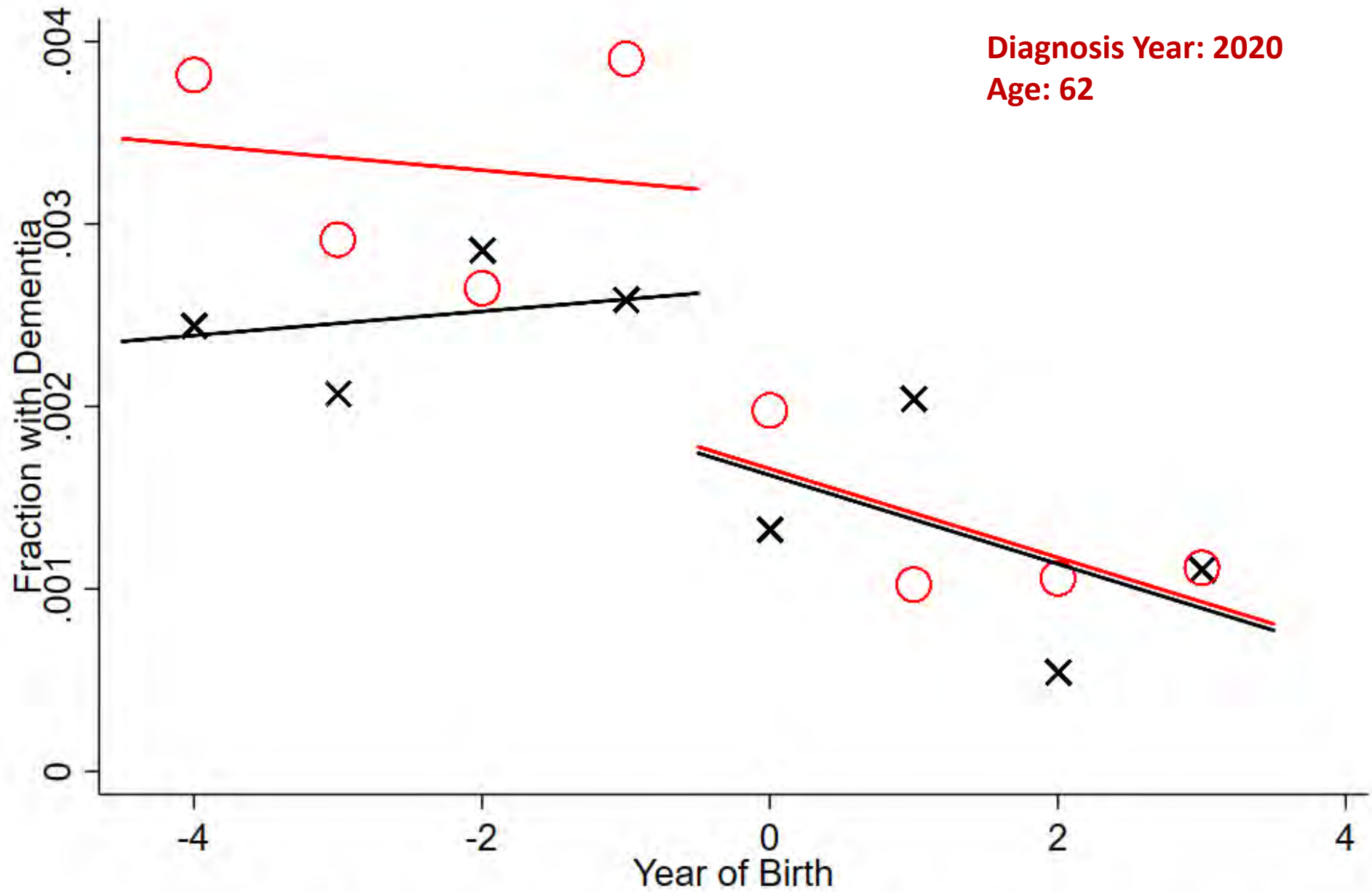
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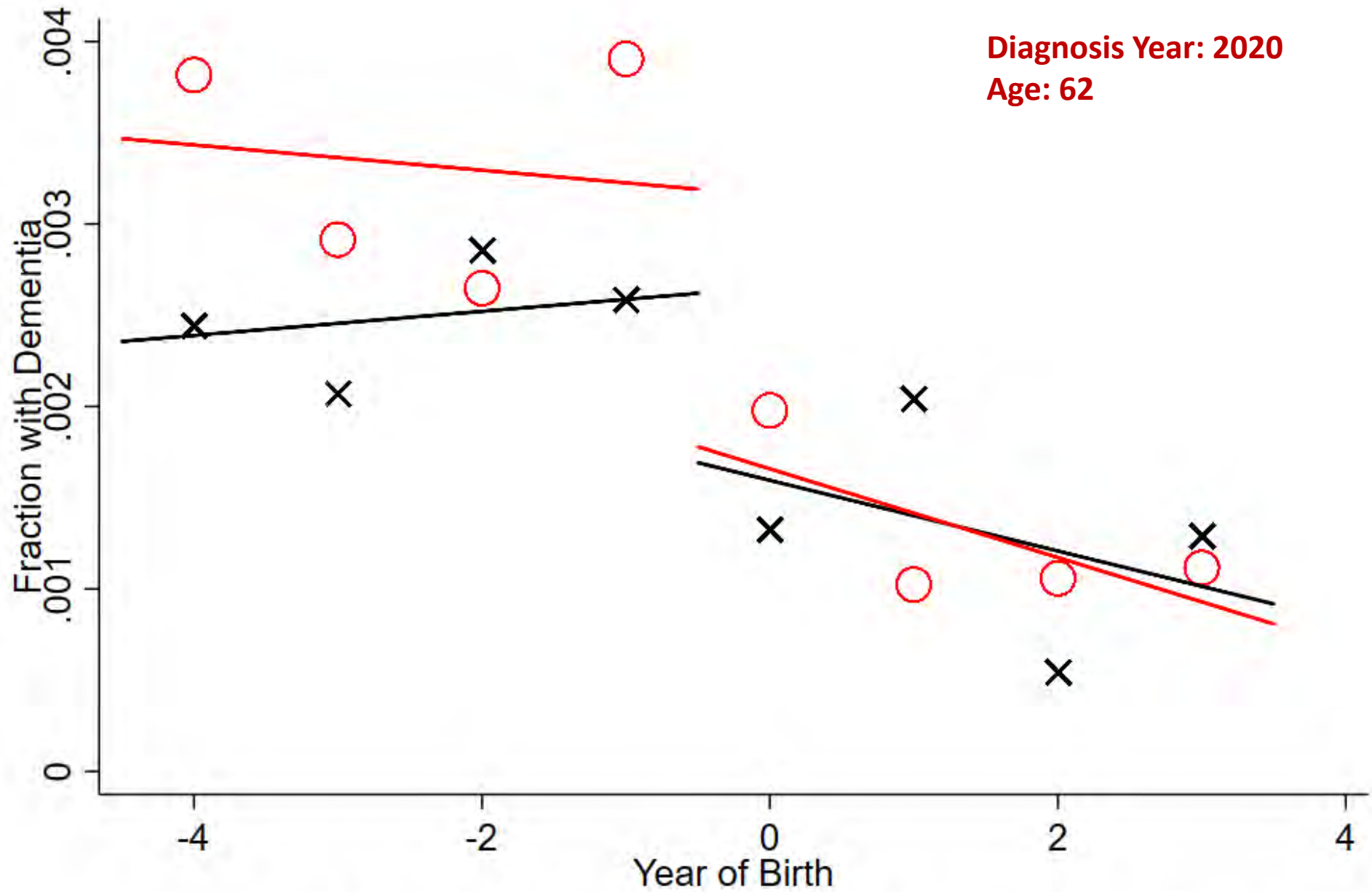
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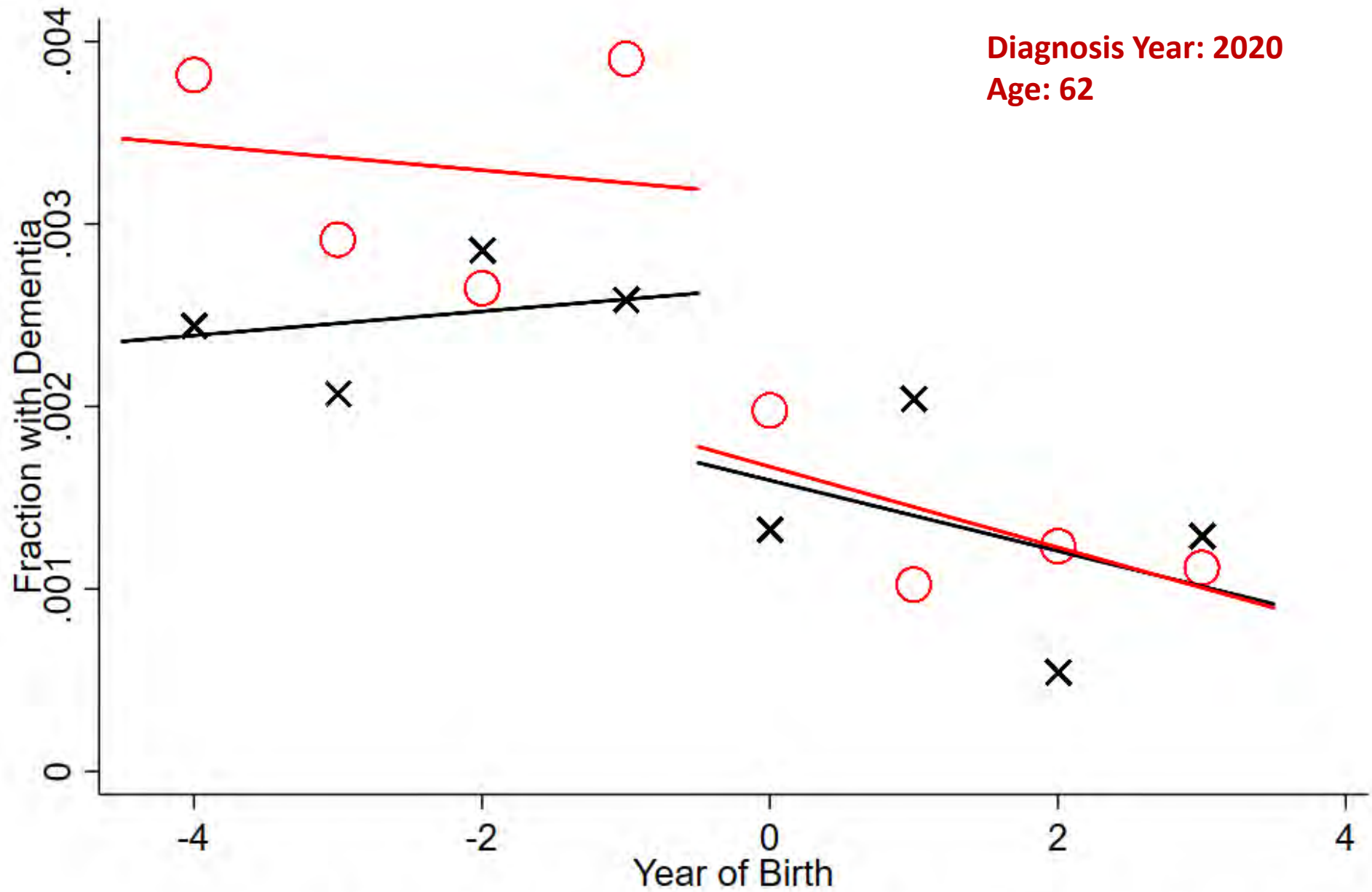
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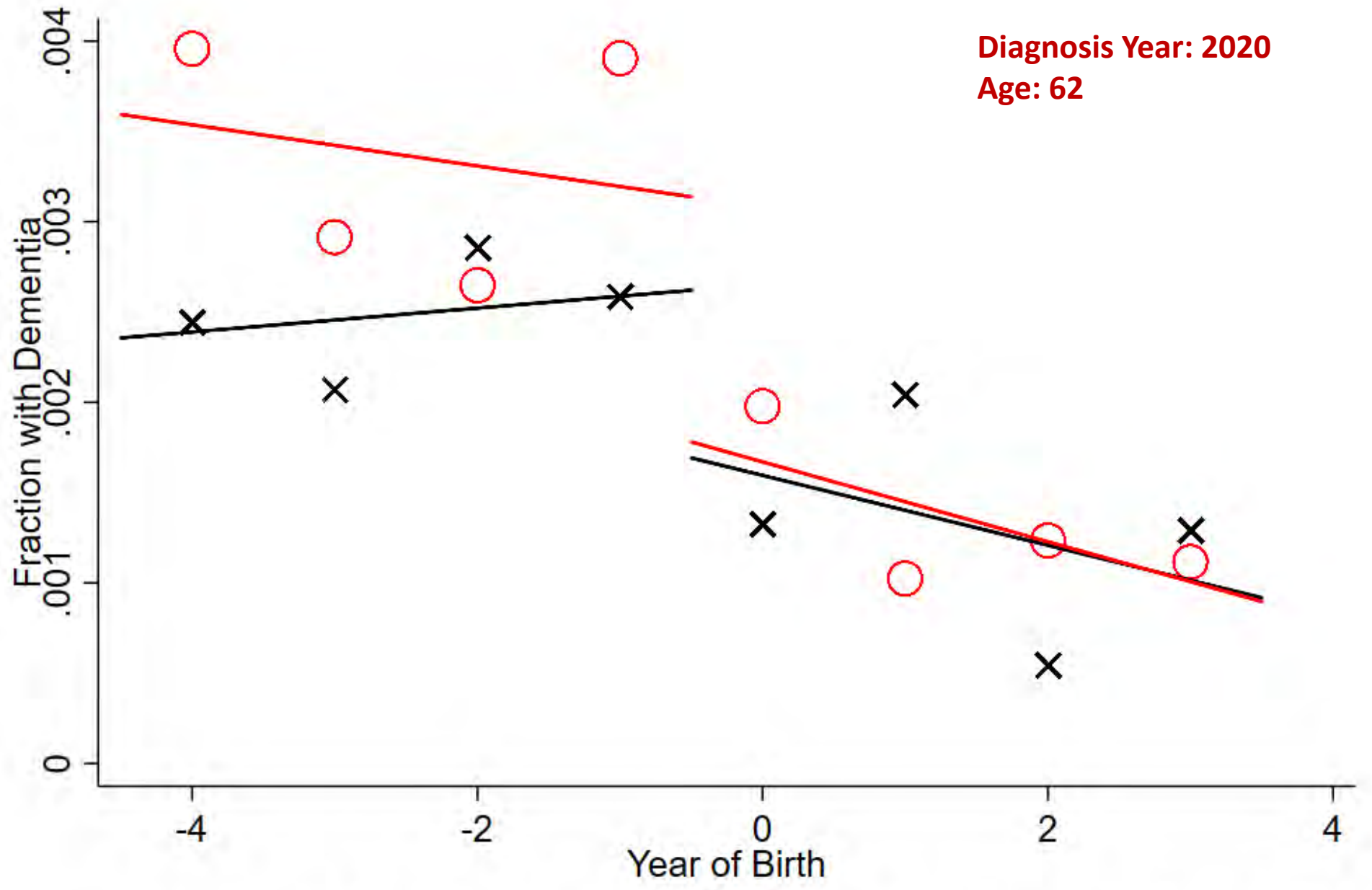
X Bottom Half Composite Genetic Risk O Top Half Composite Genetic Risk



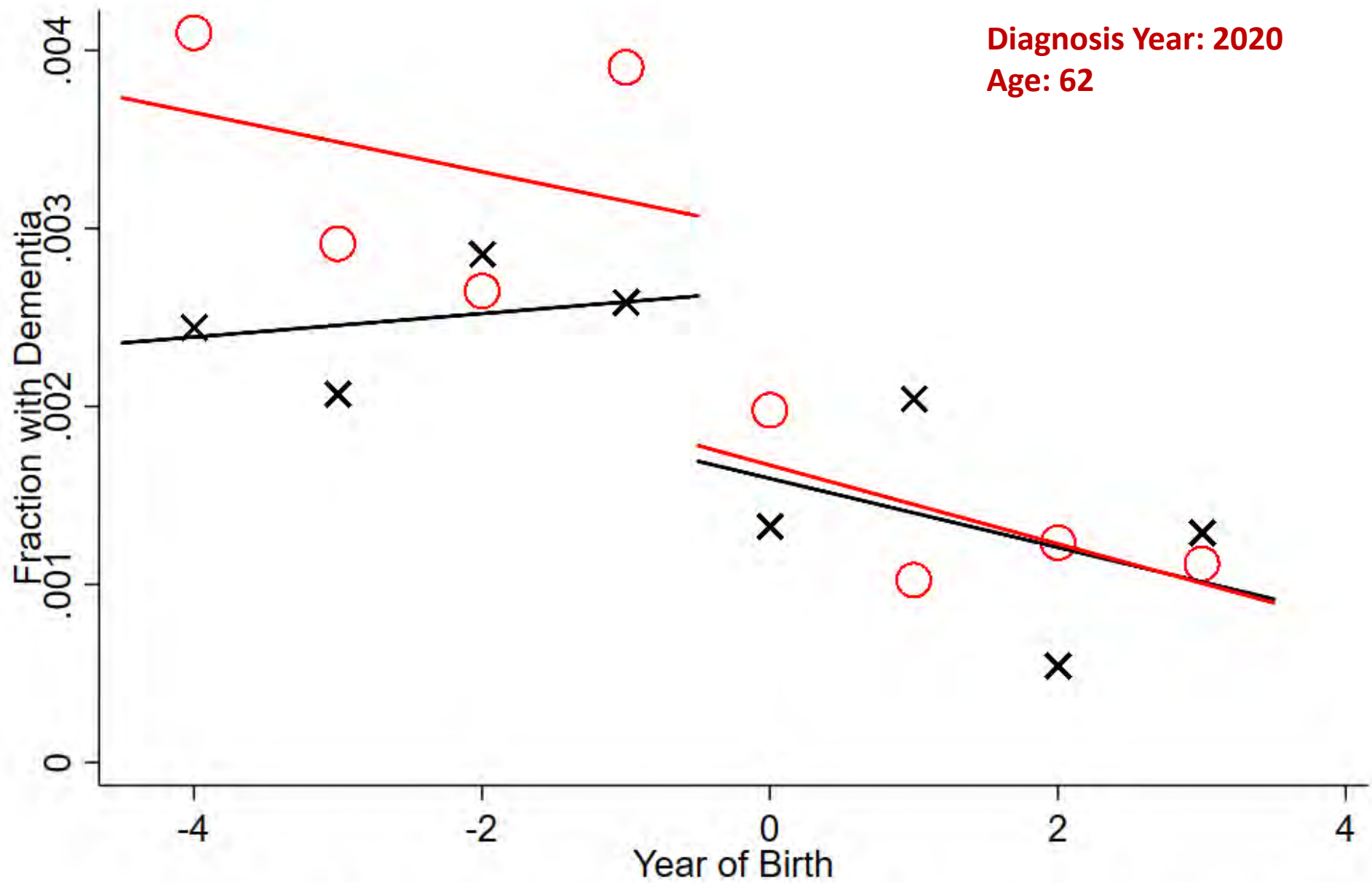
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



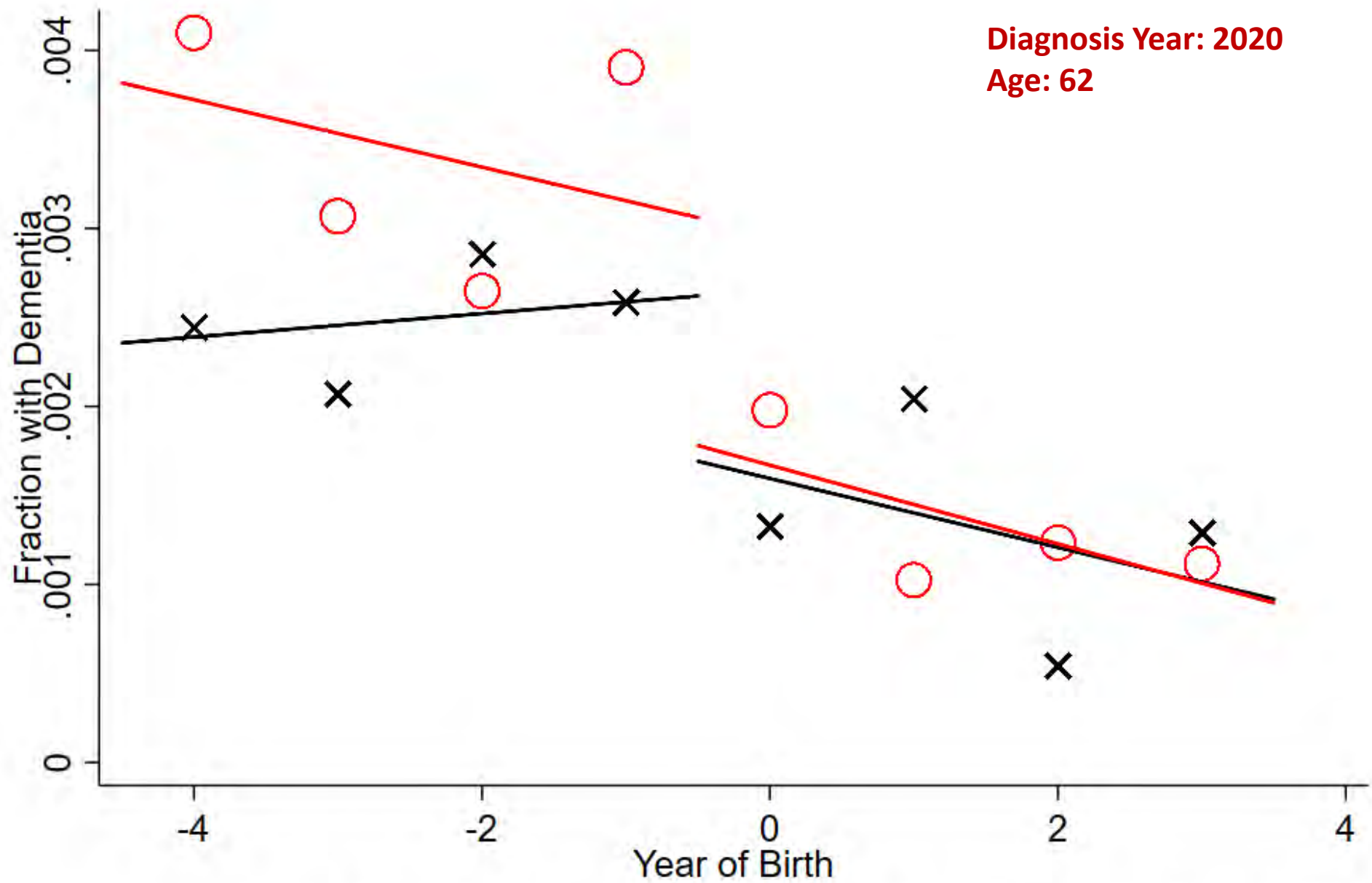
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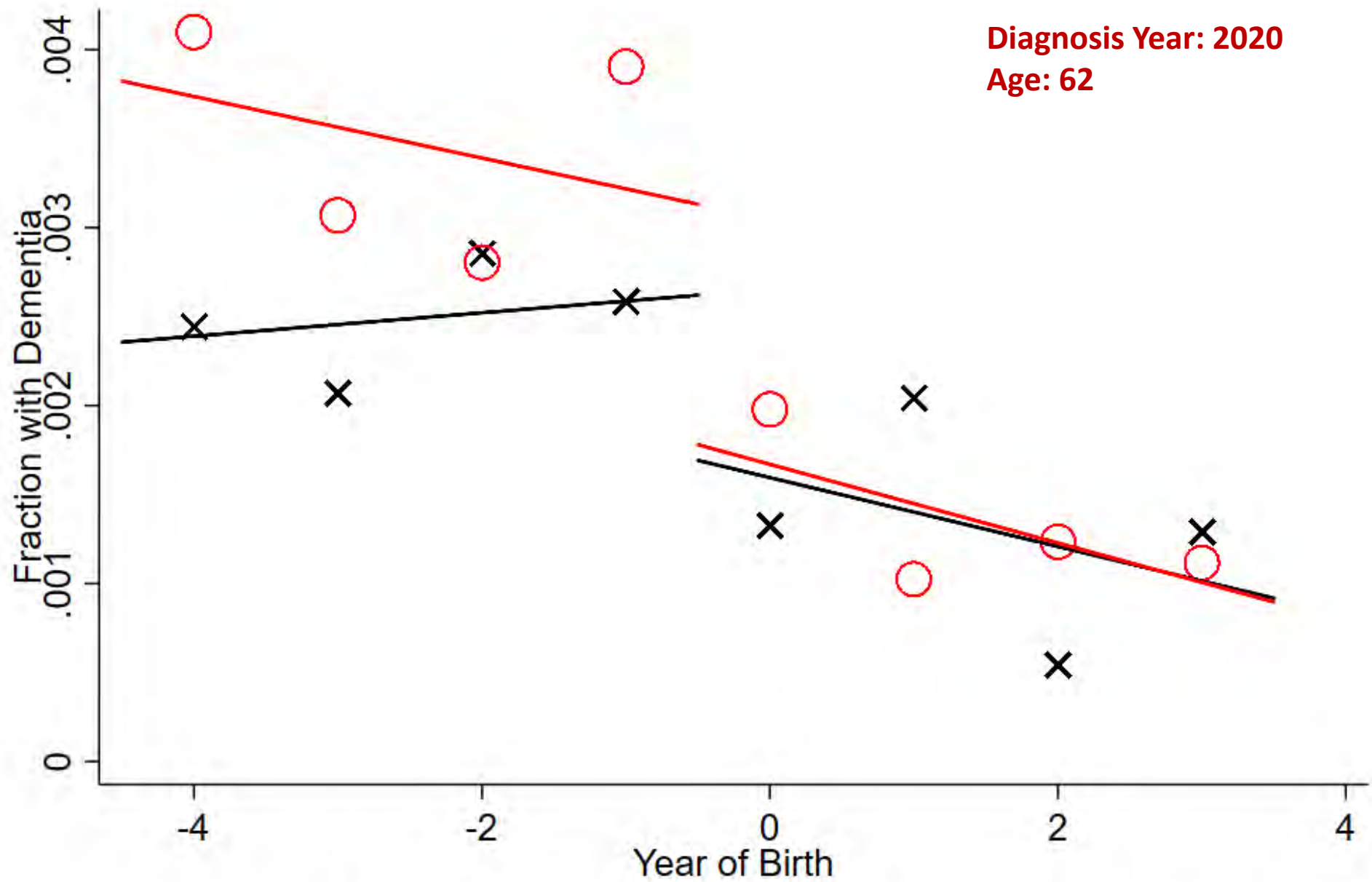
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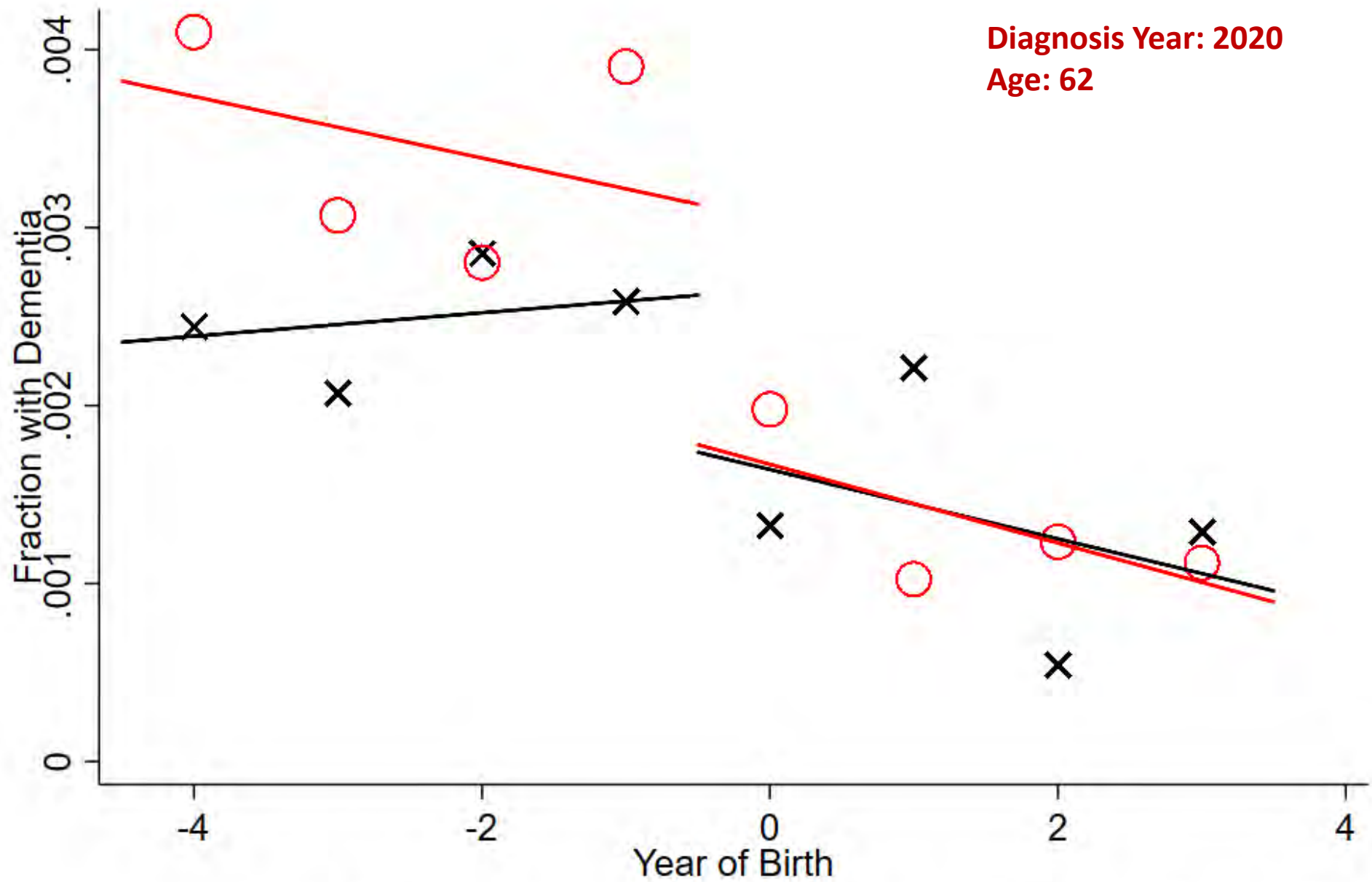
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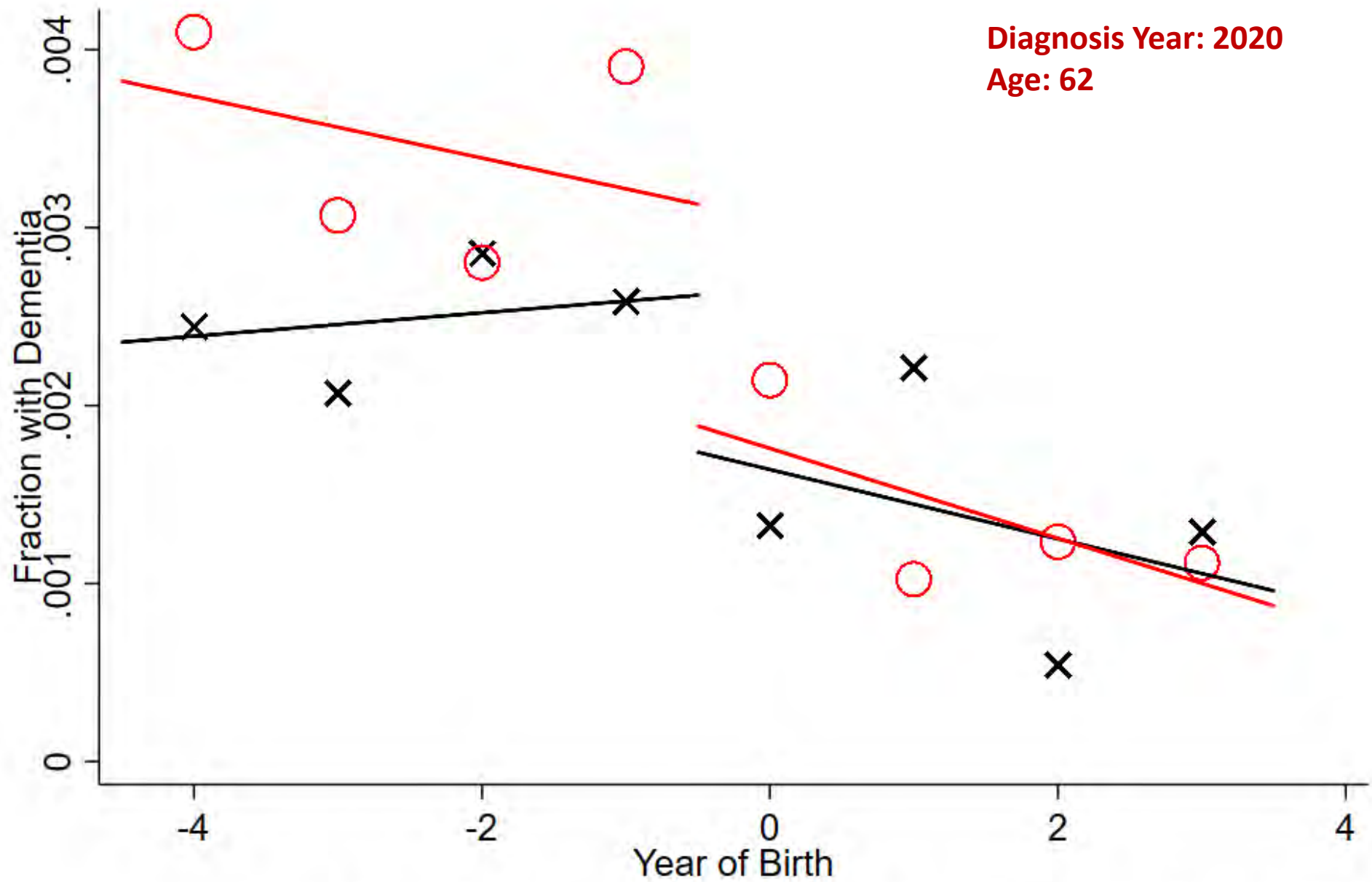
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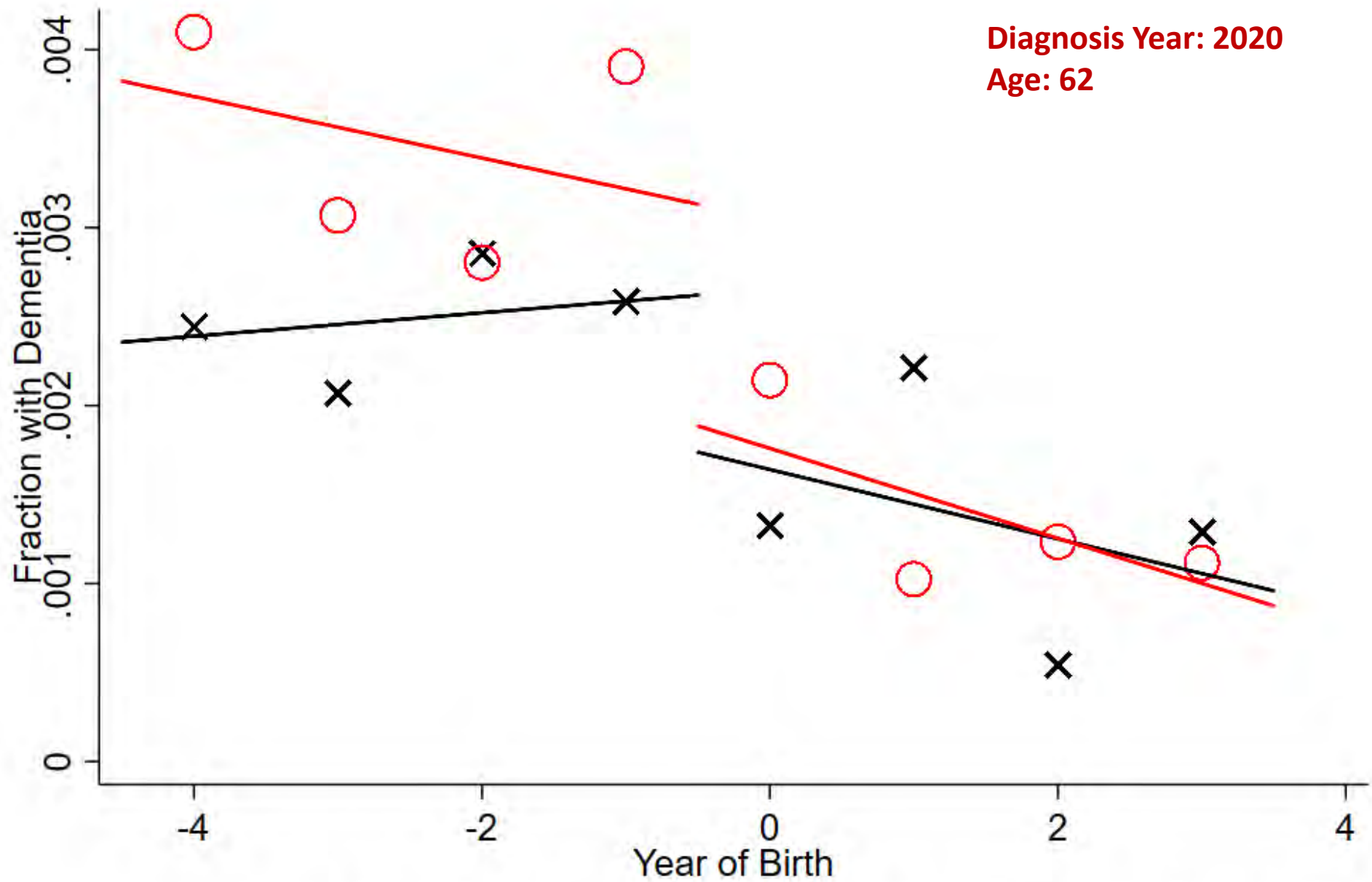
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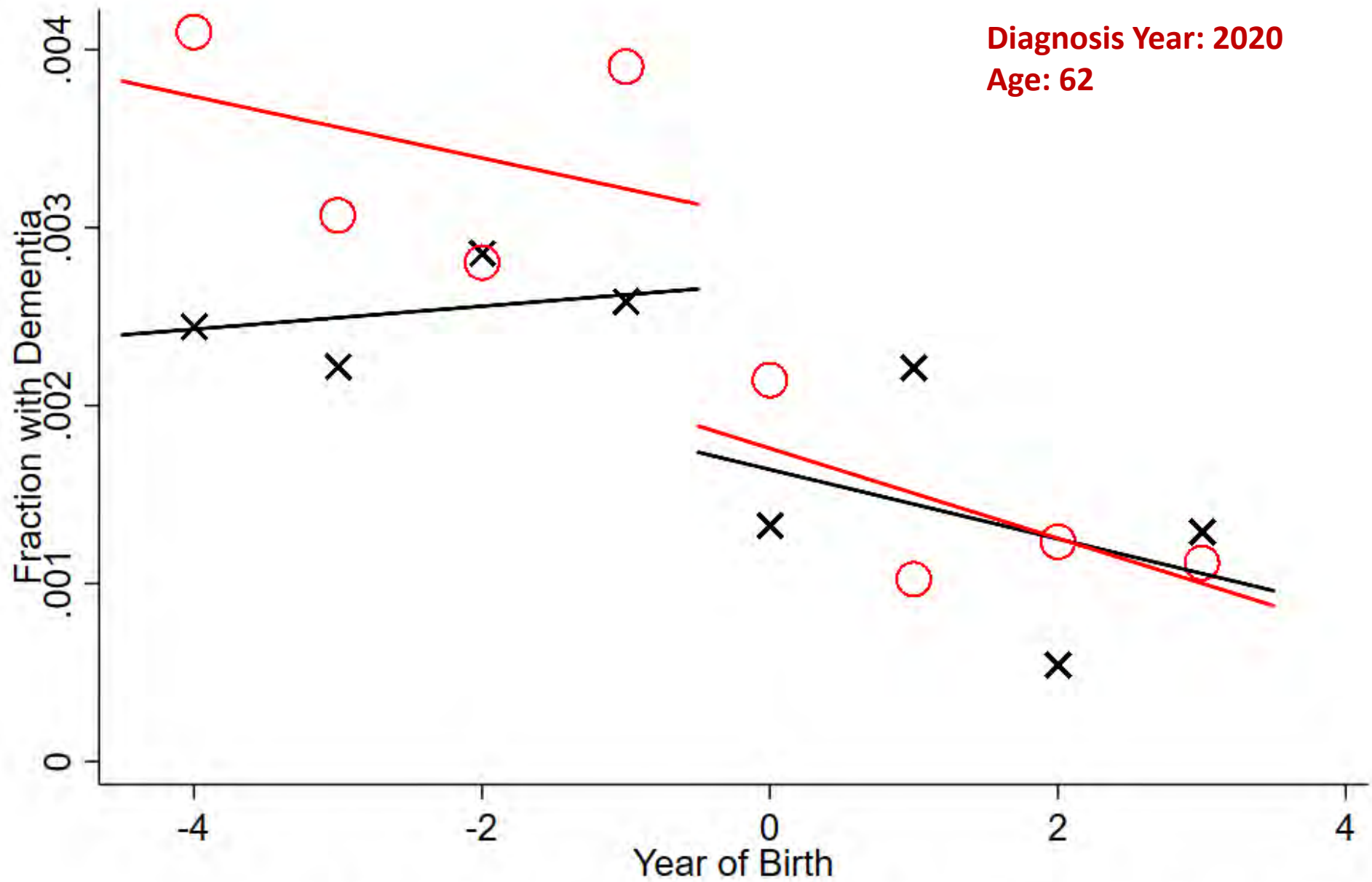
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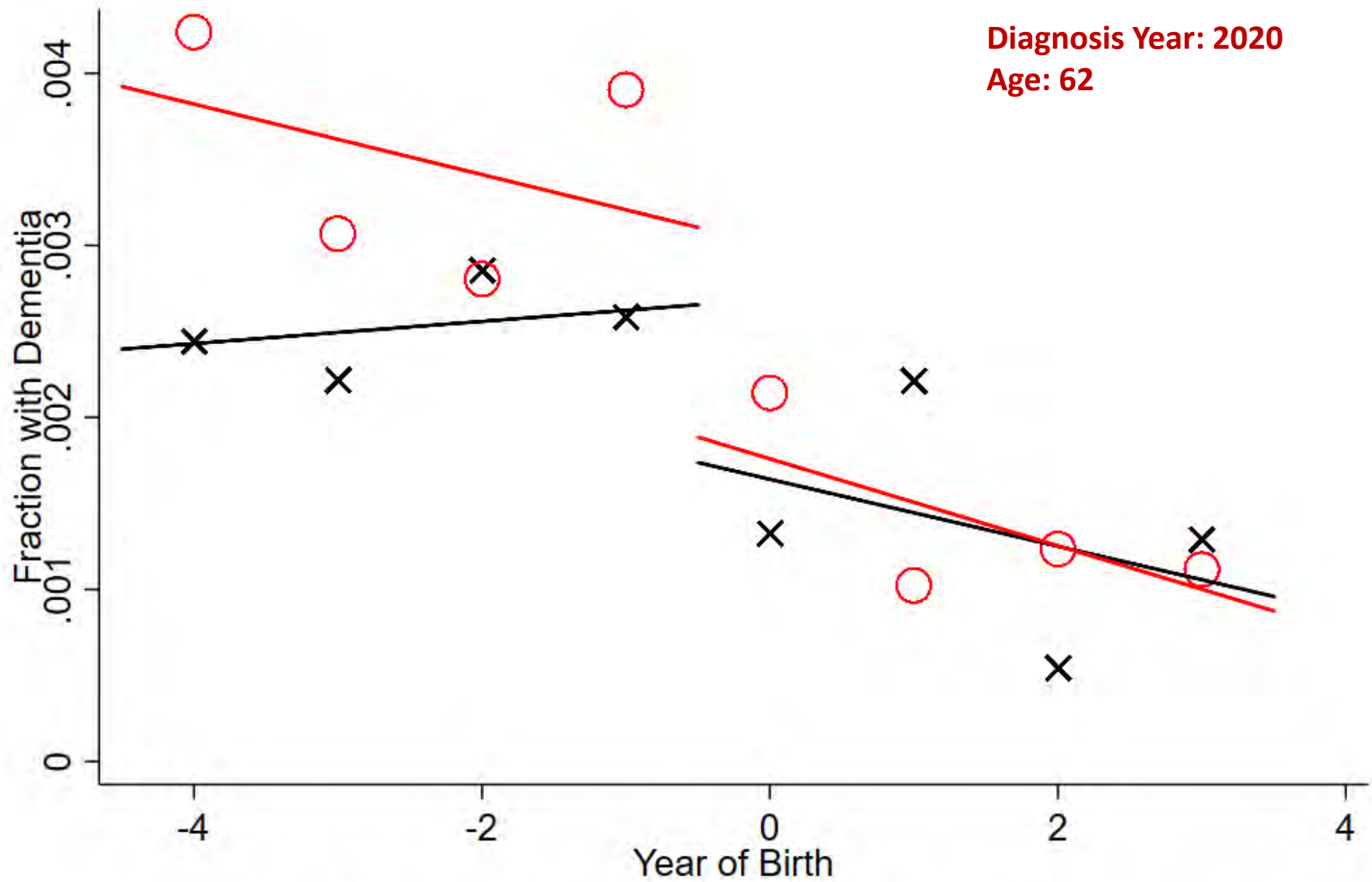
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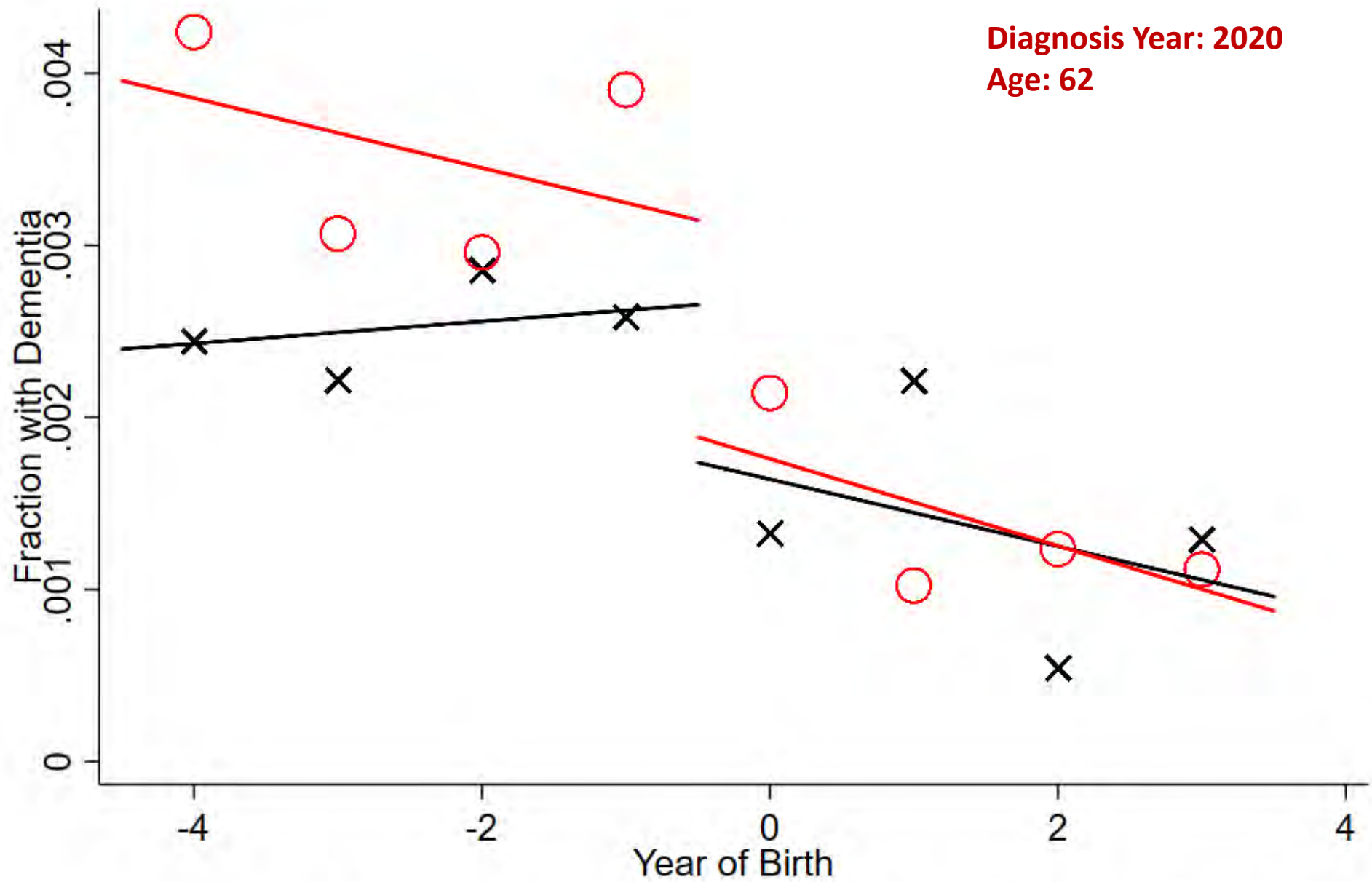
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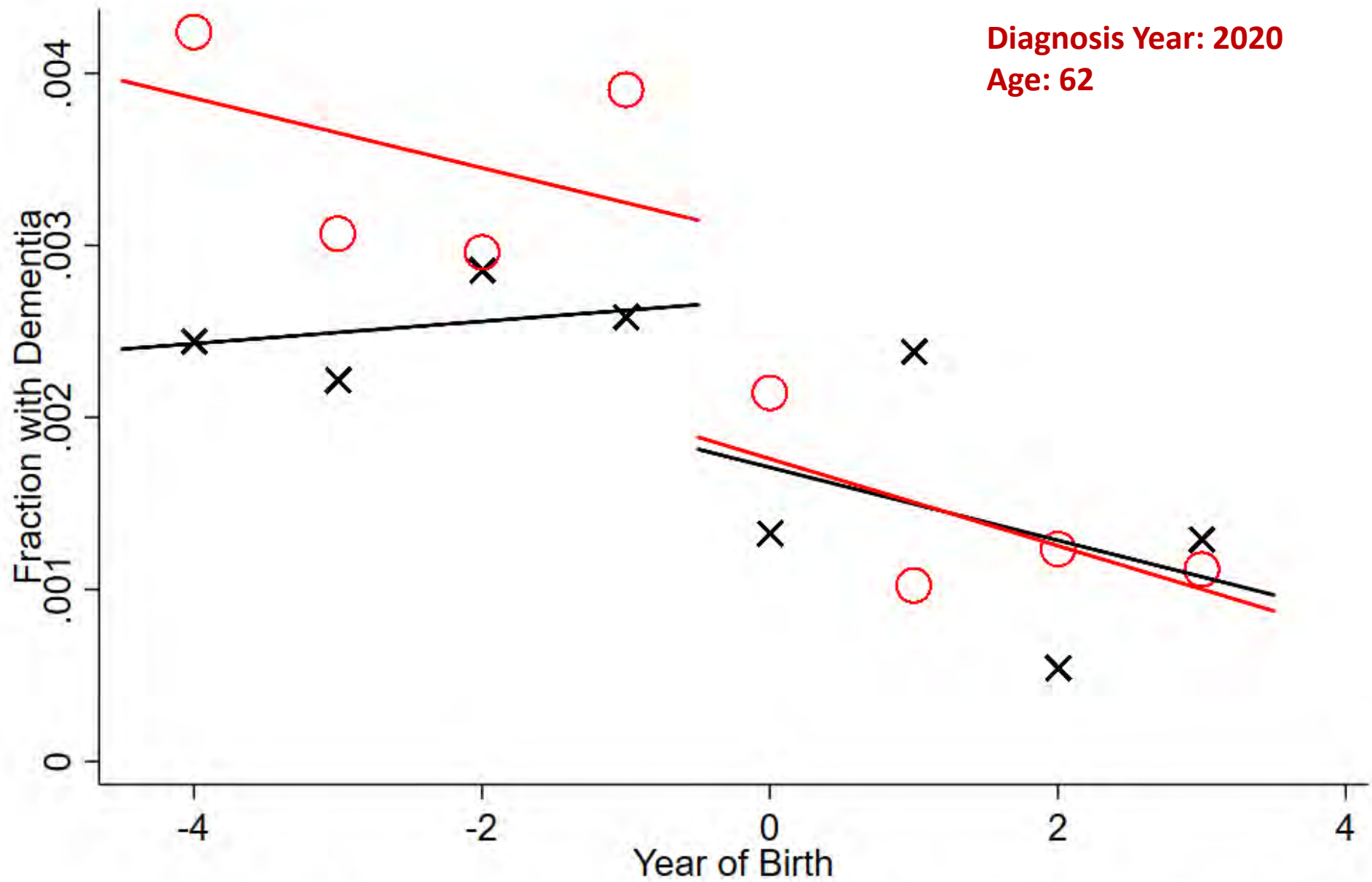
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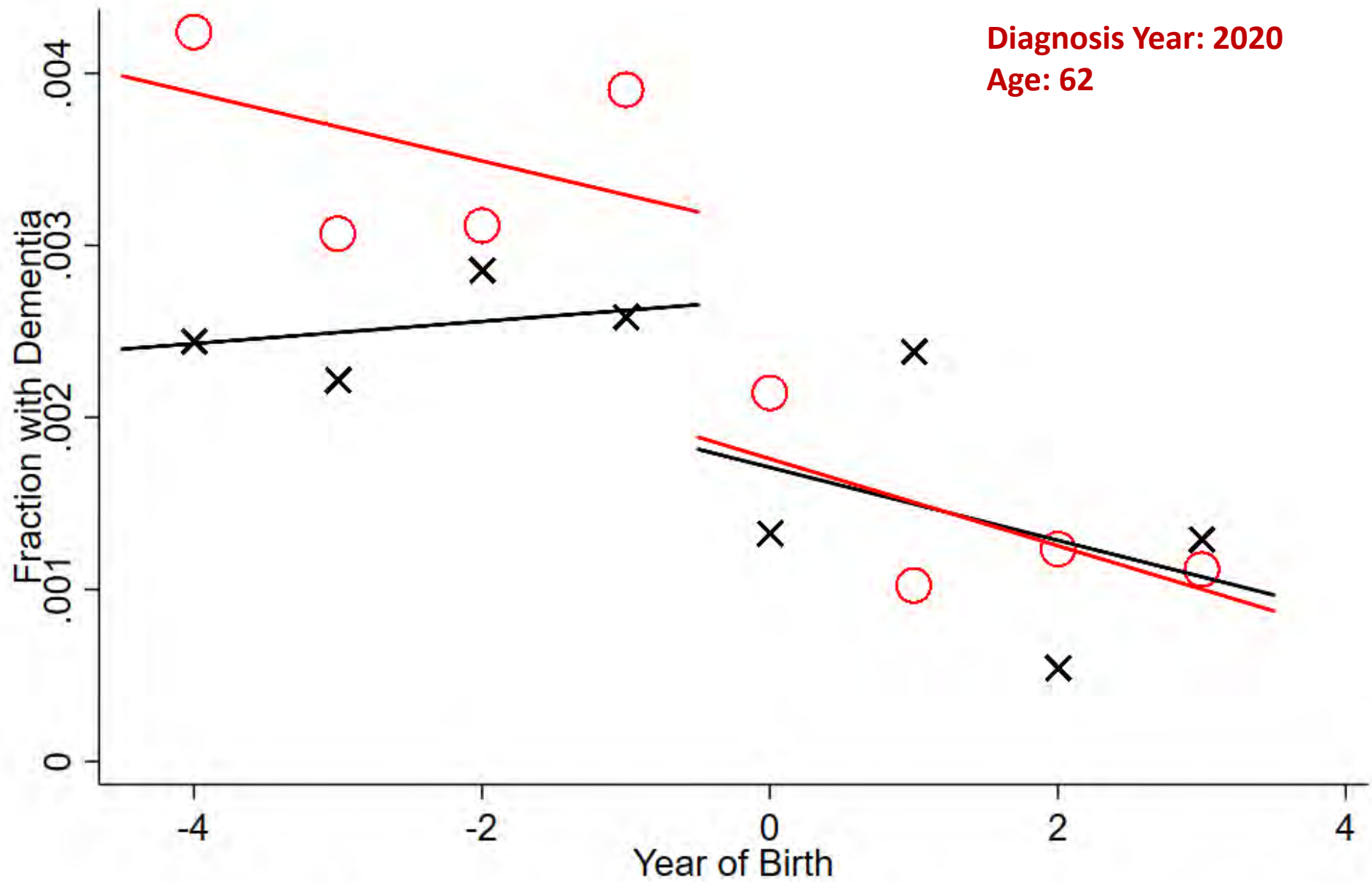
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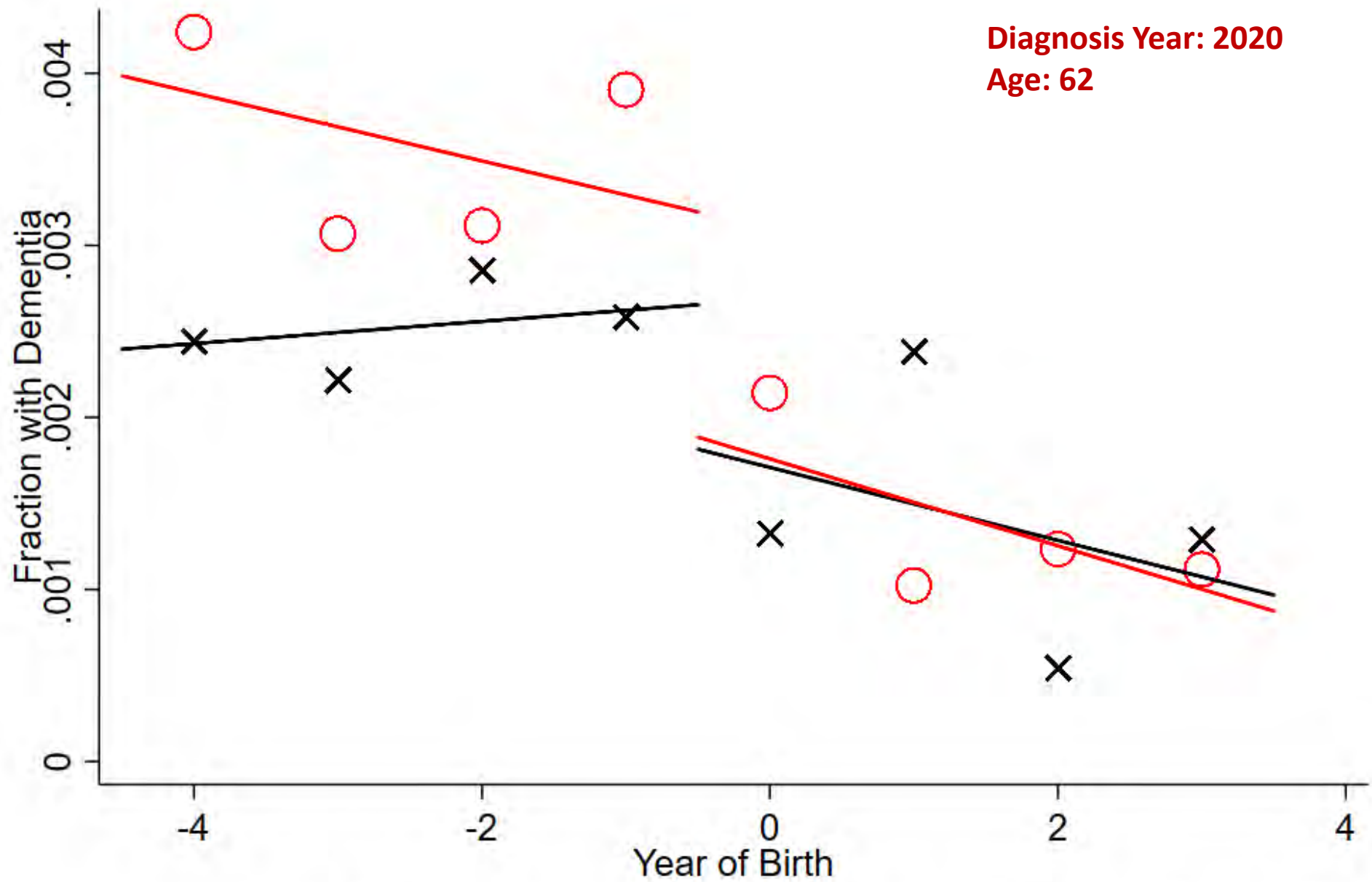
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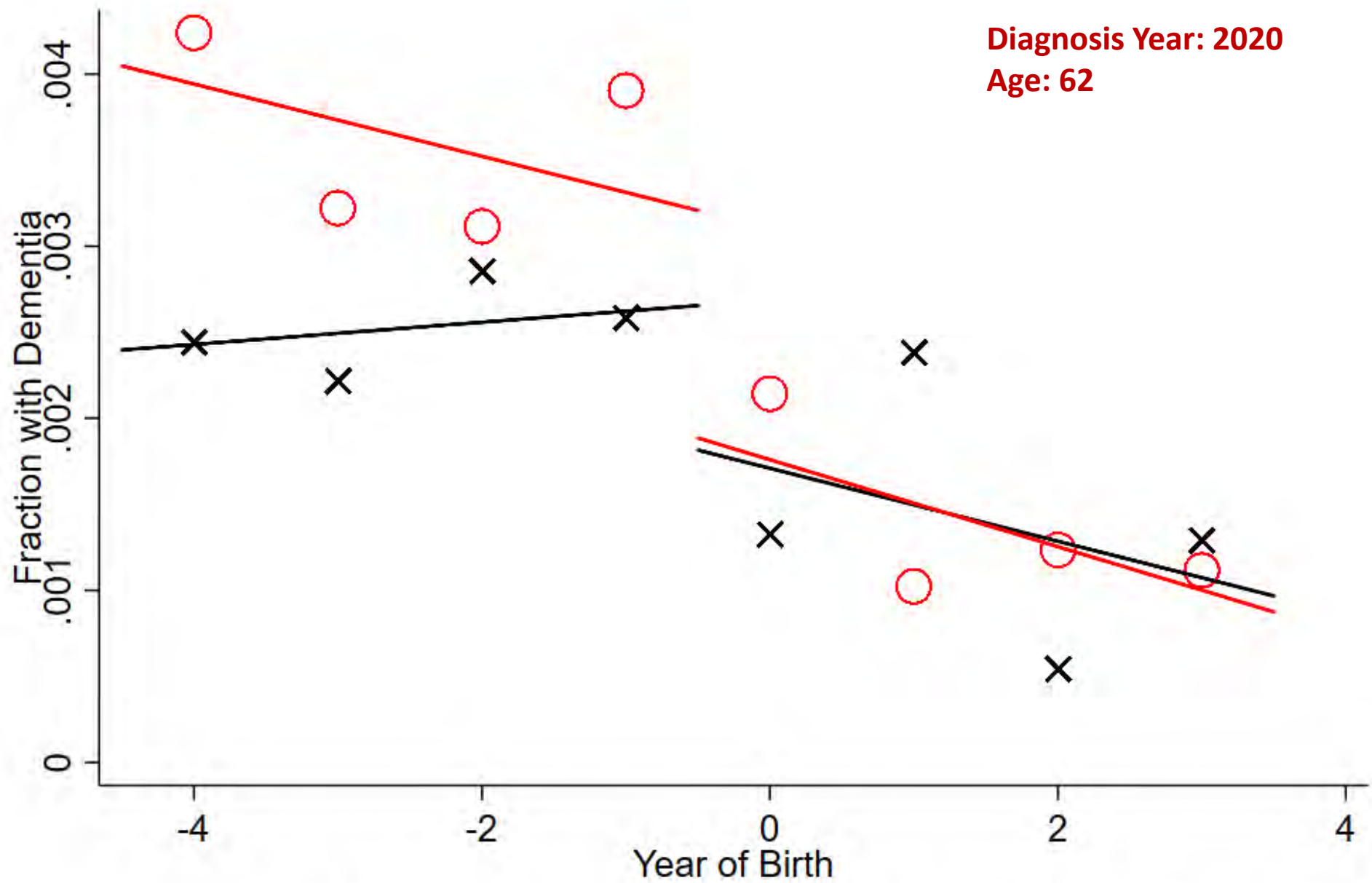
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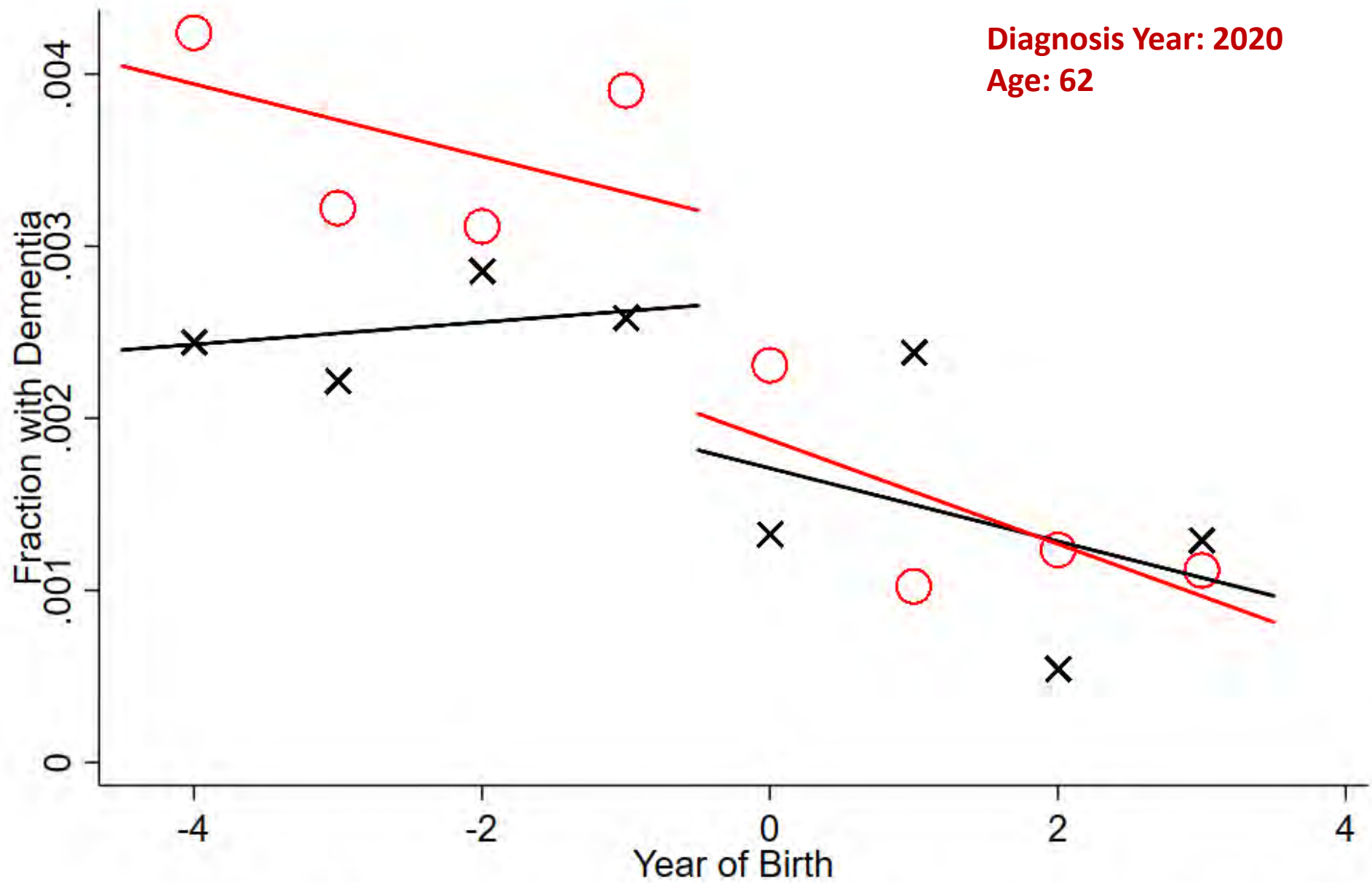
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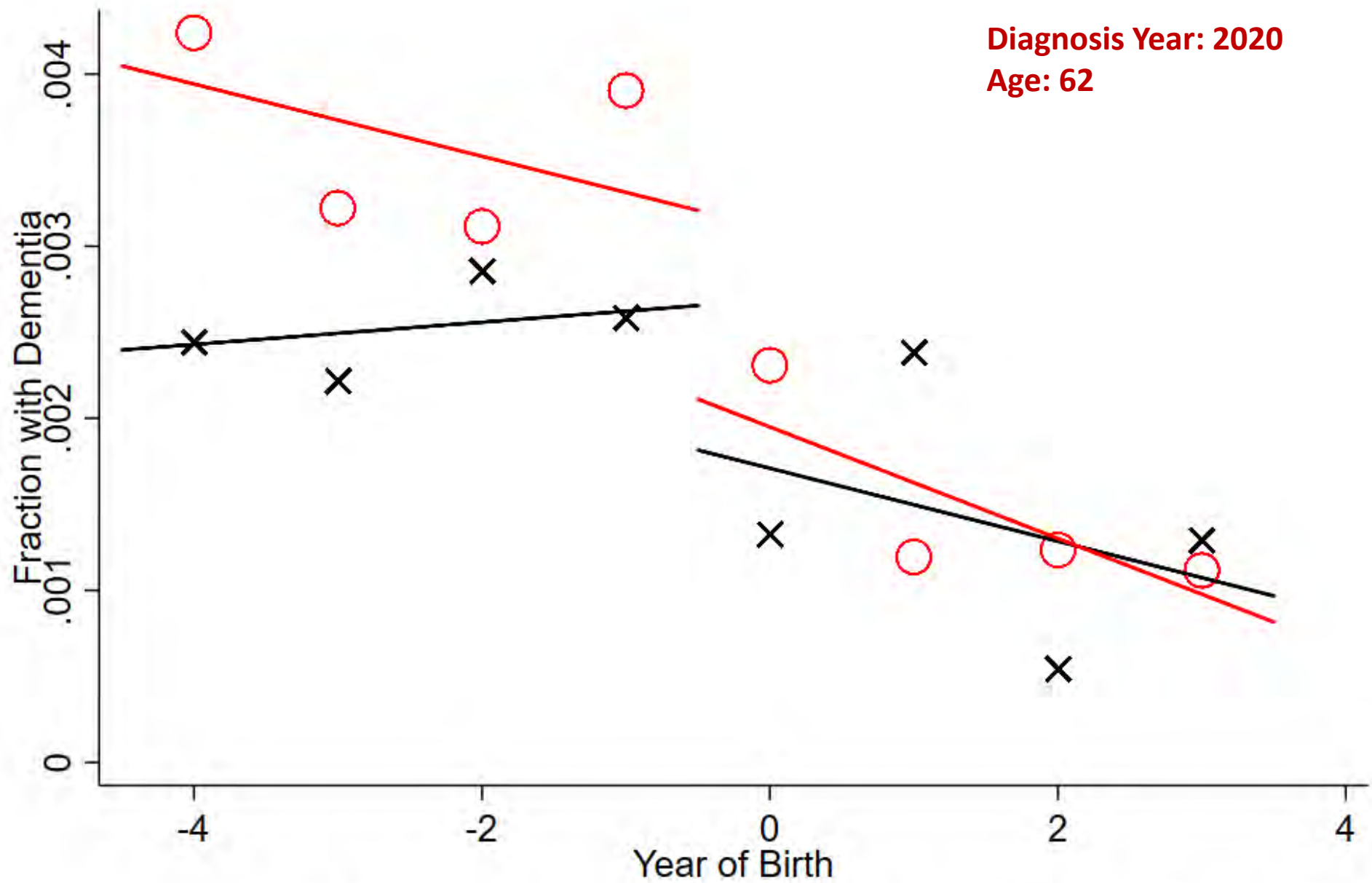
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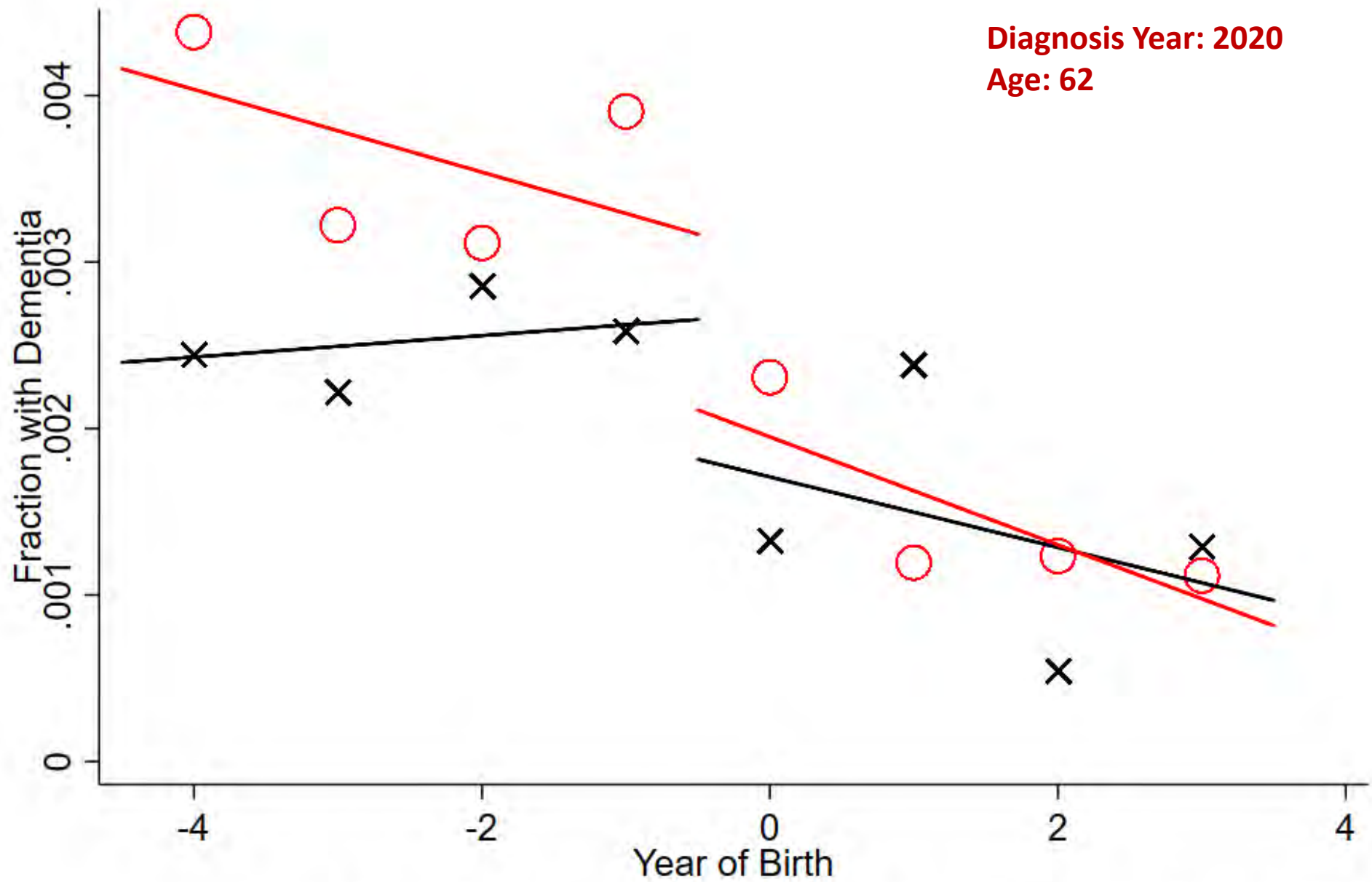
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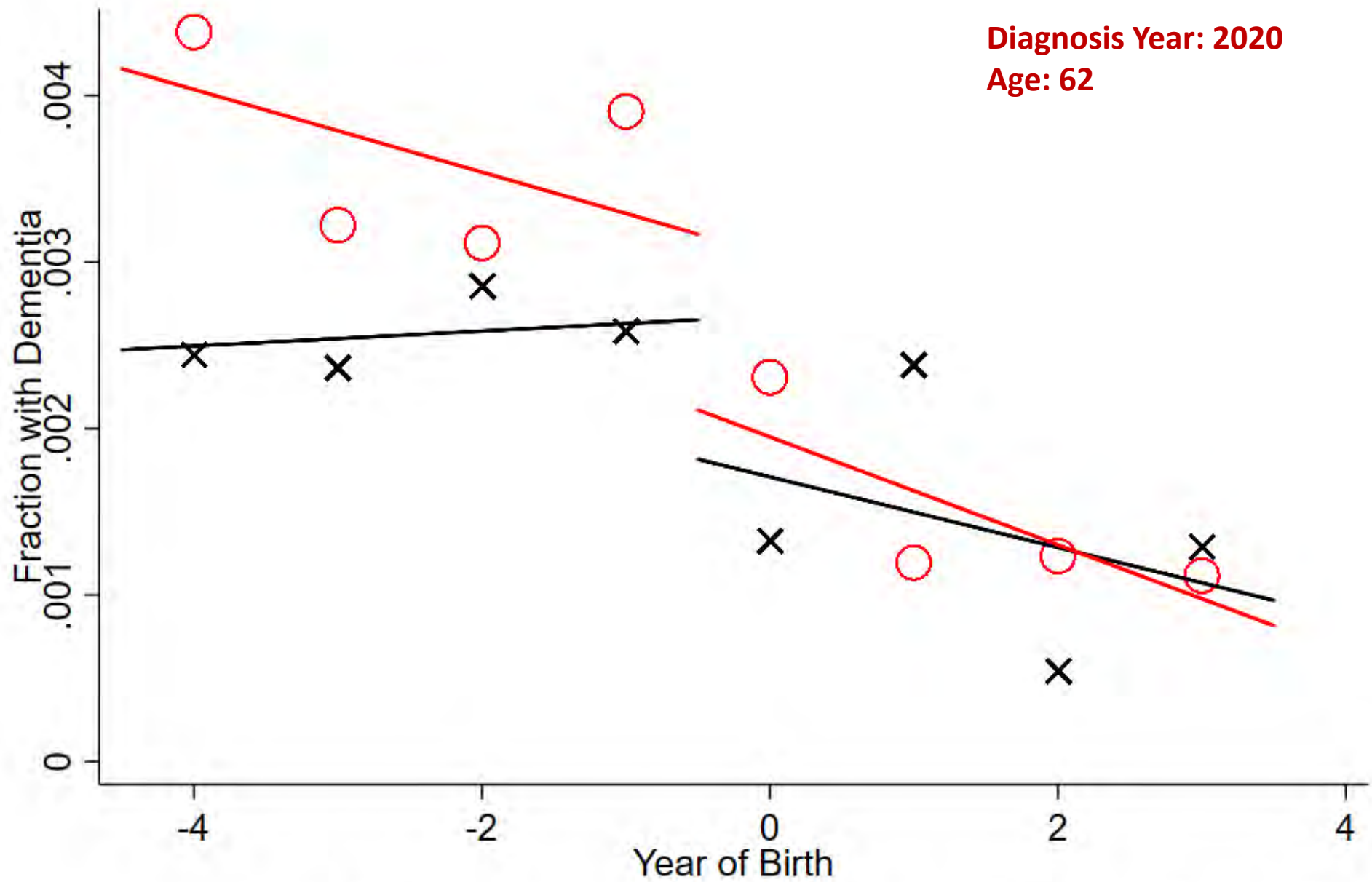
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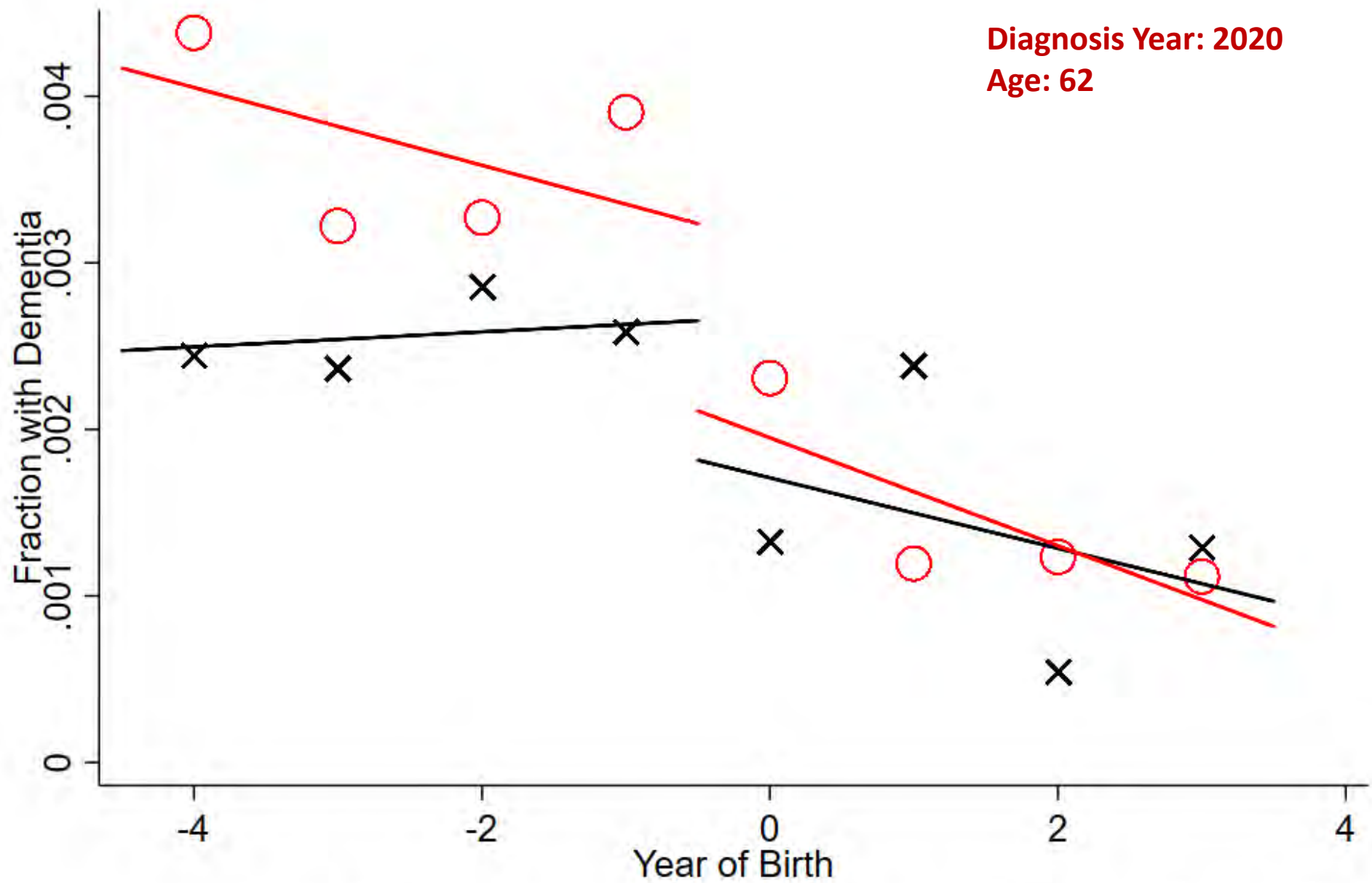
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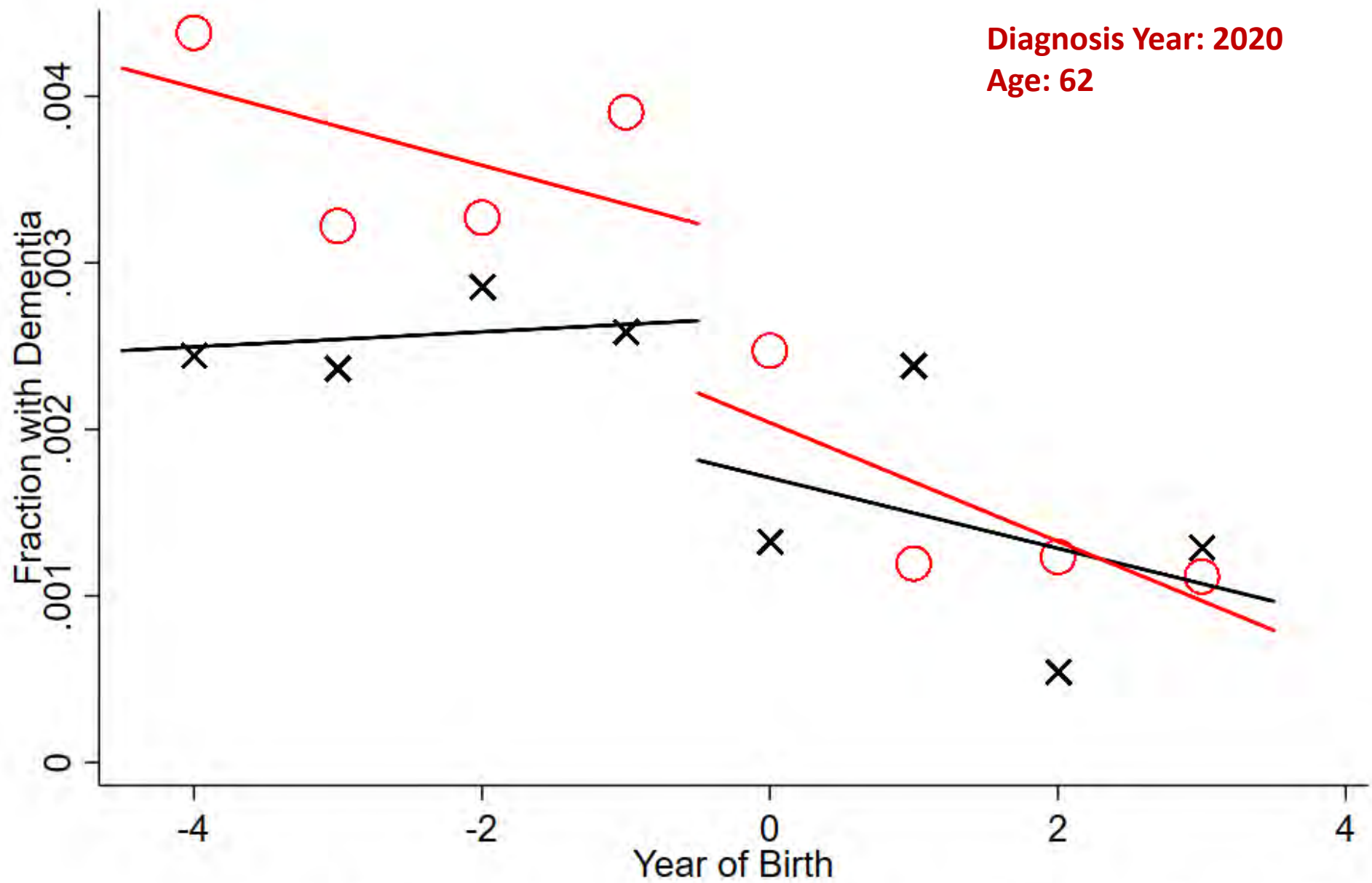
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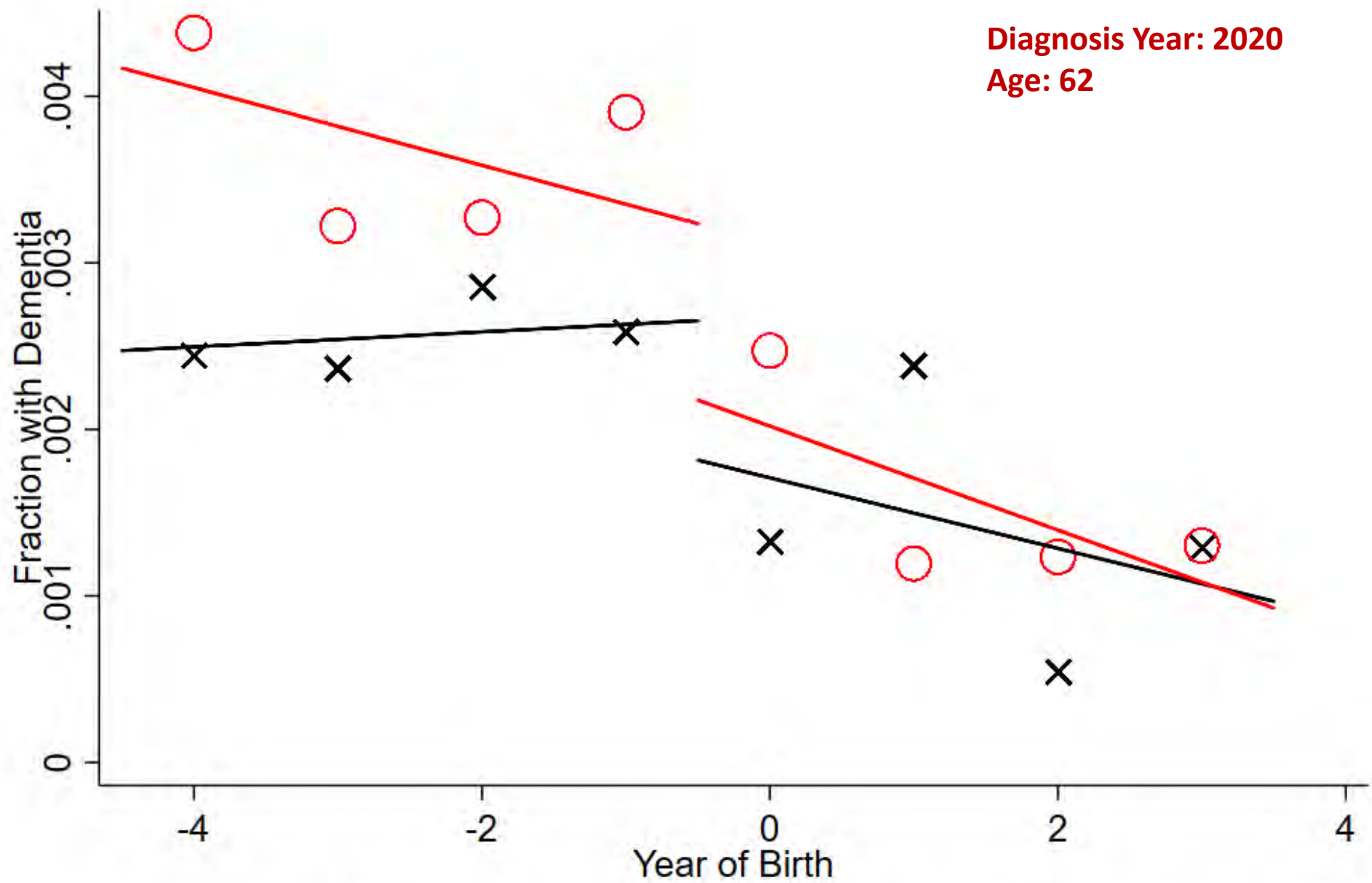
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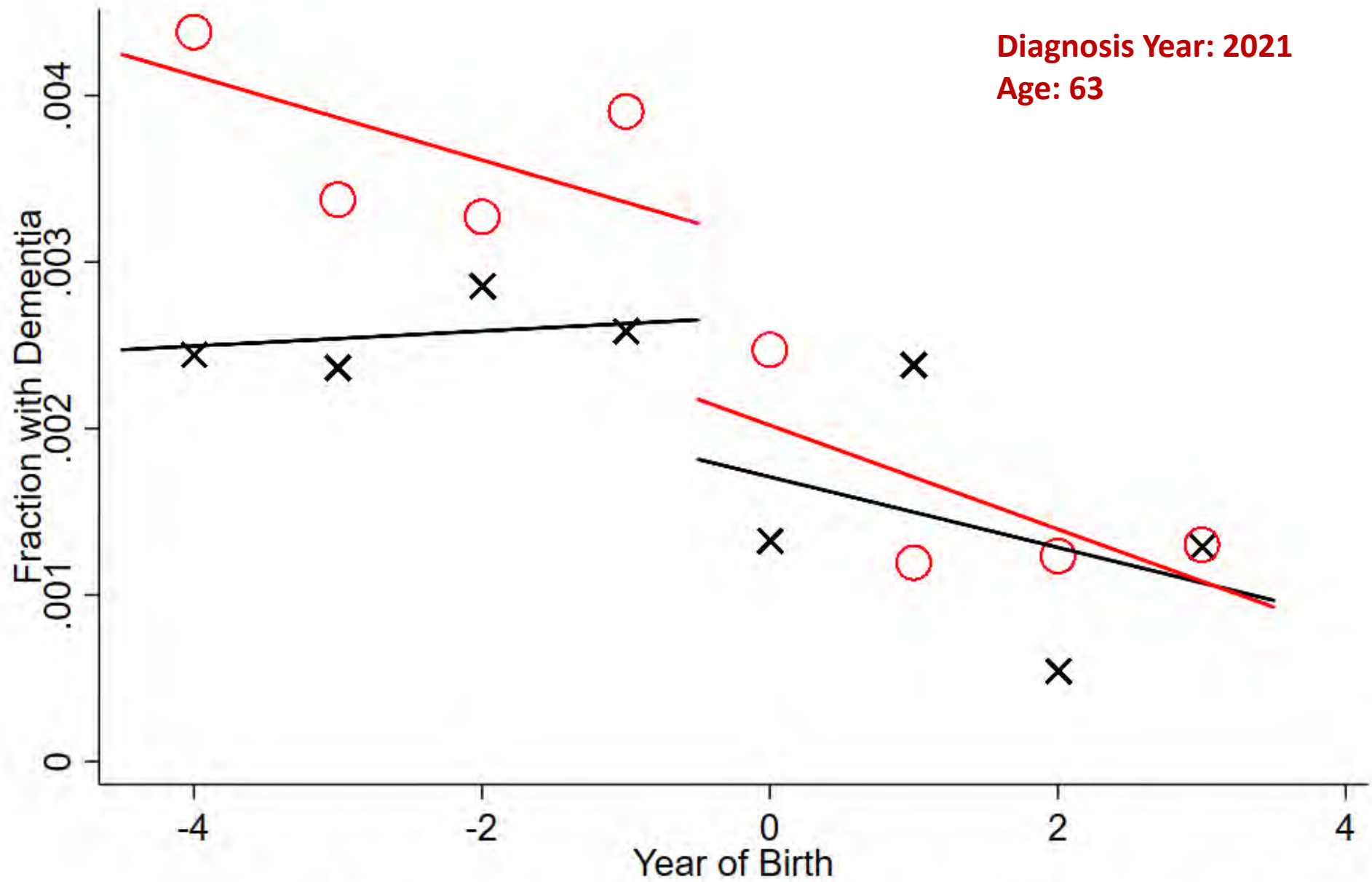
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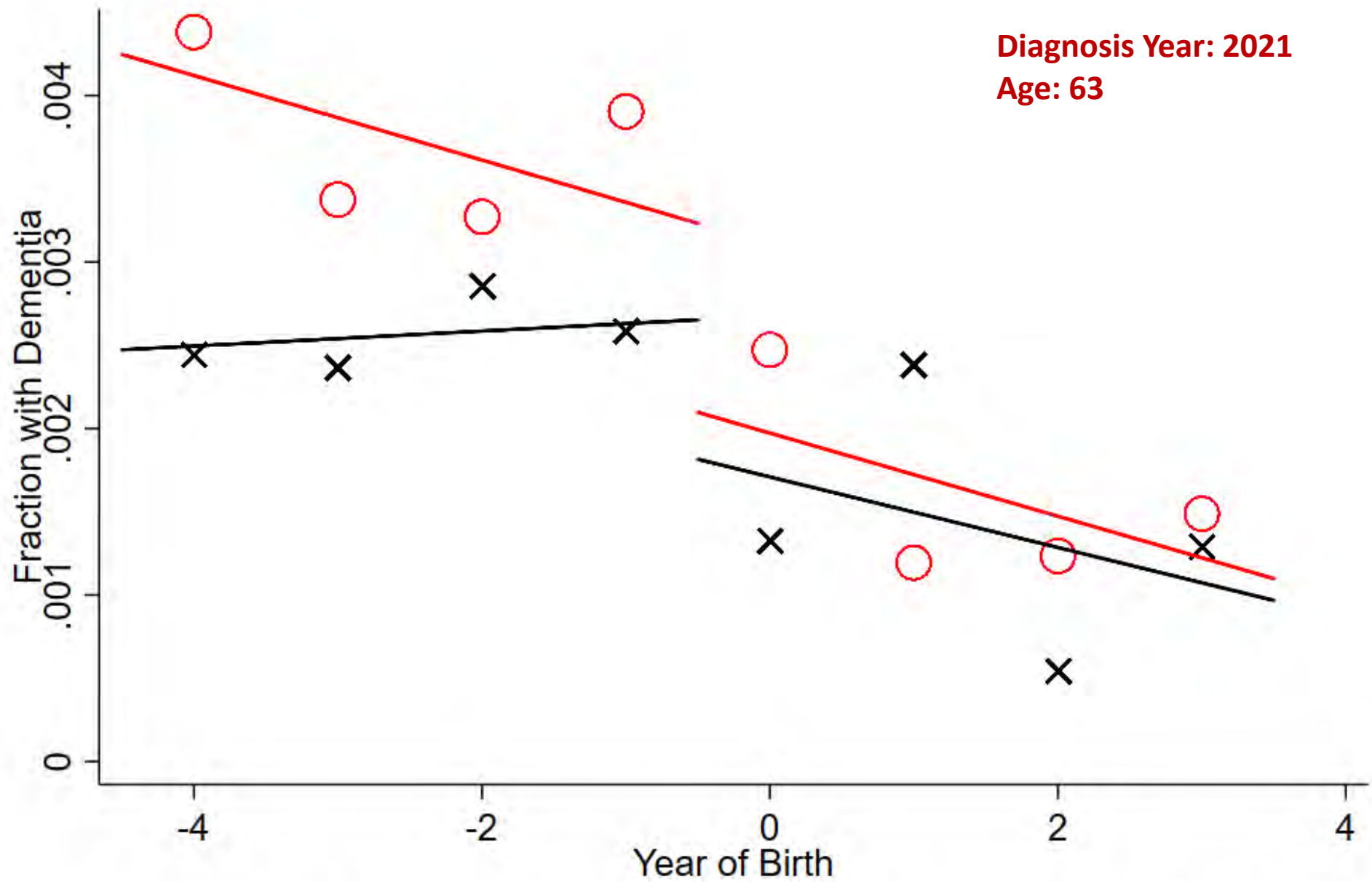
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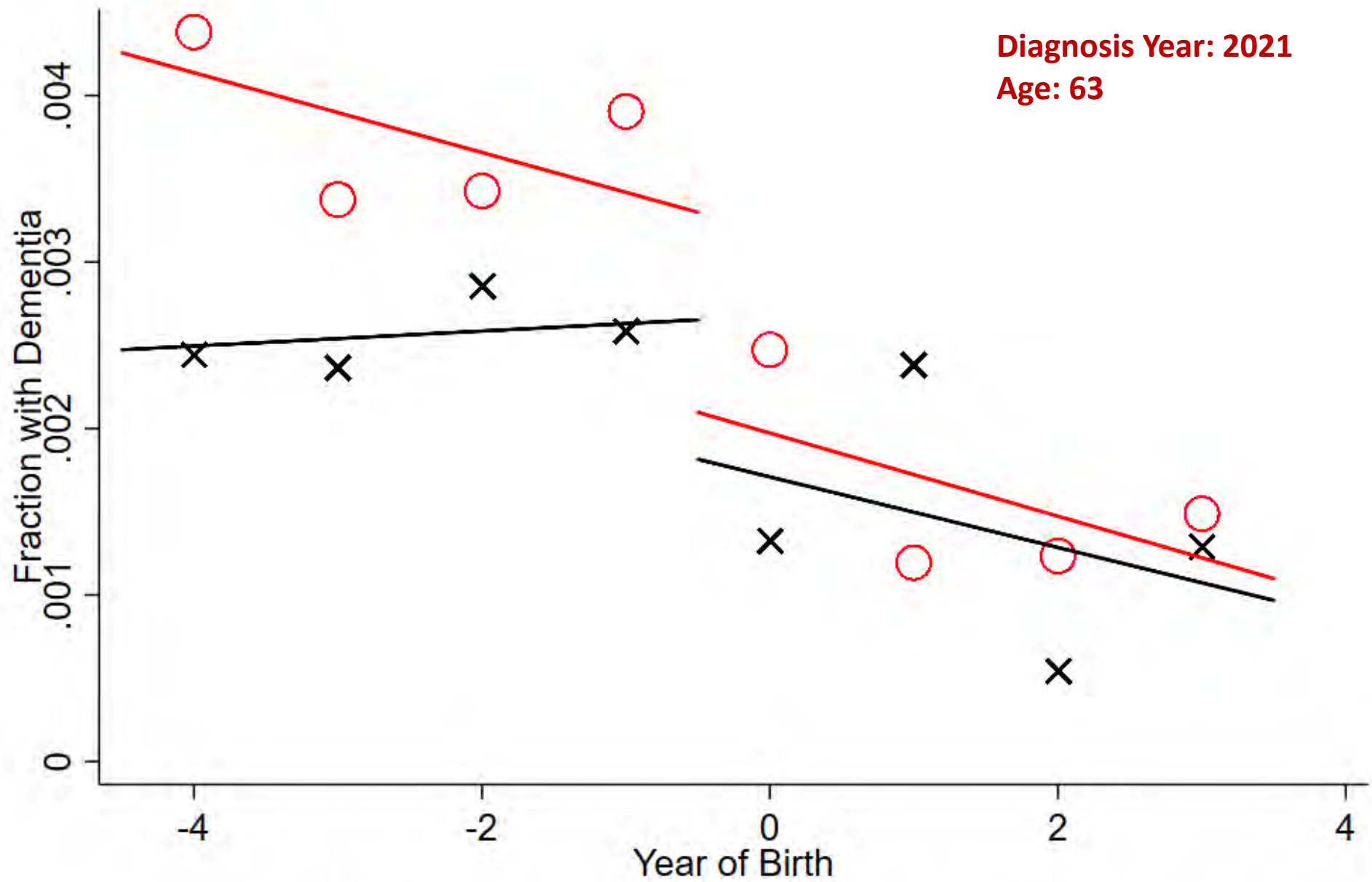
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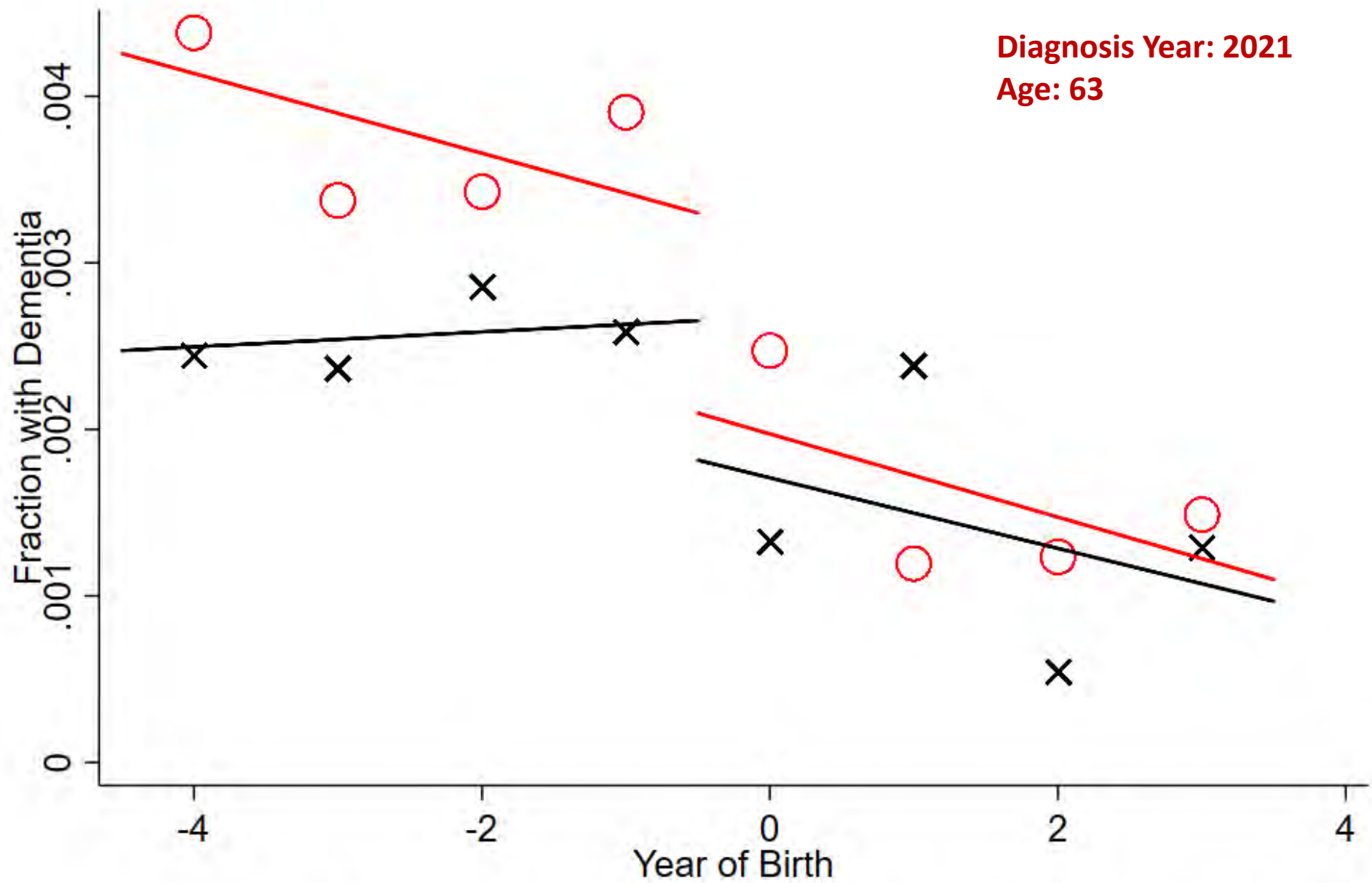
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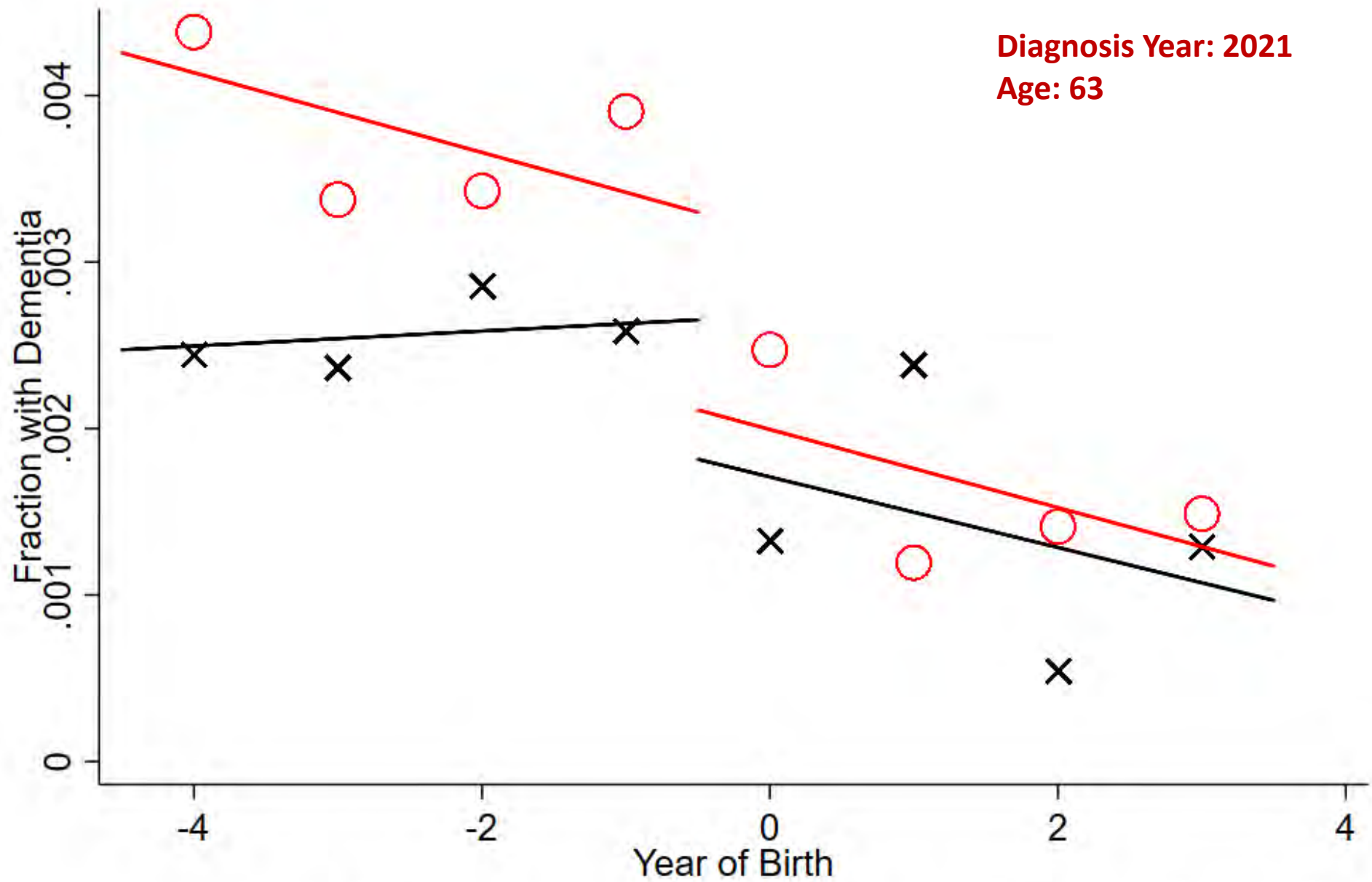
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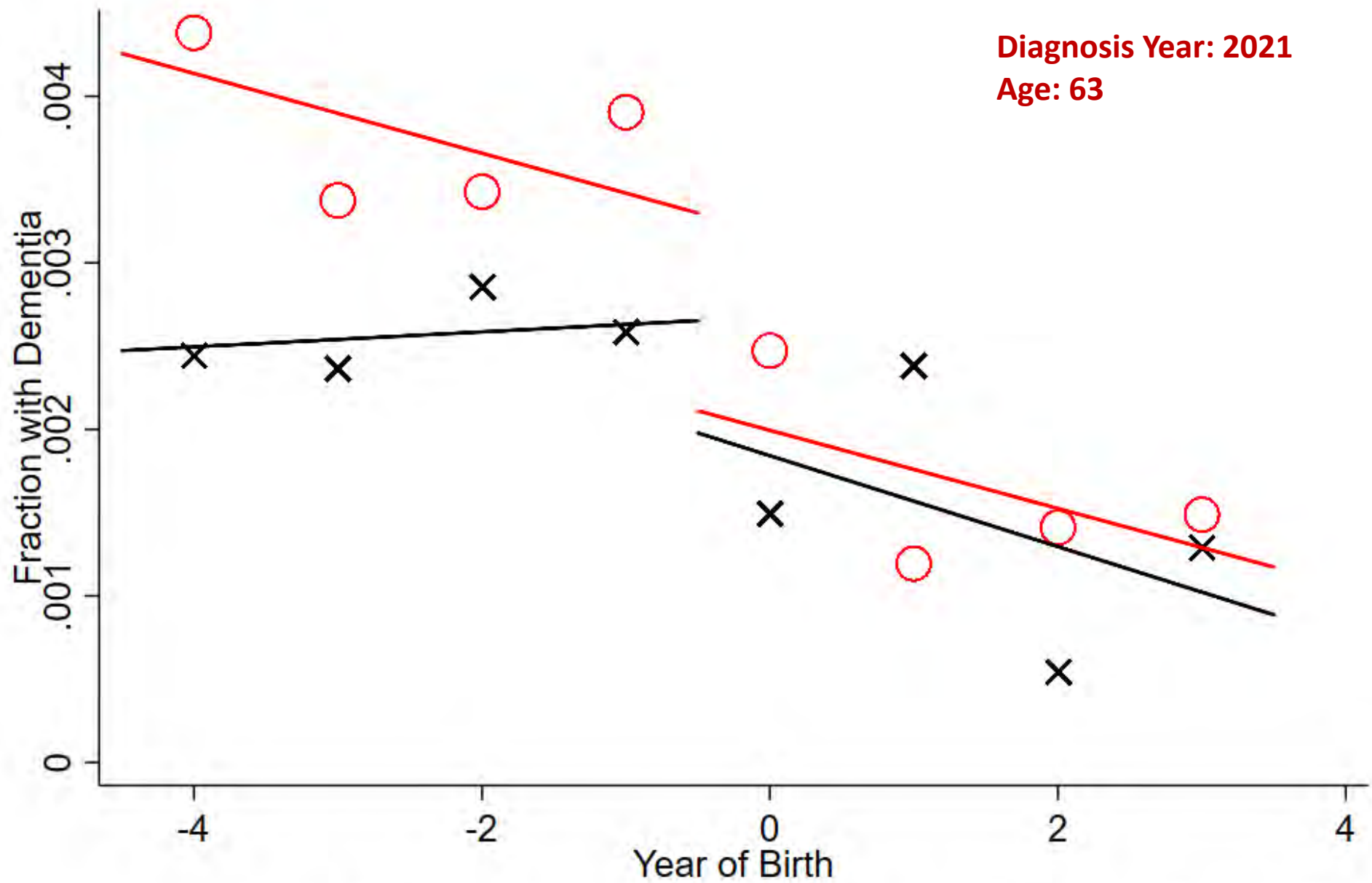
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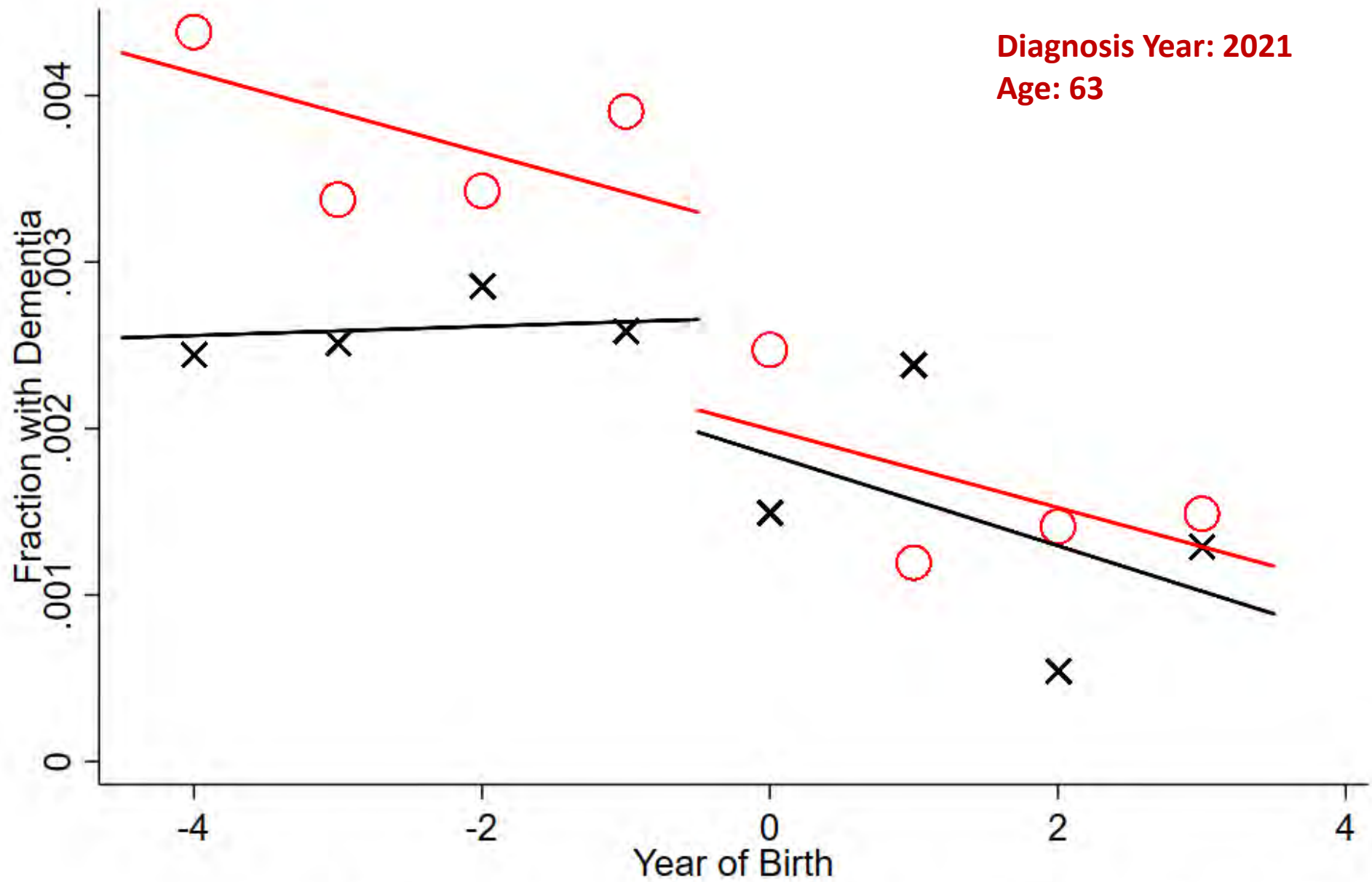
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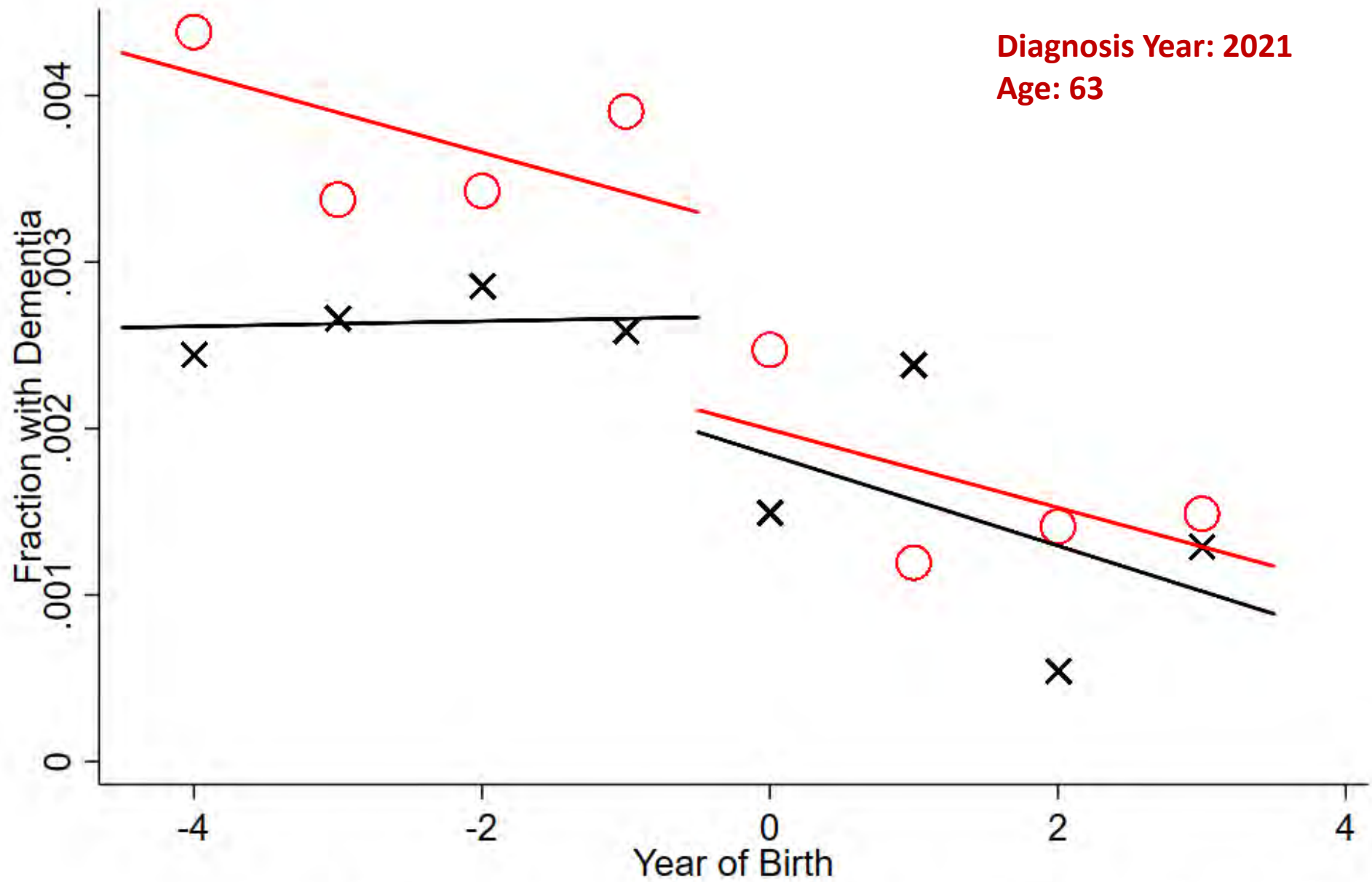
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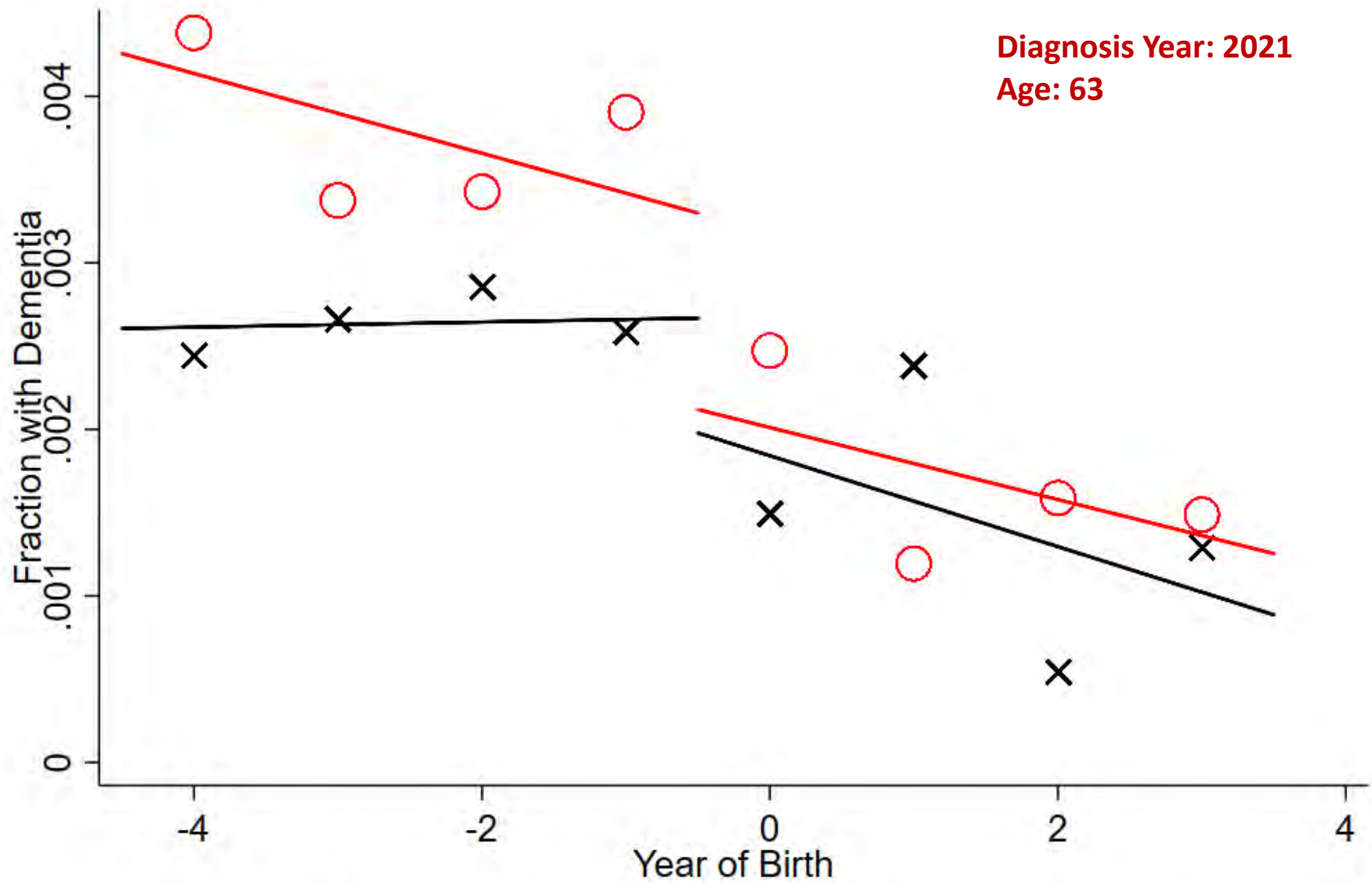
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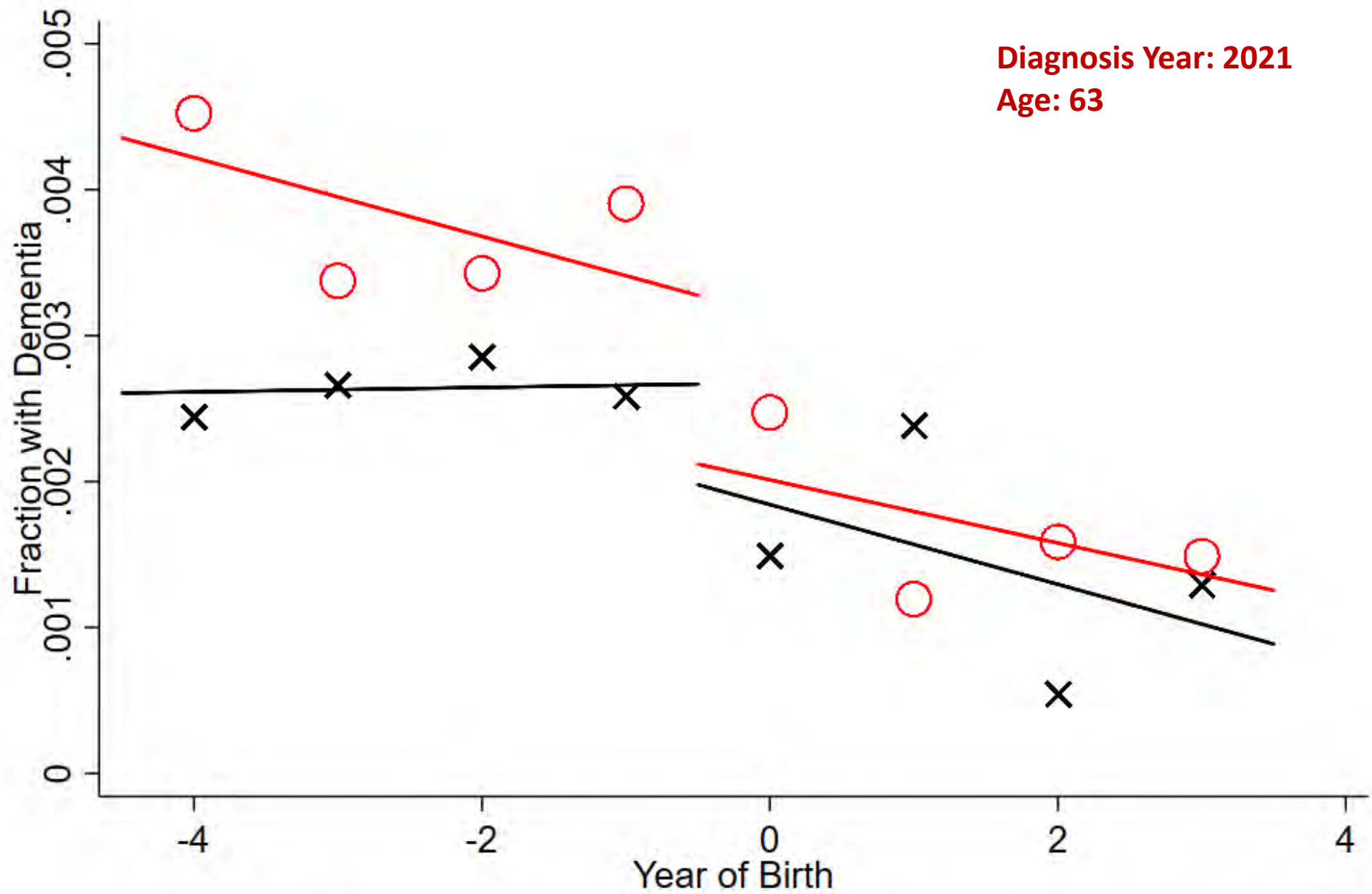
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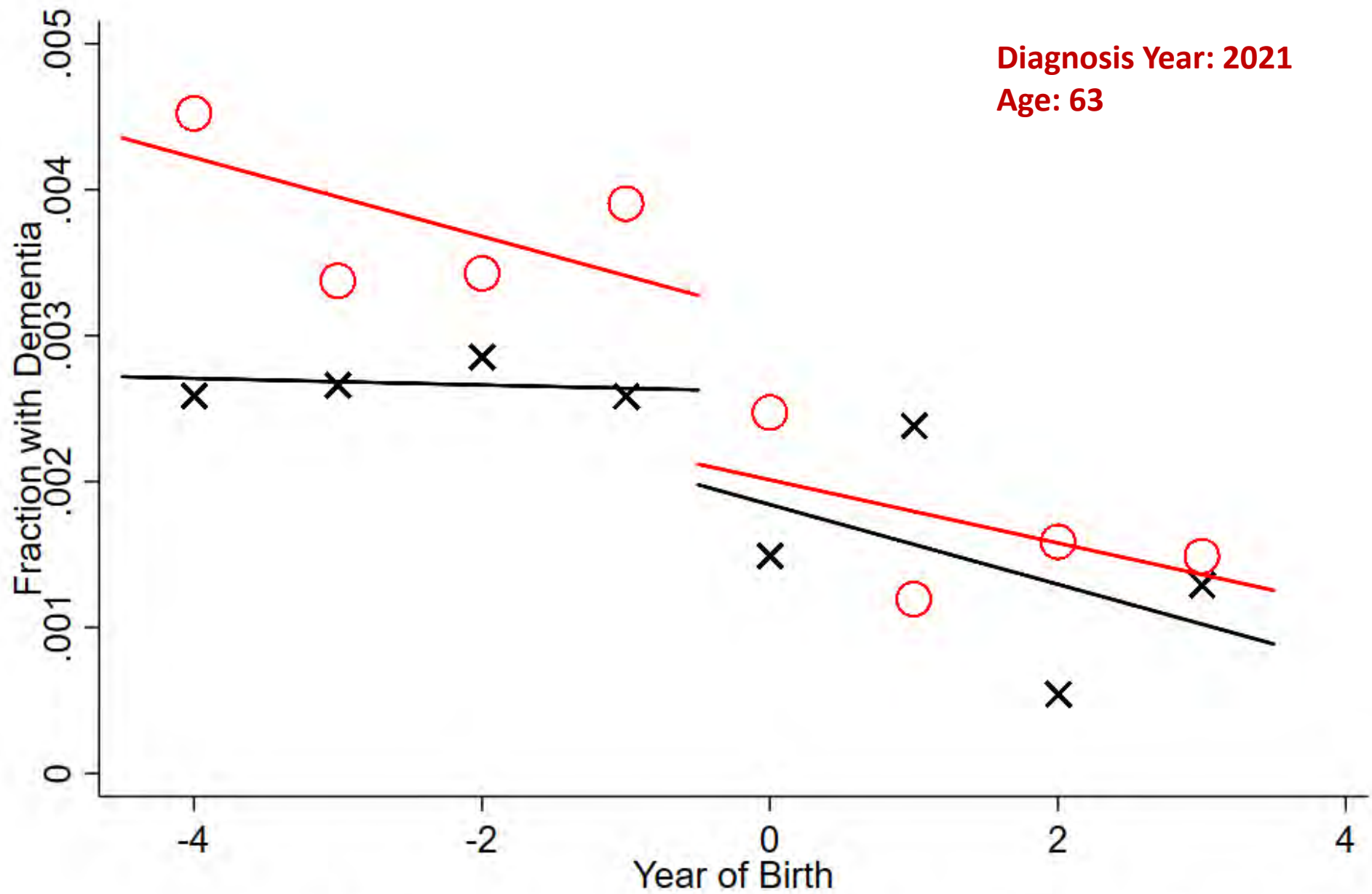


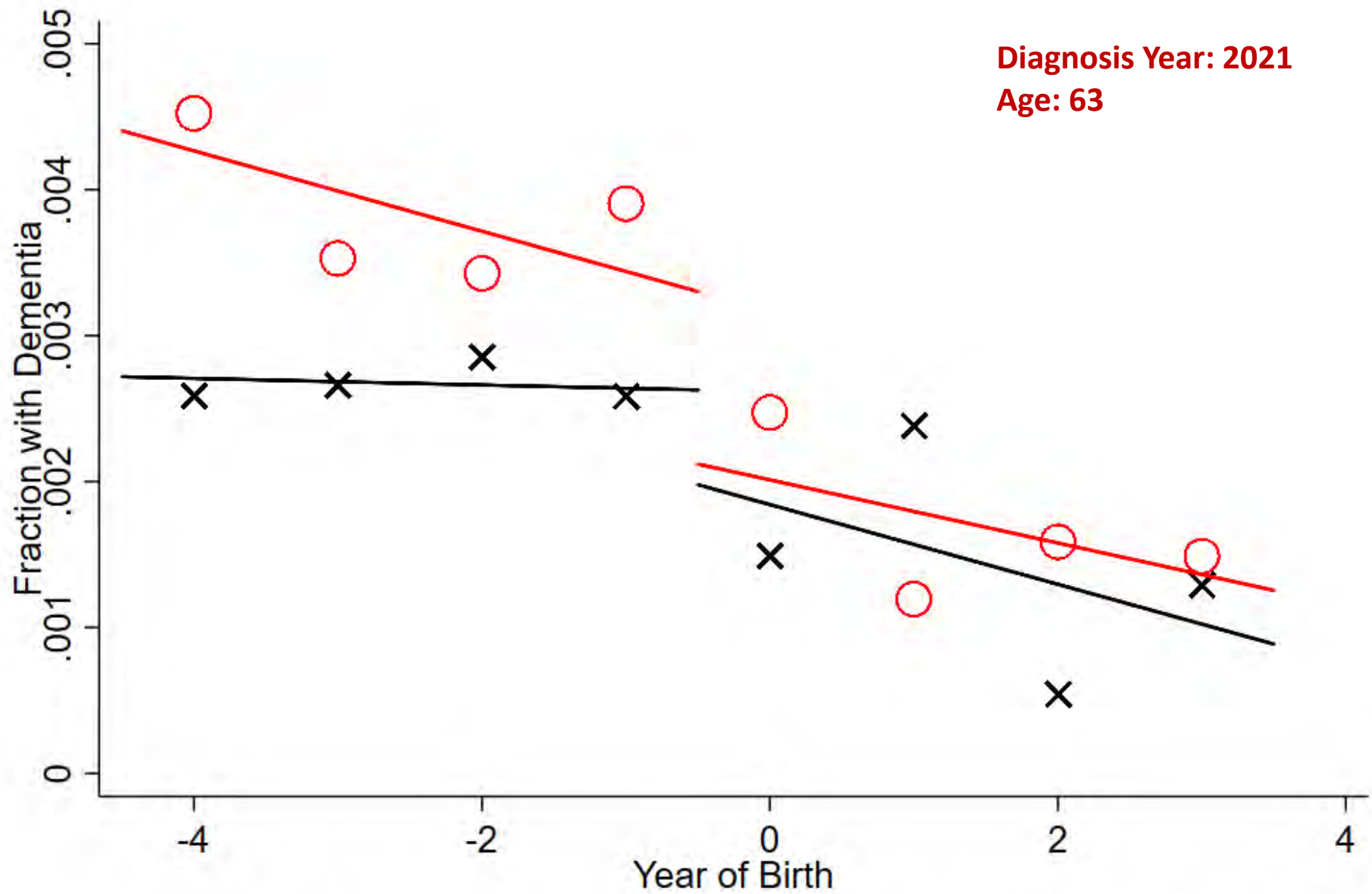
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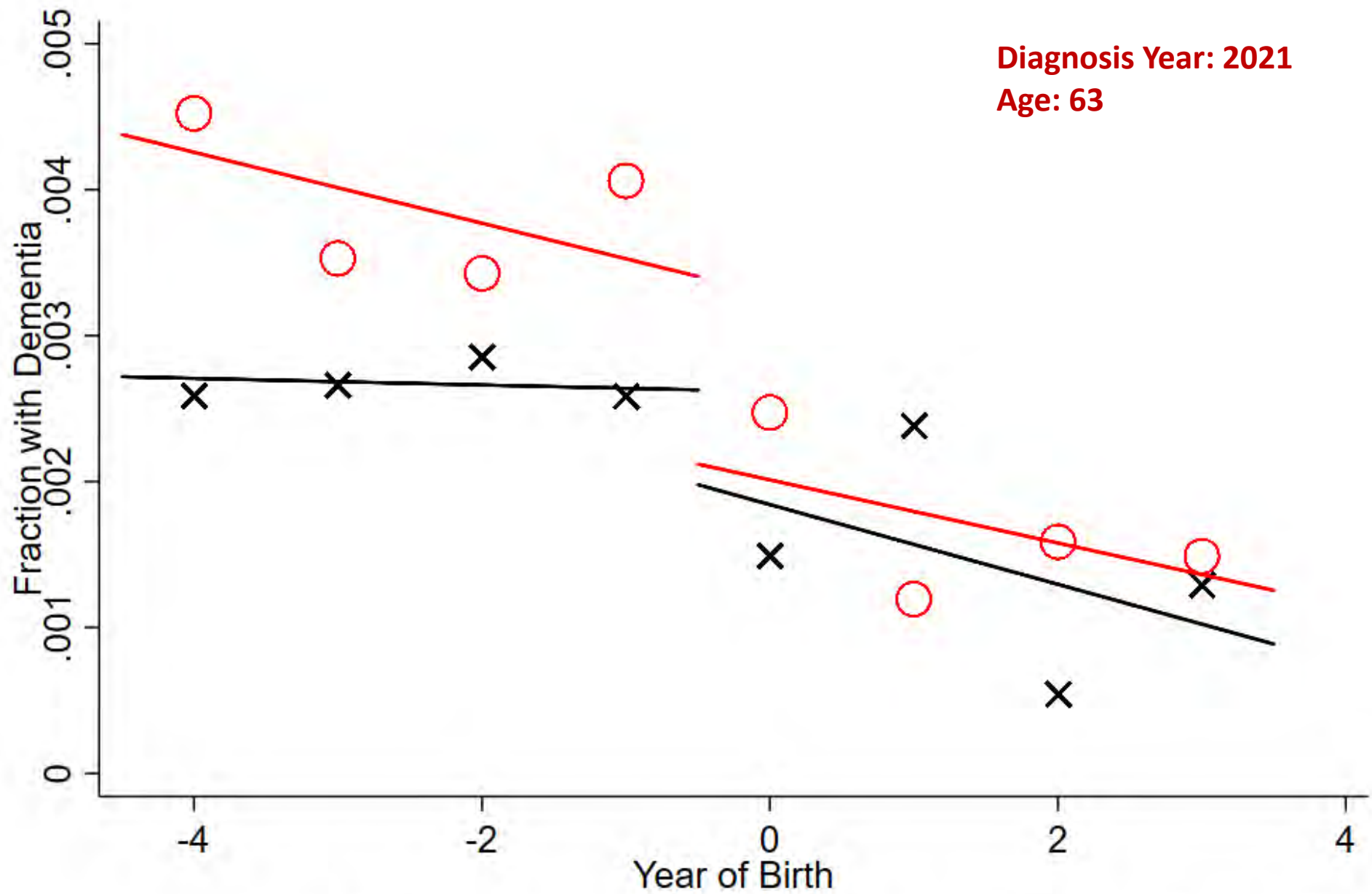
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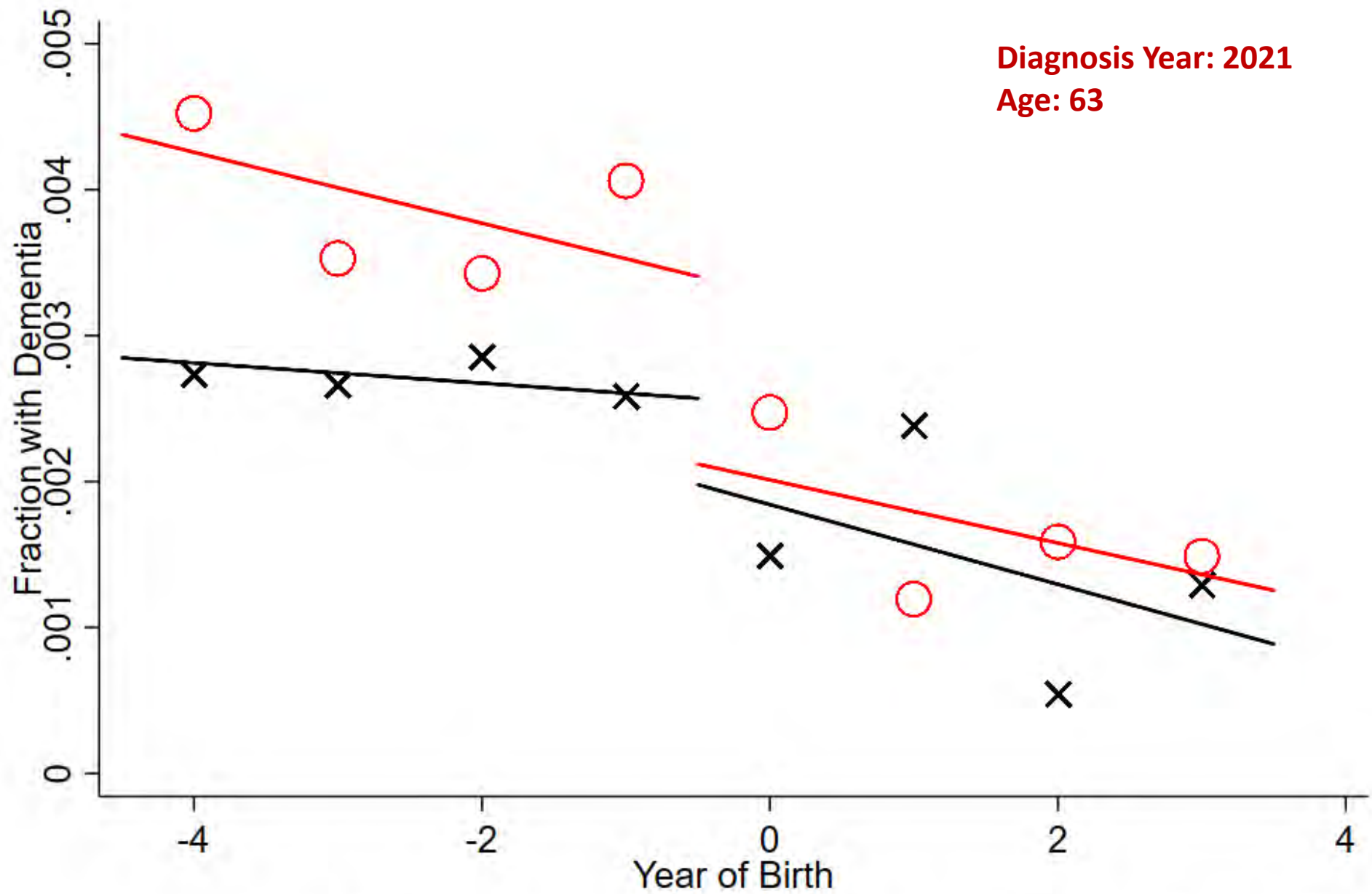




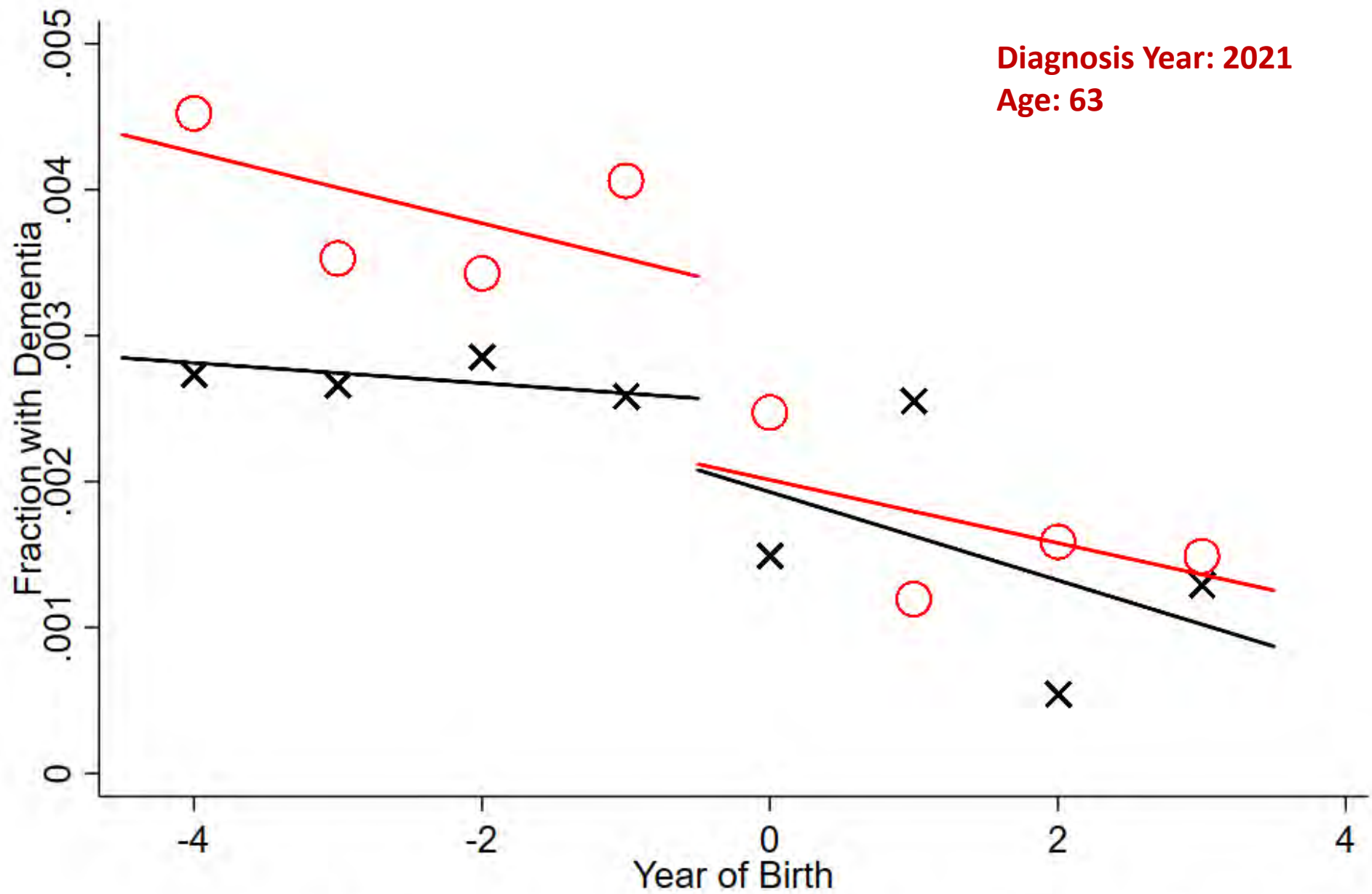
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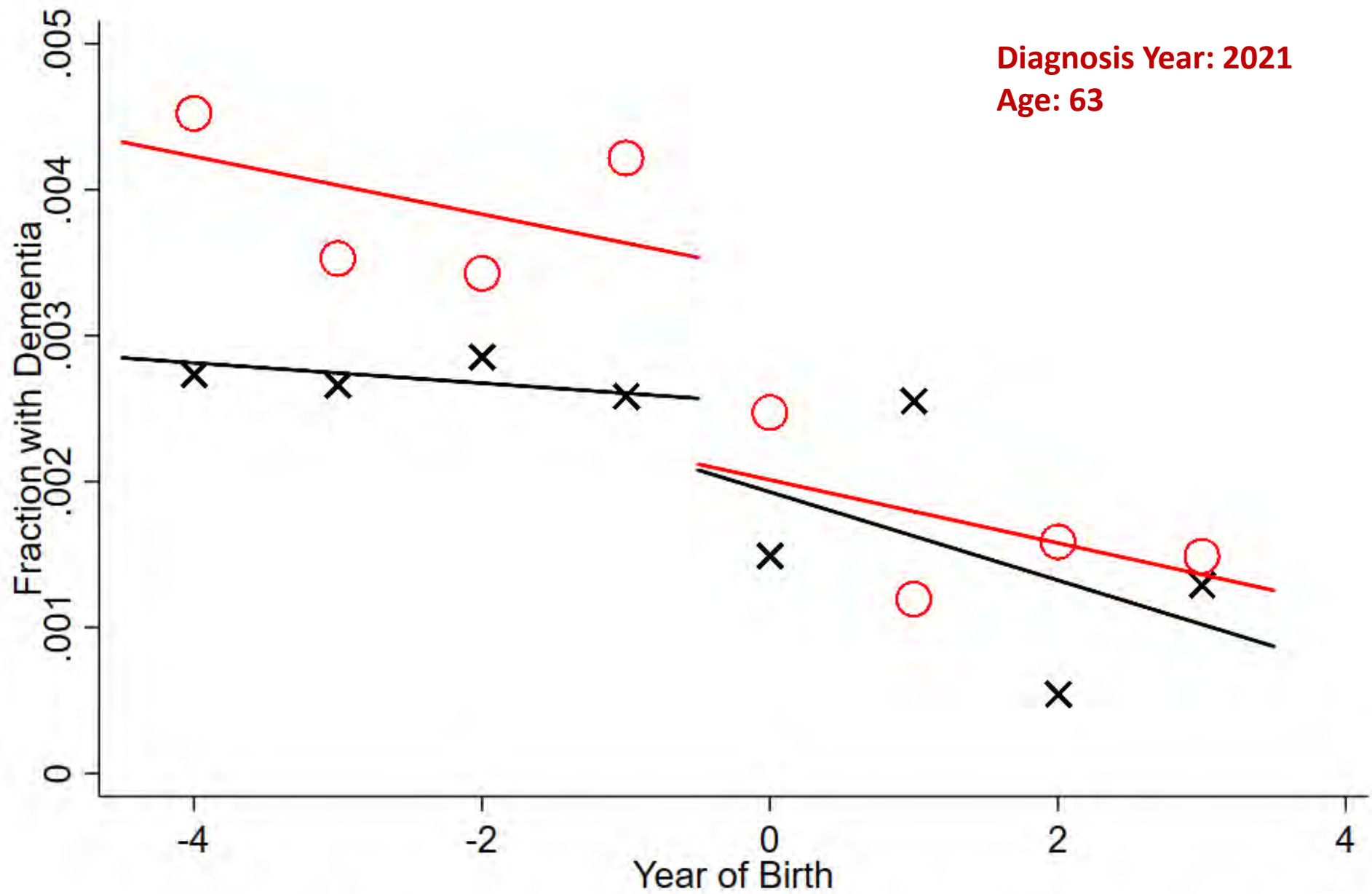
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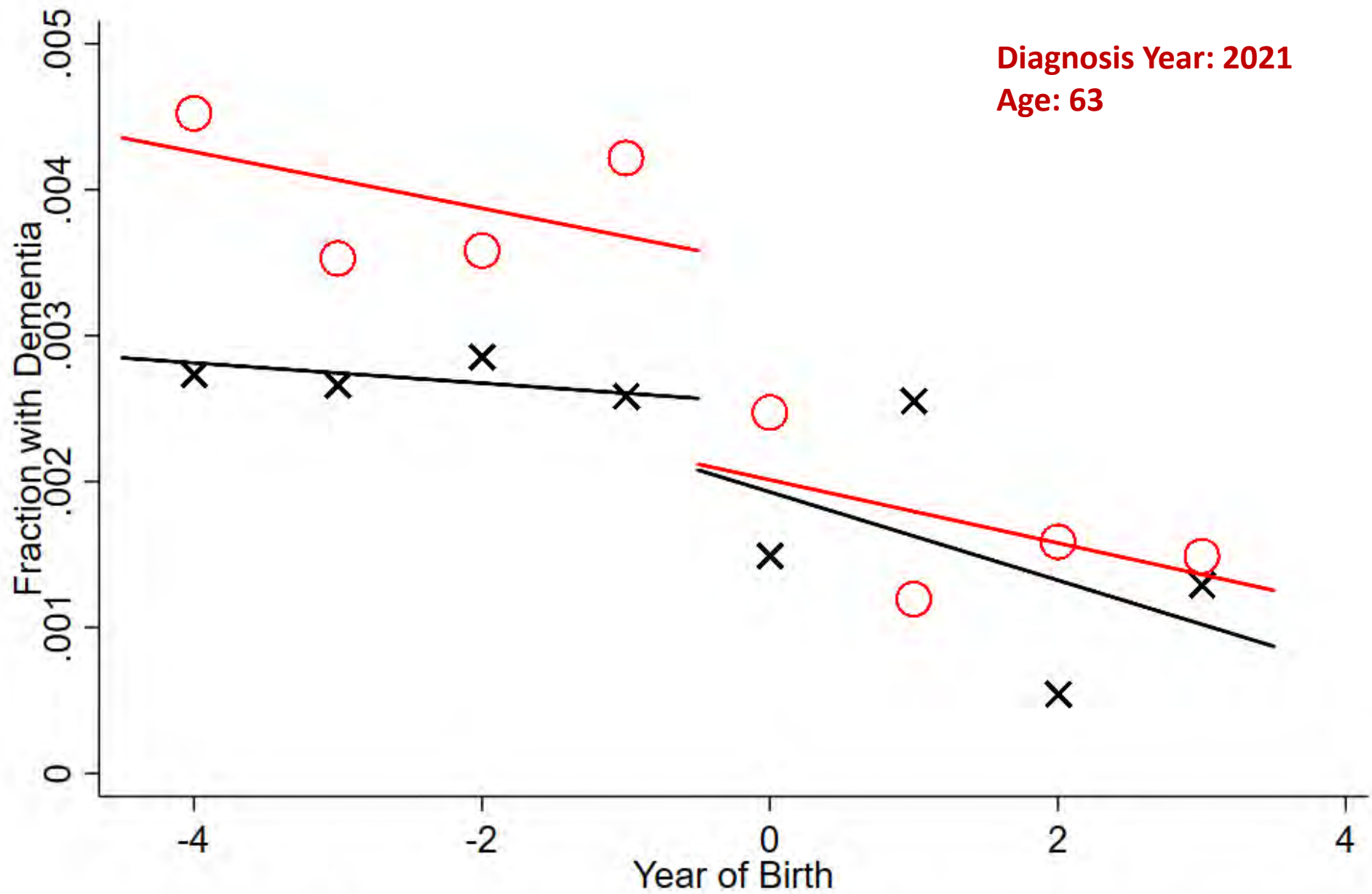
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× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

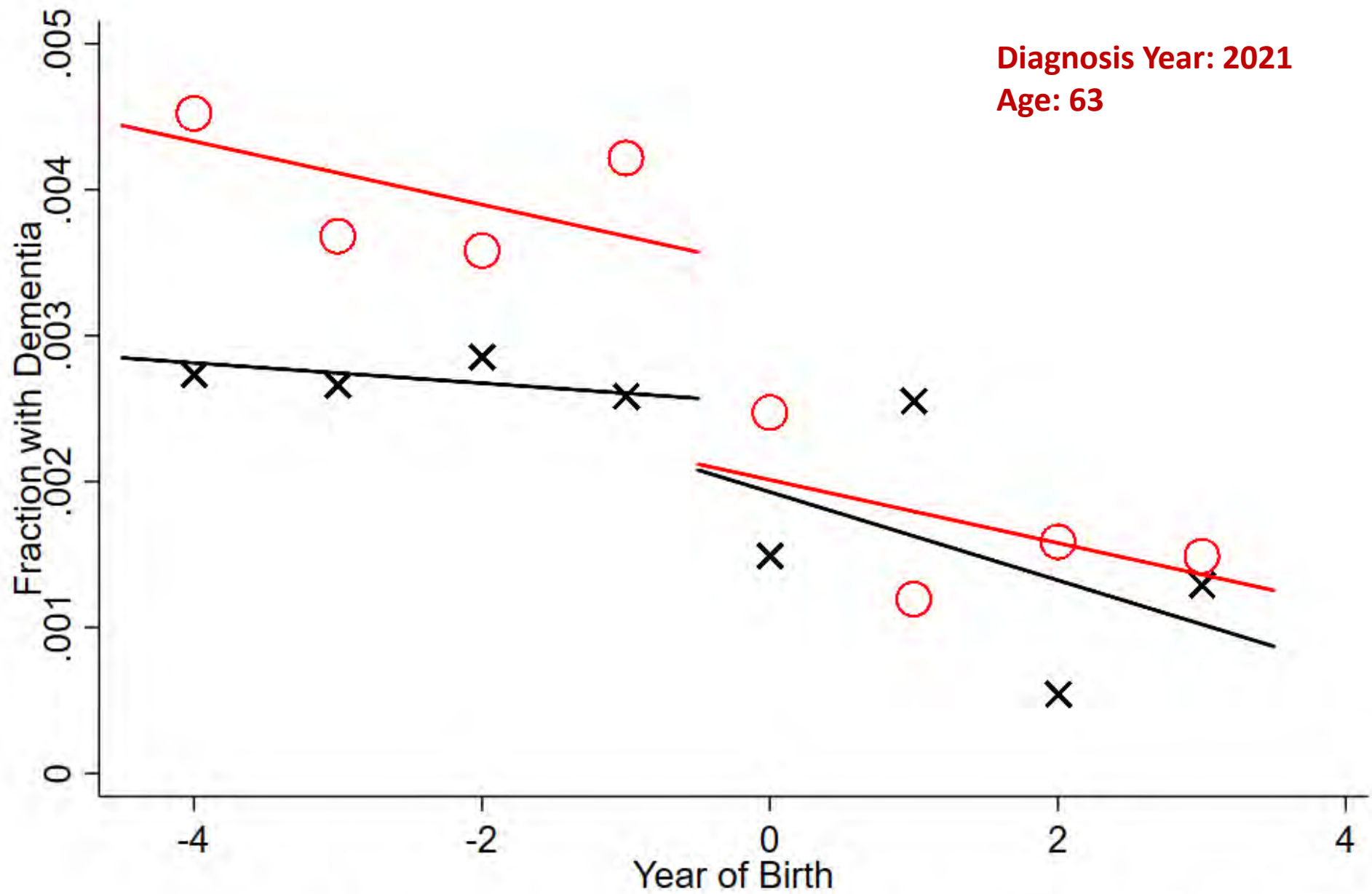


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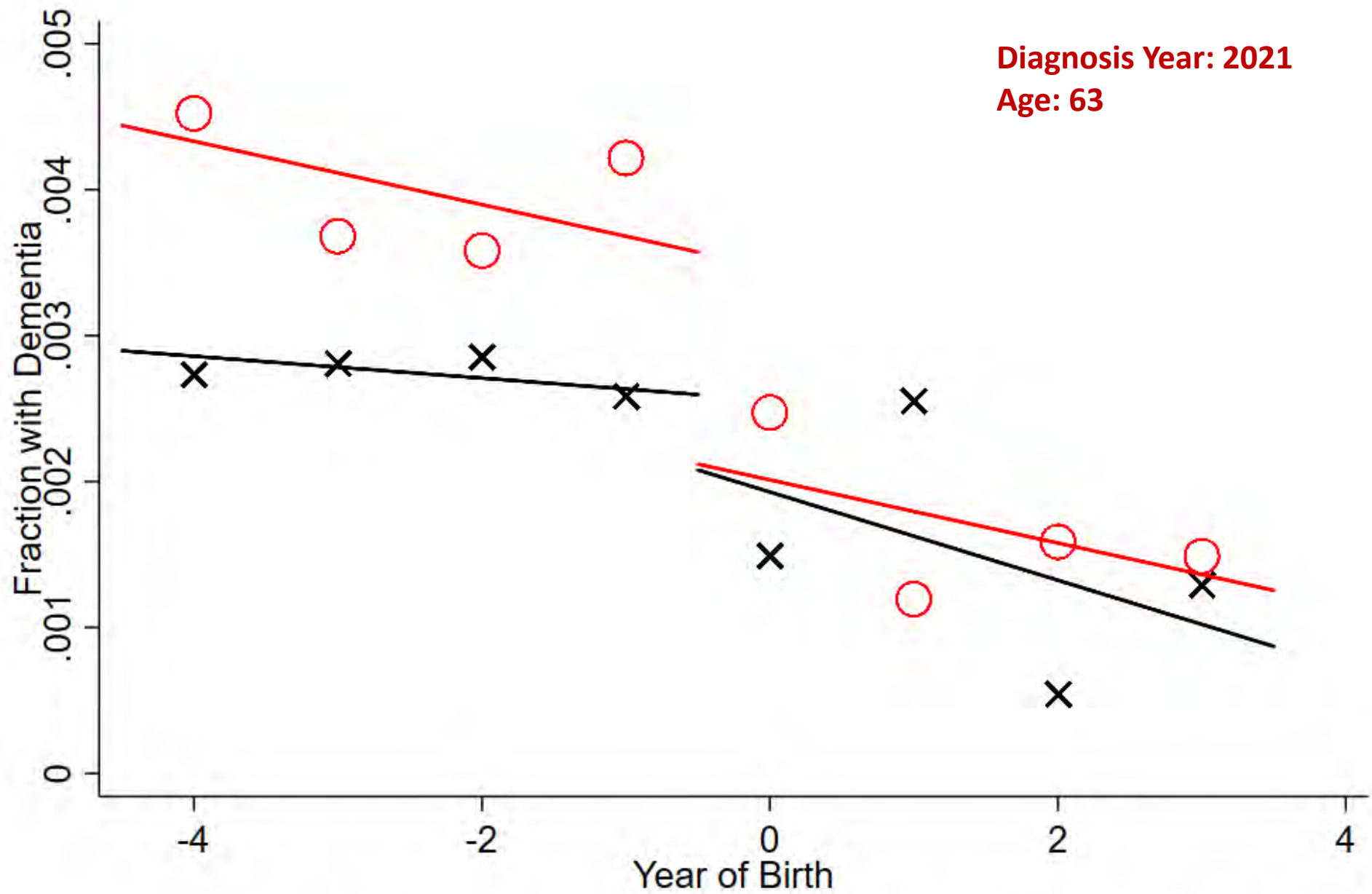


Diagnosis Year: 2021
Age: 63

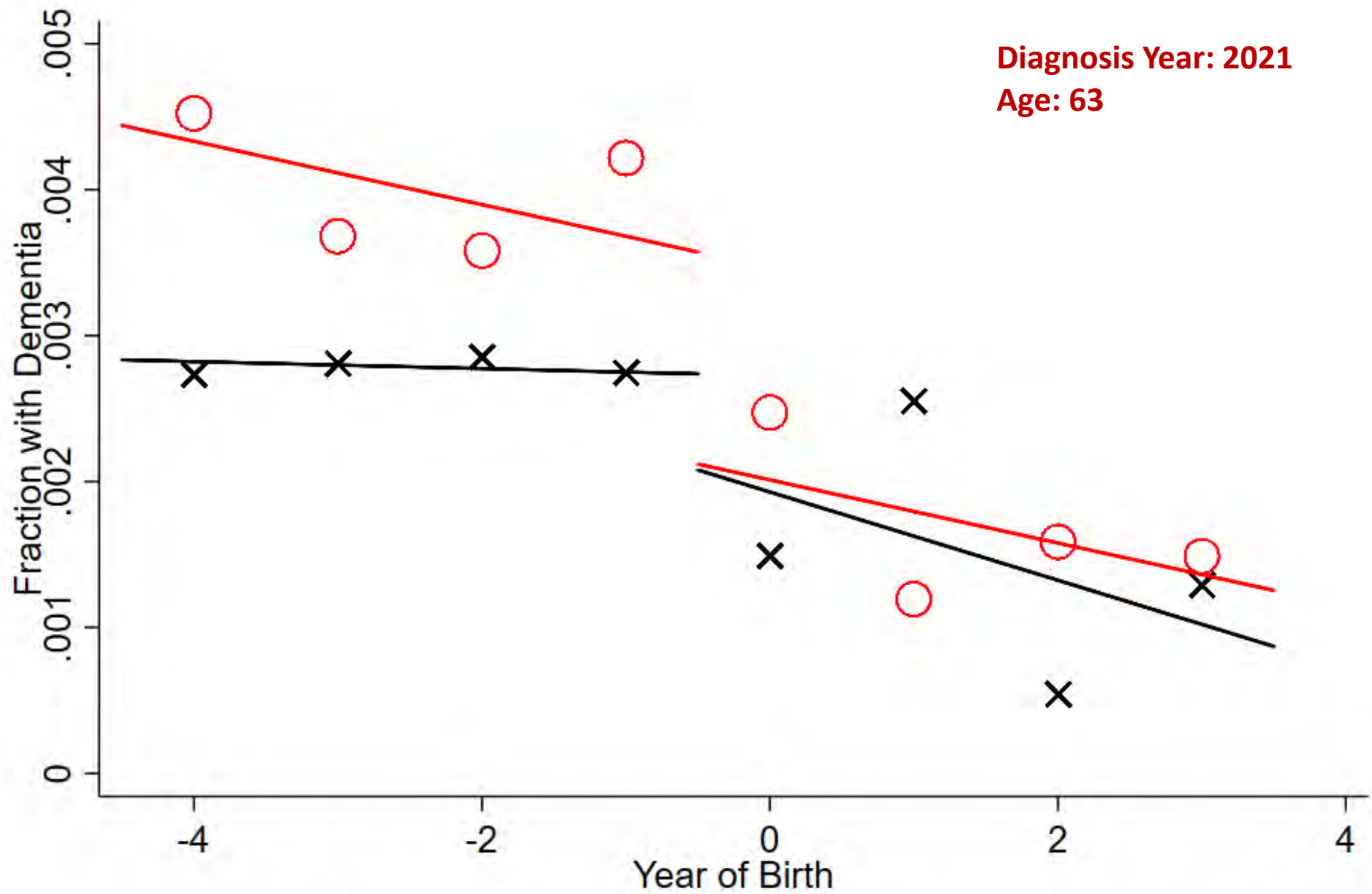
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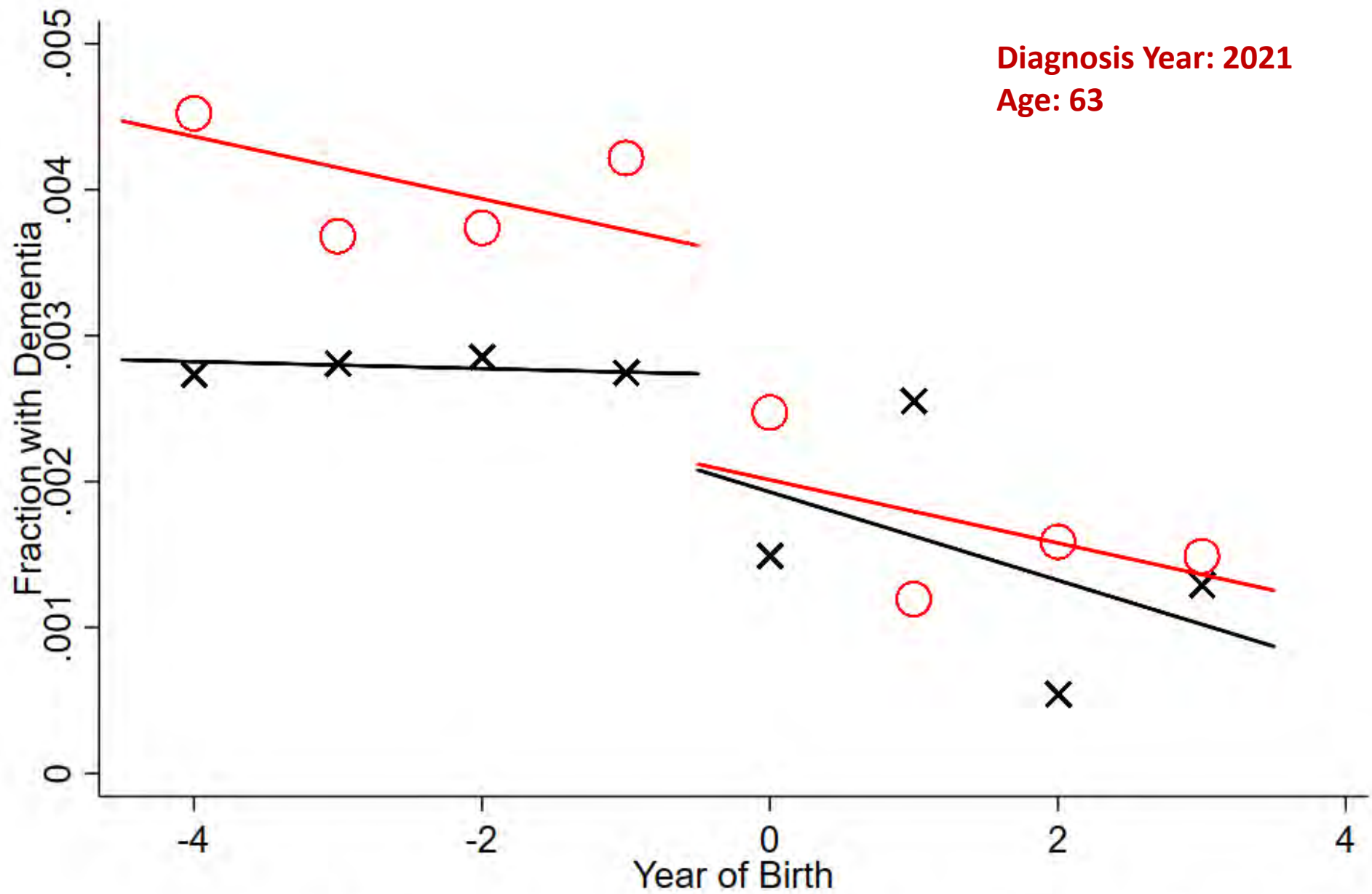
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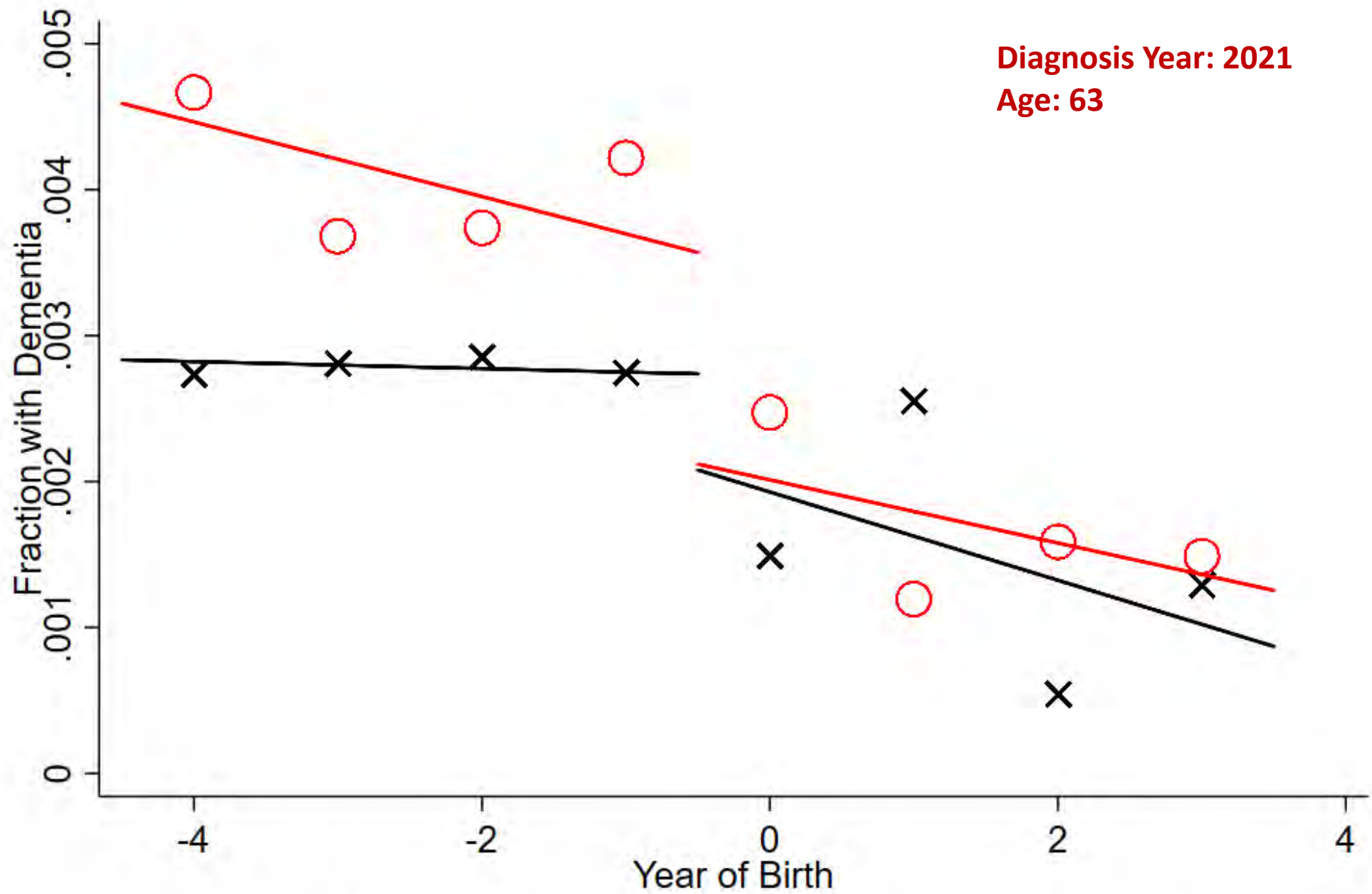
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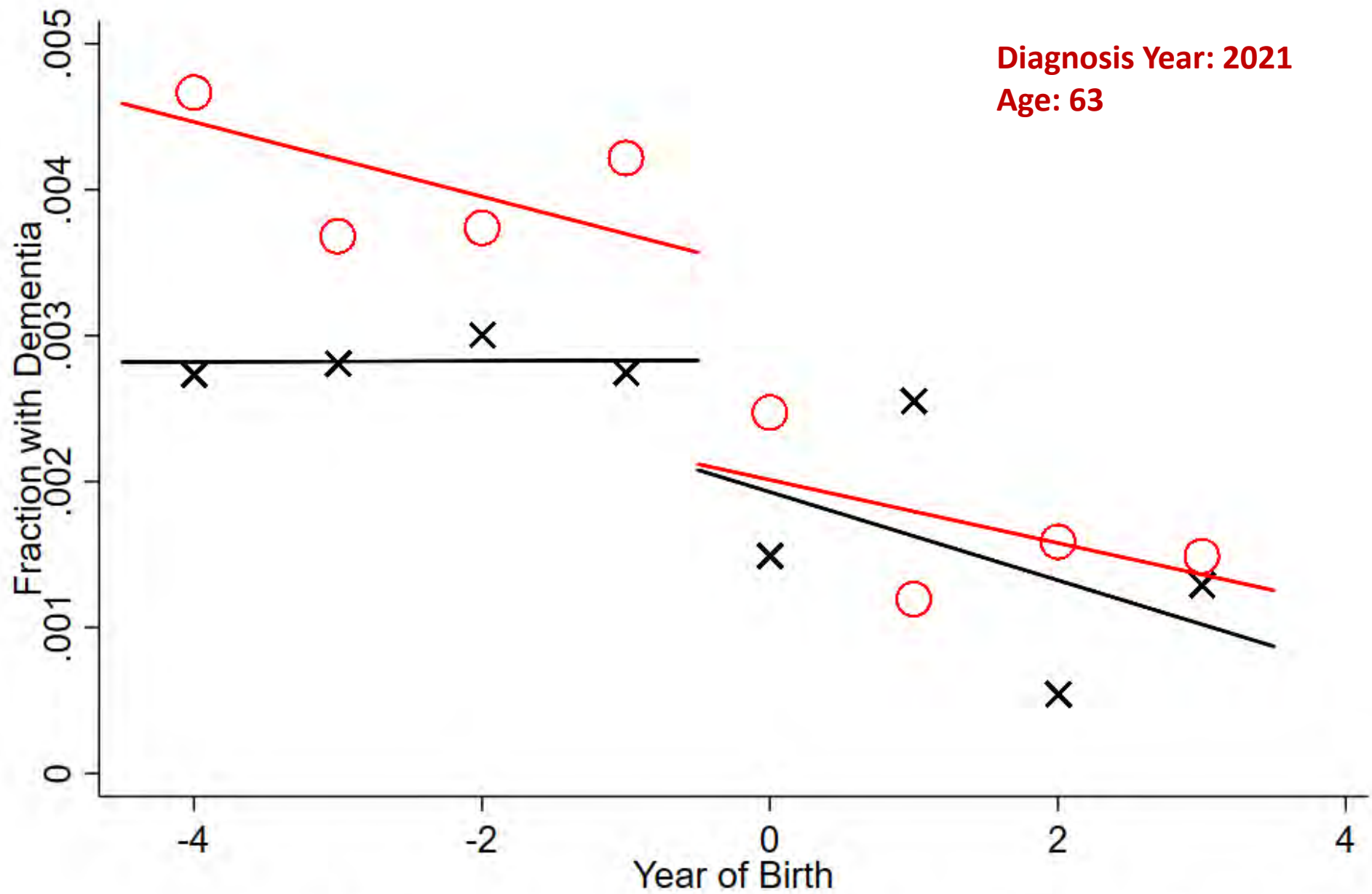
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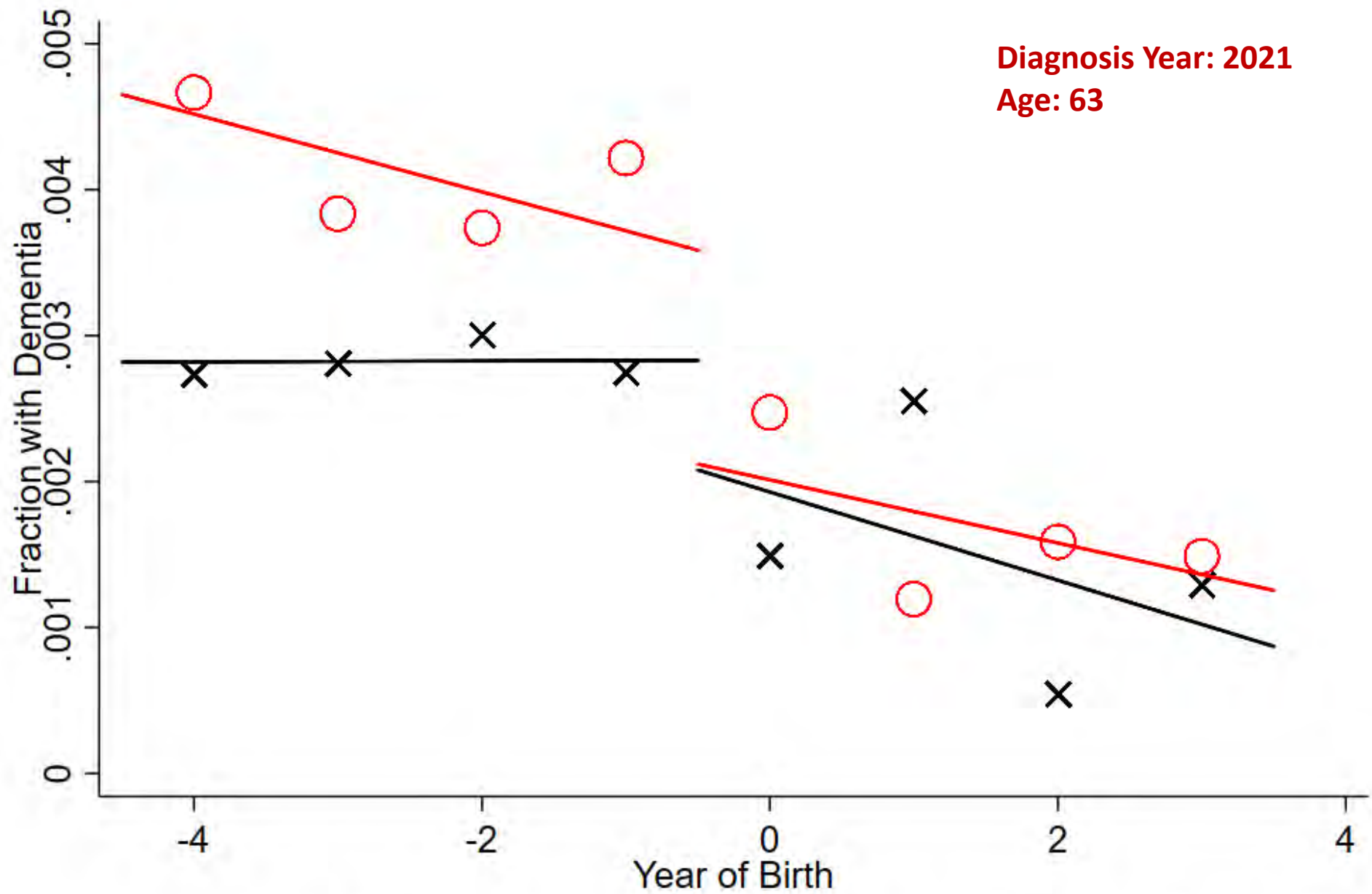
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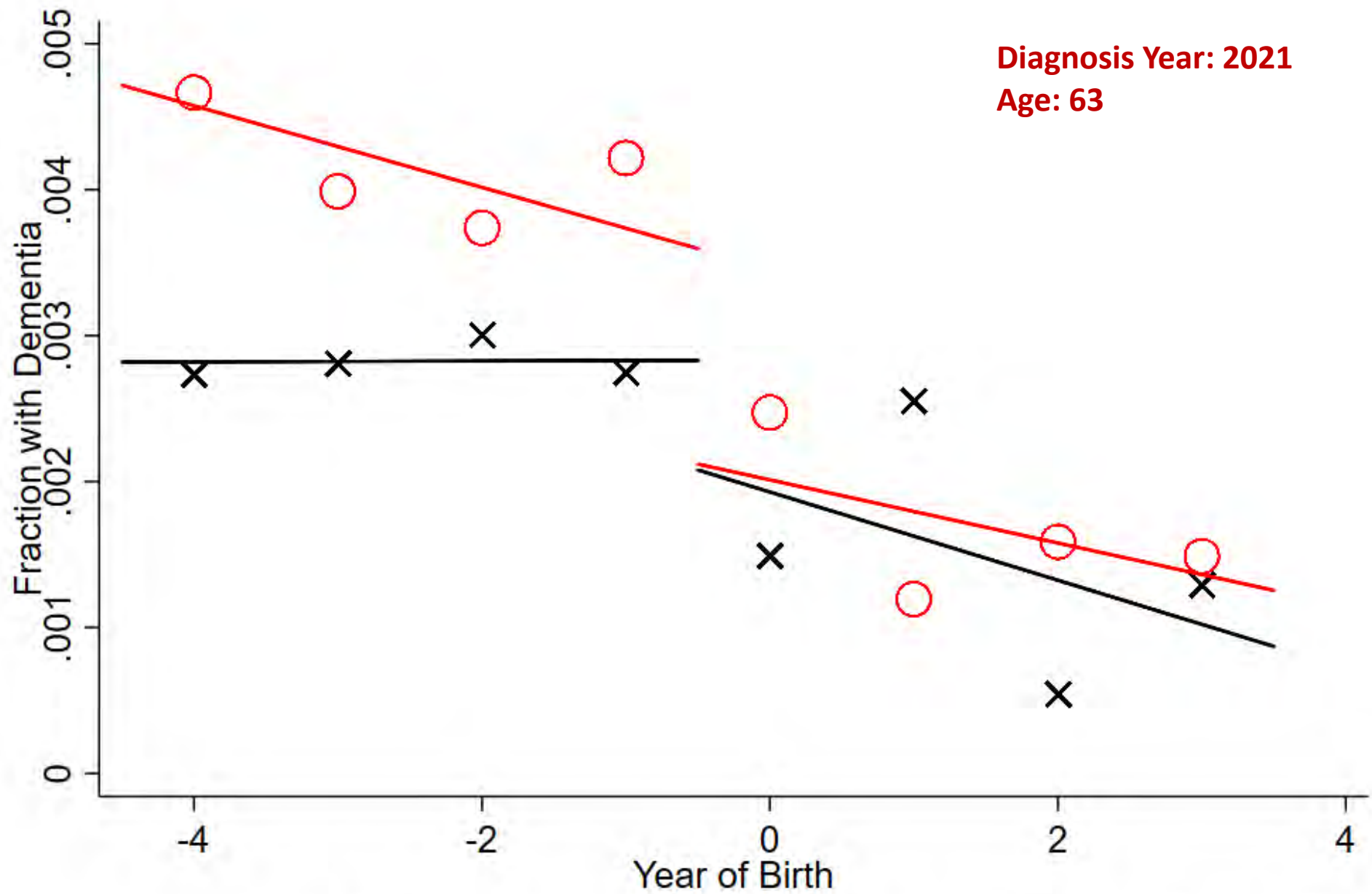
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X Bottom Half Composite Genetic Risk O Top Half Composite Genetic Risk

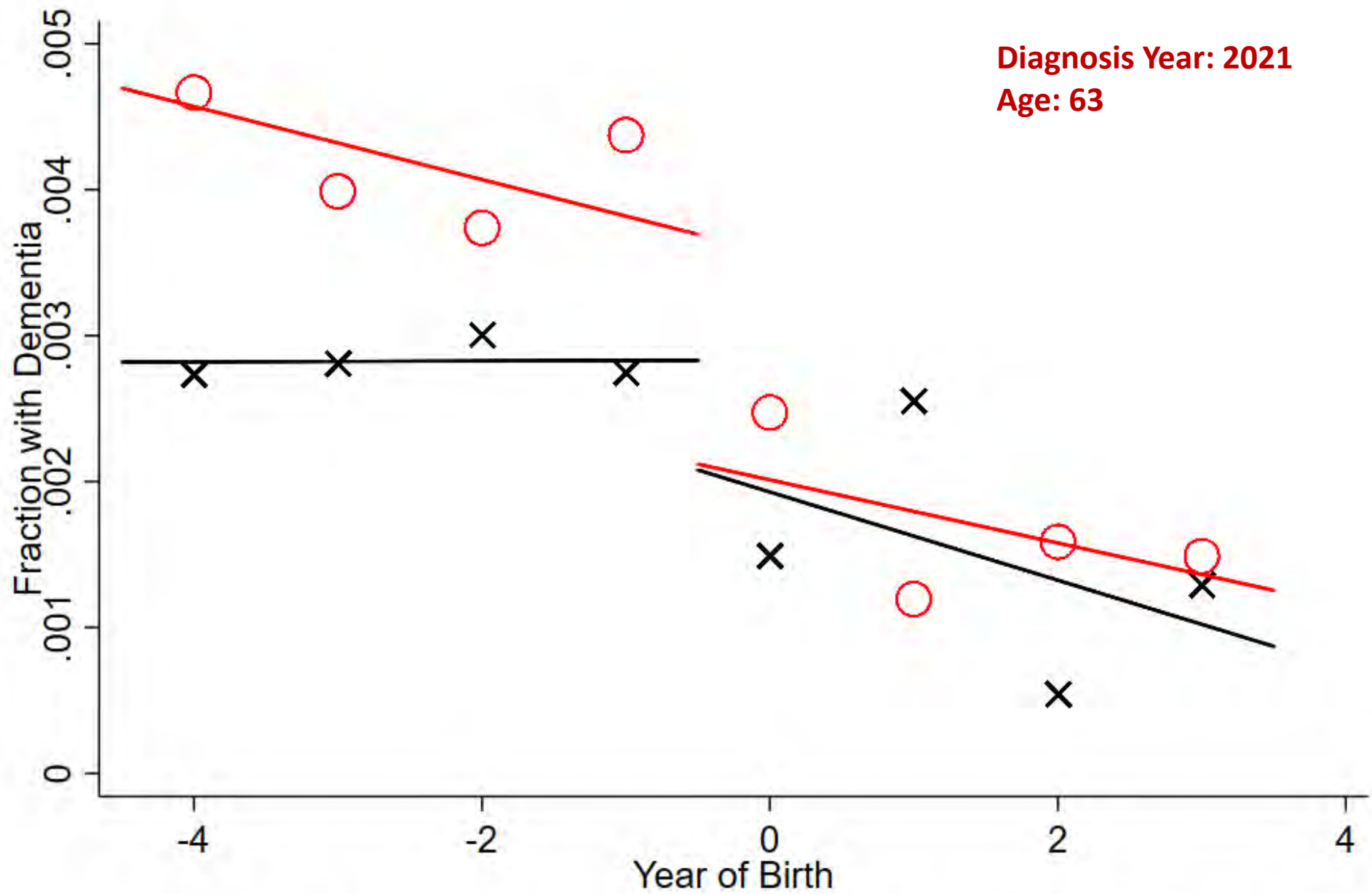


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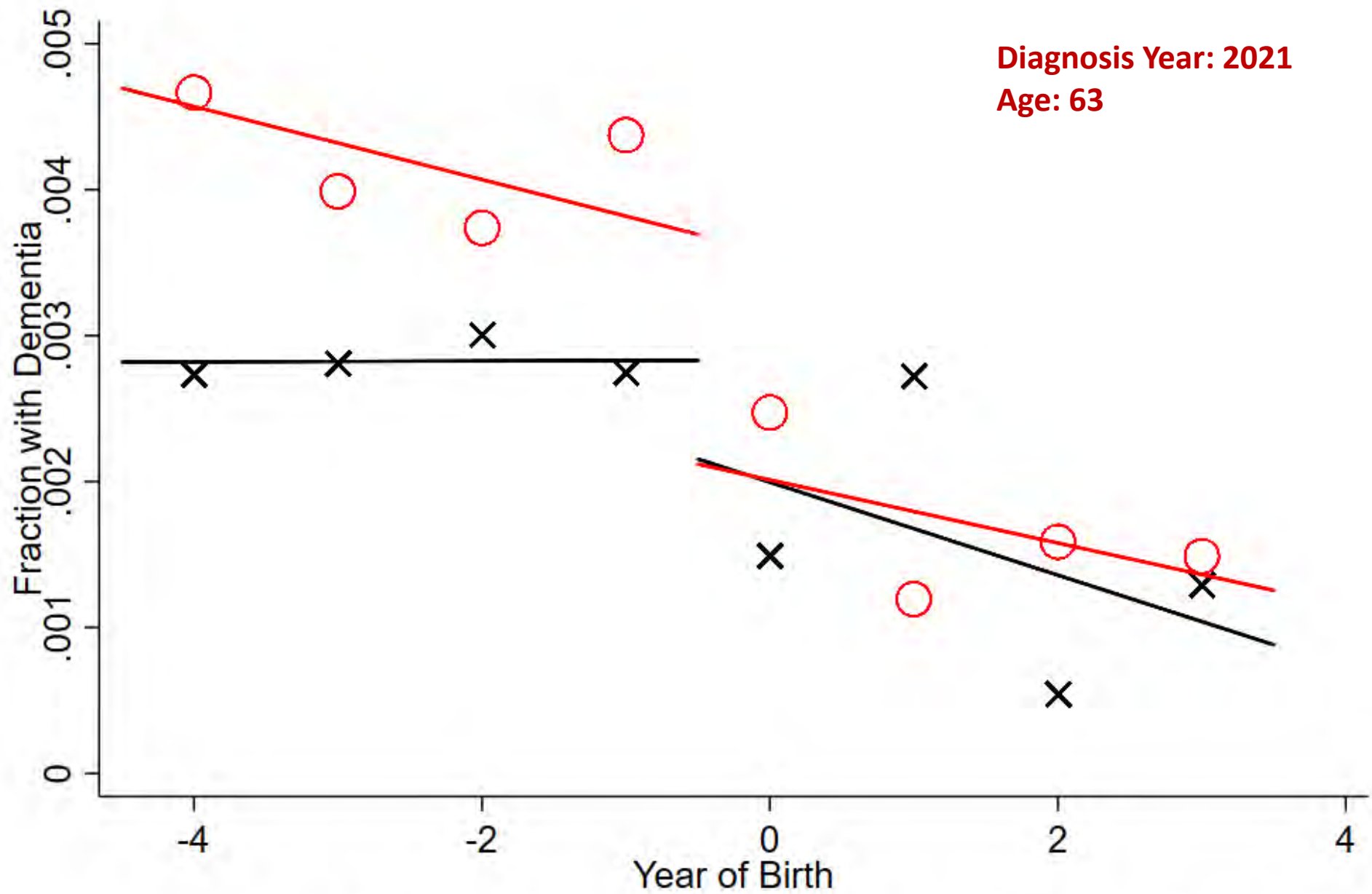


Diagnosis Year: 2021
Age: 63

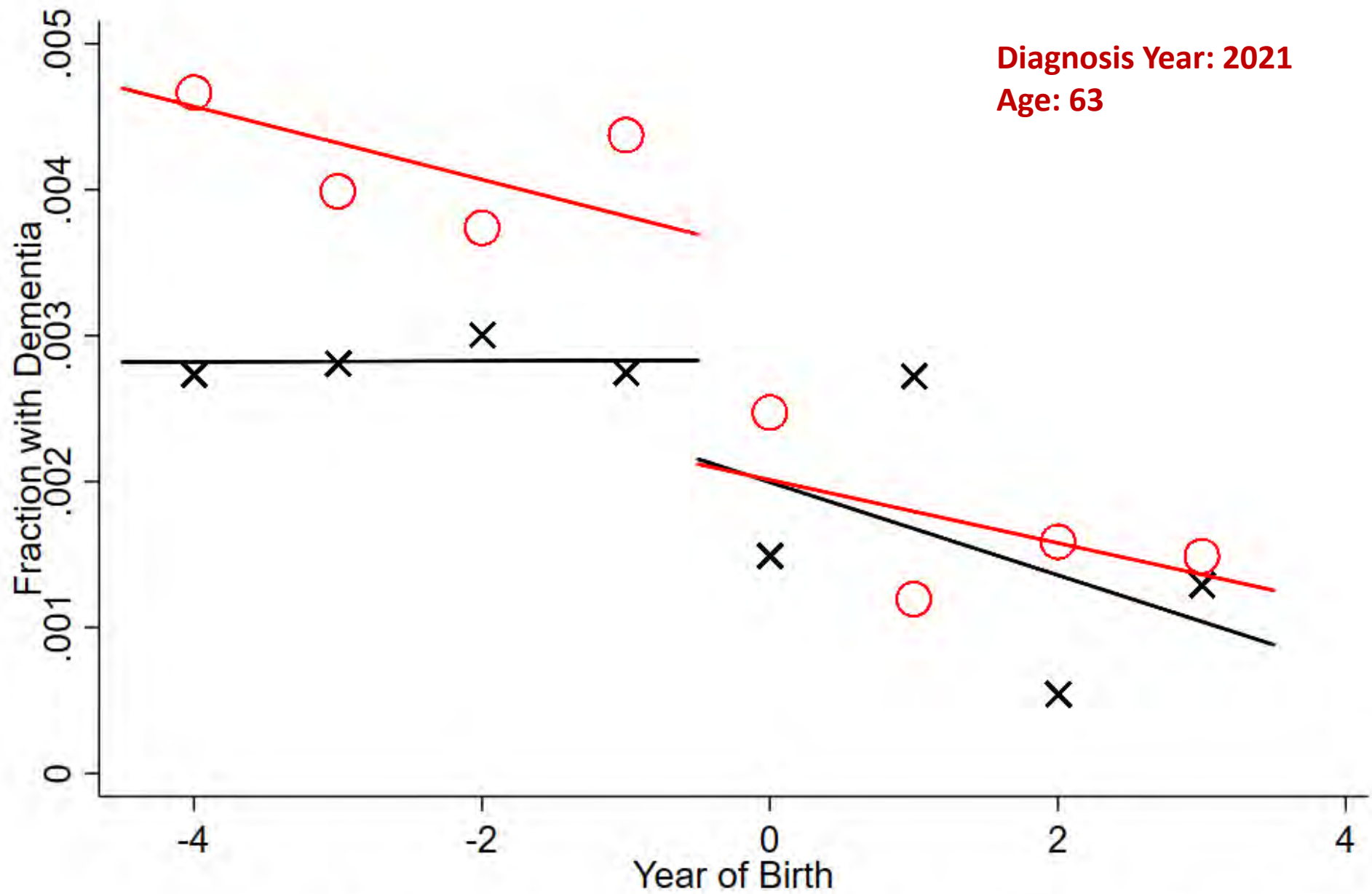
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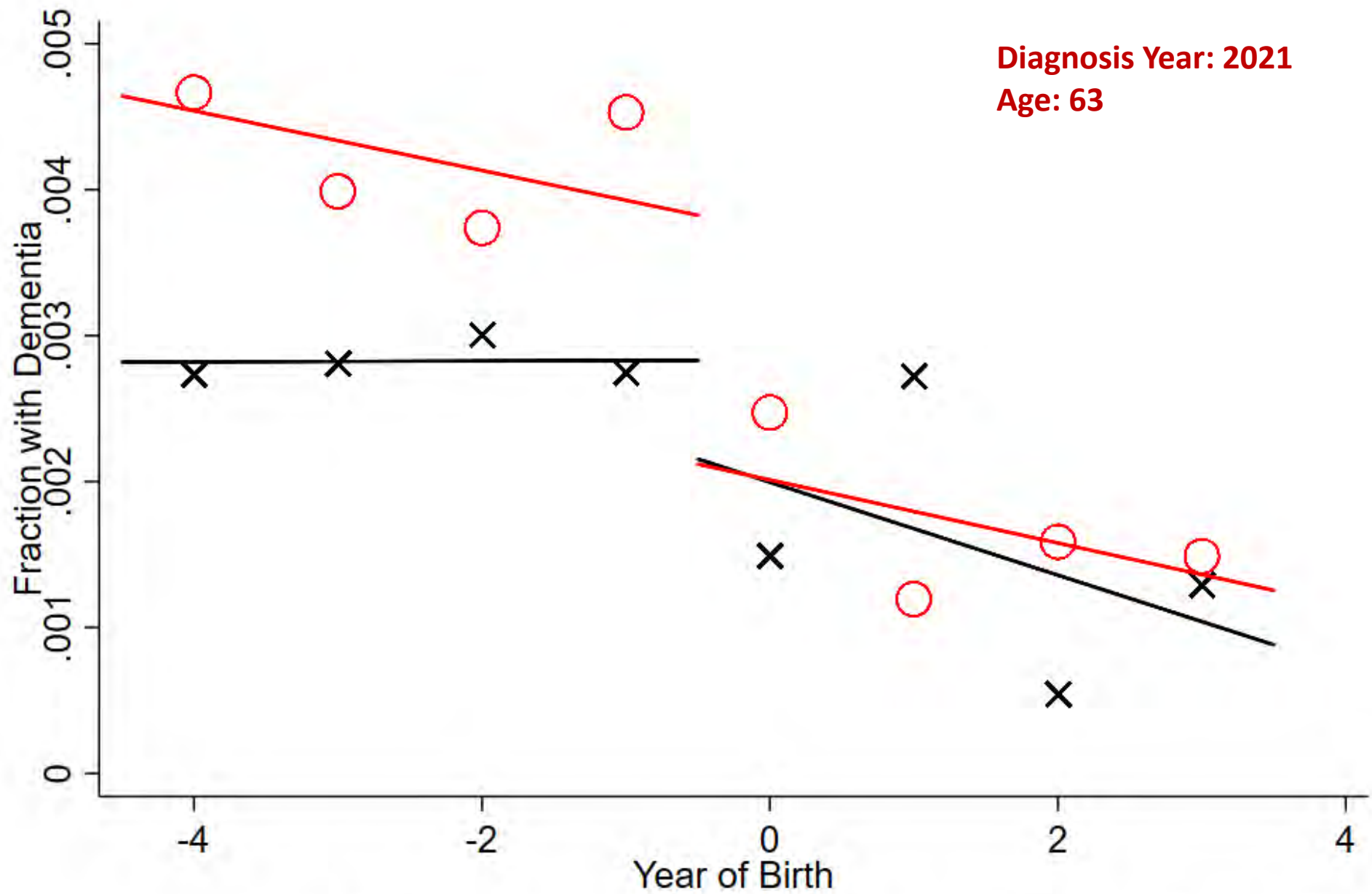
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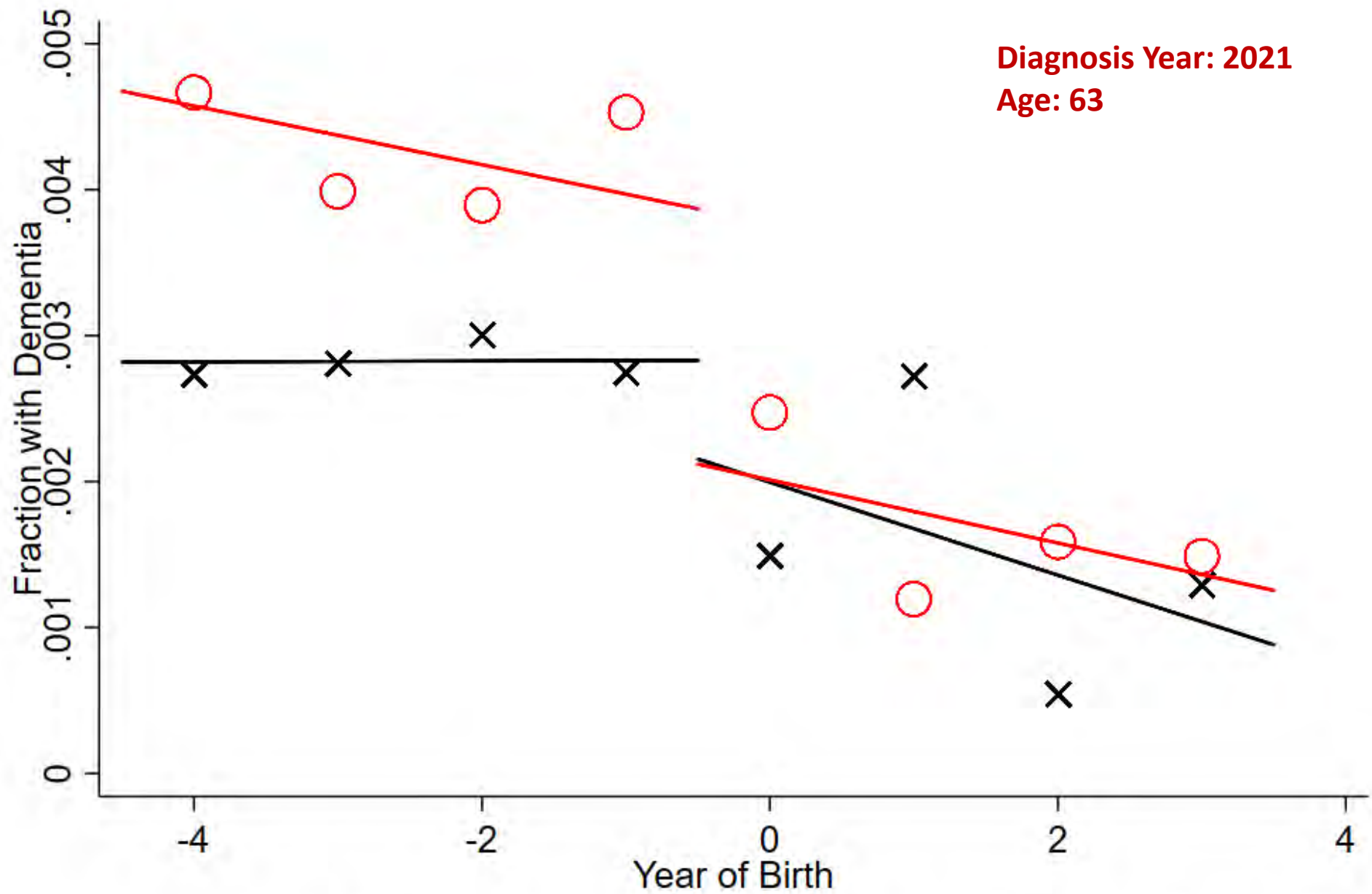


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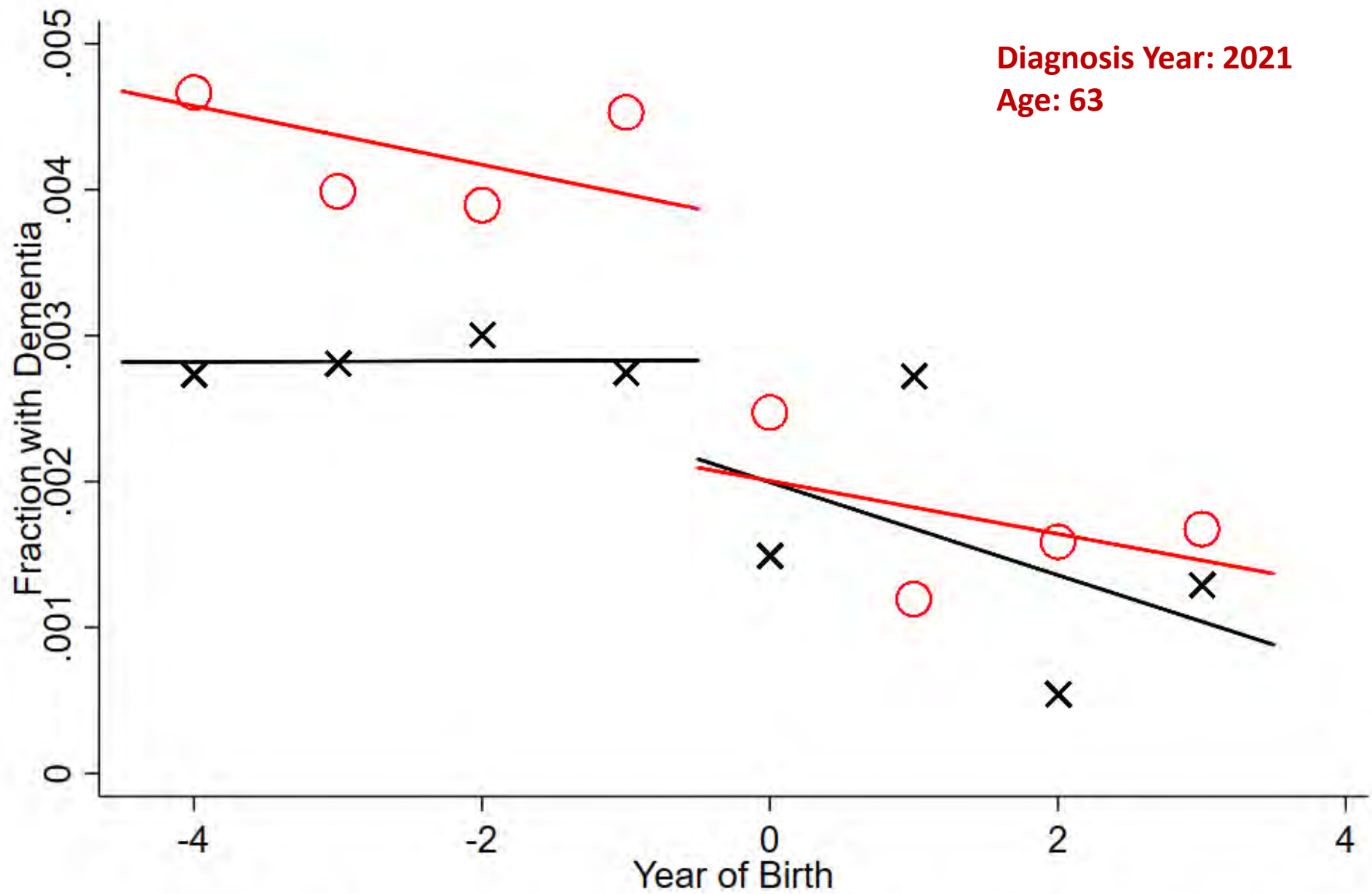


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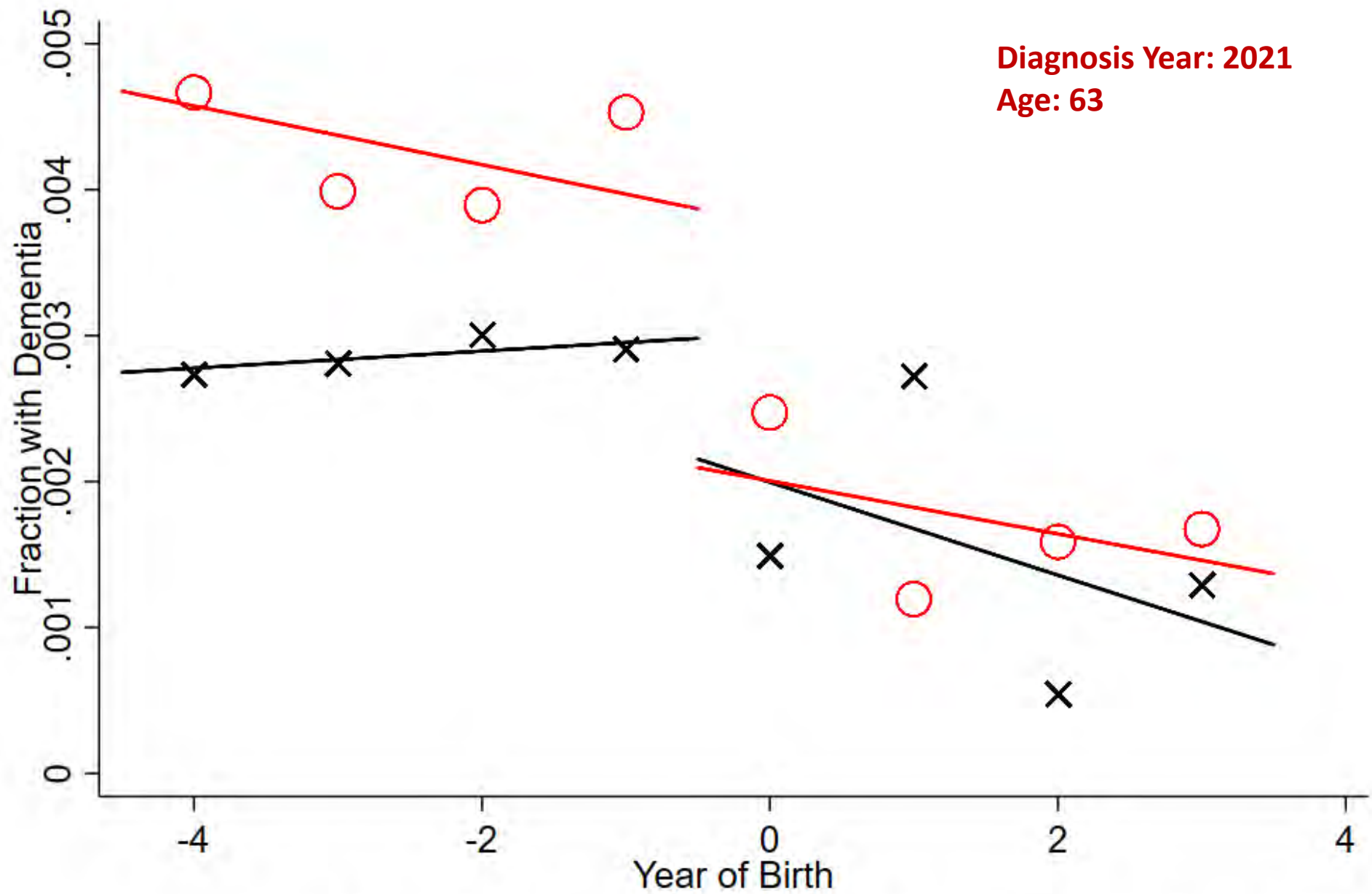




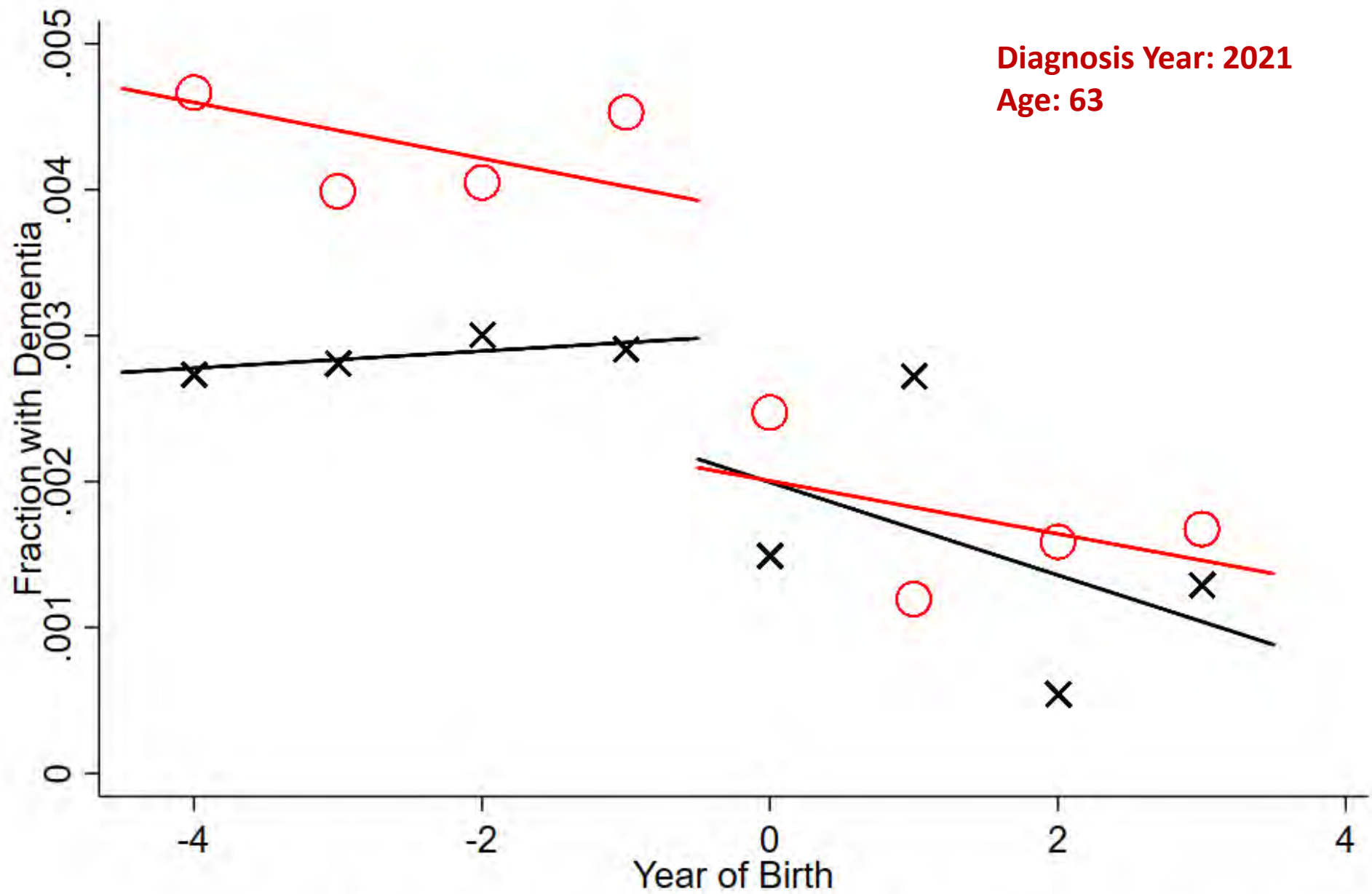
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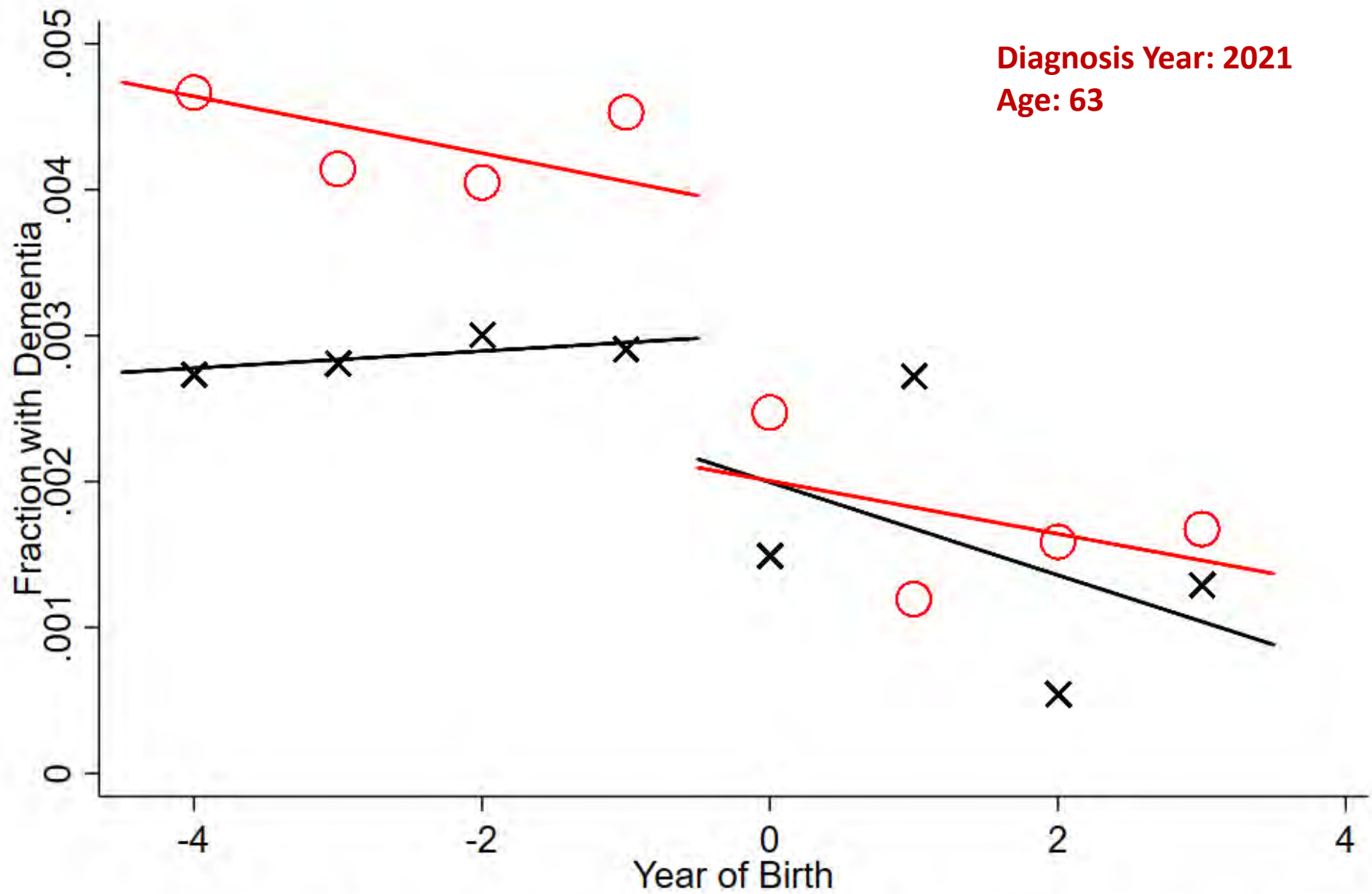
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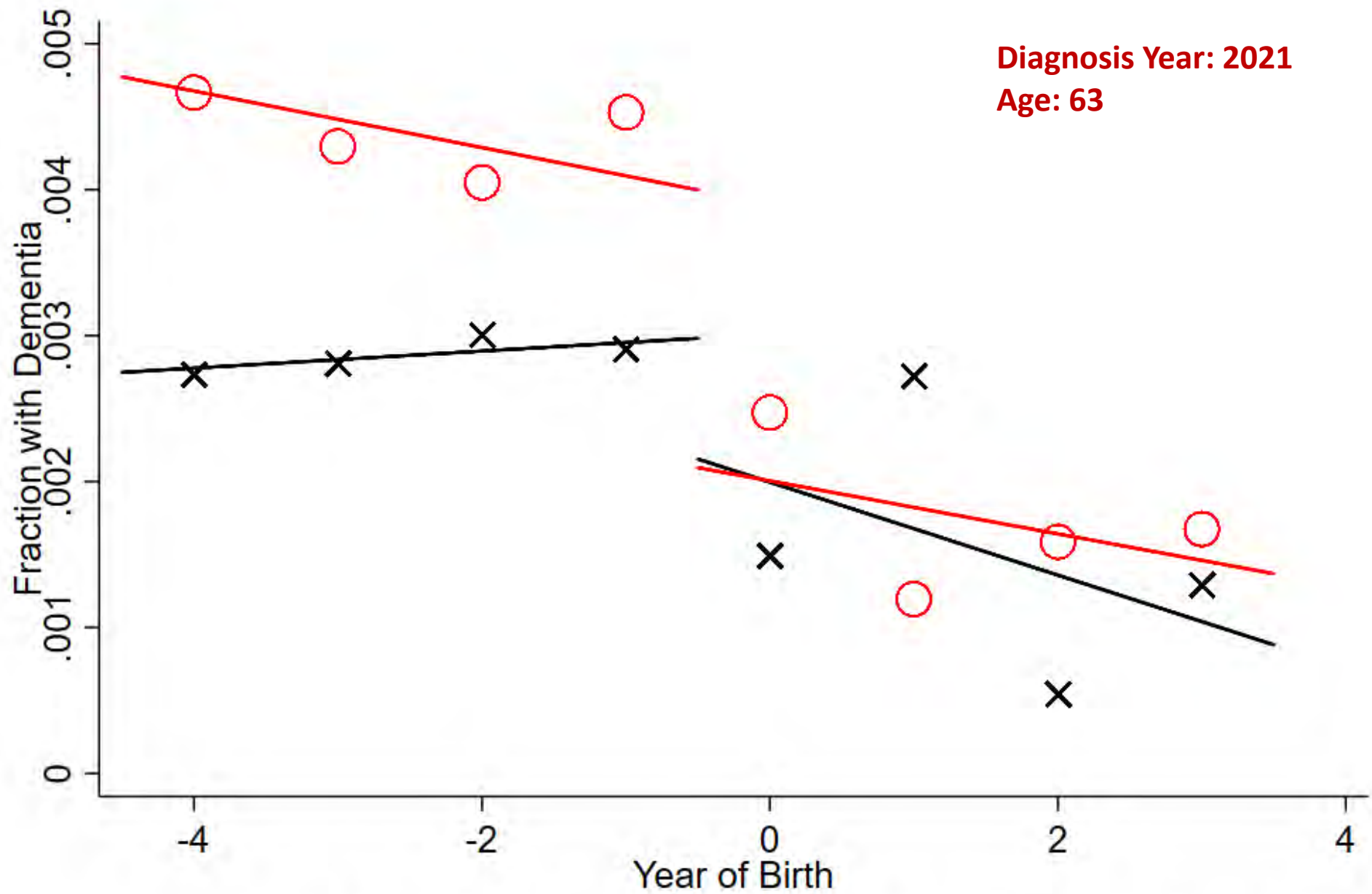
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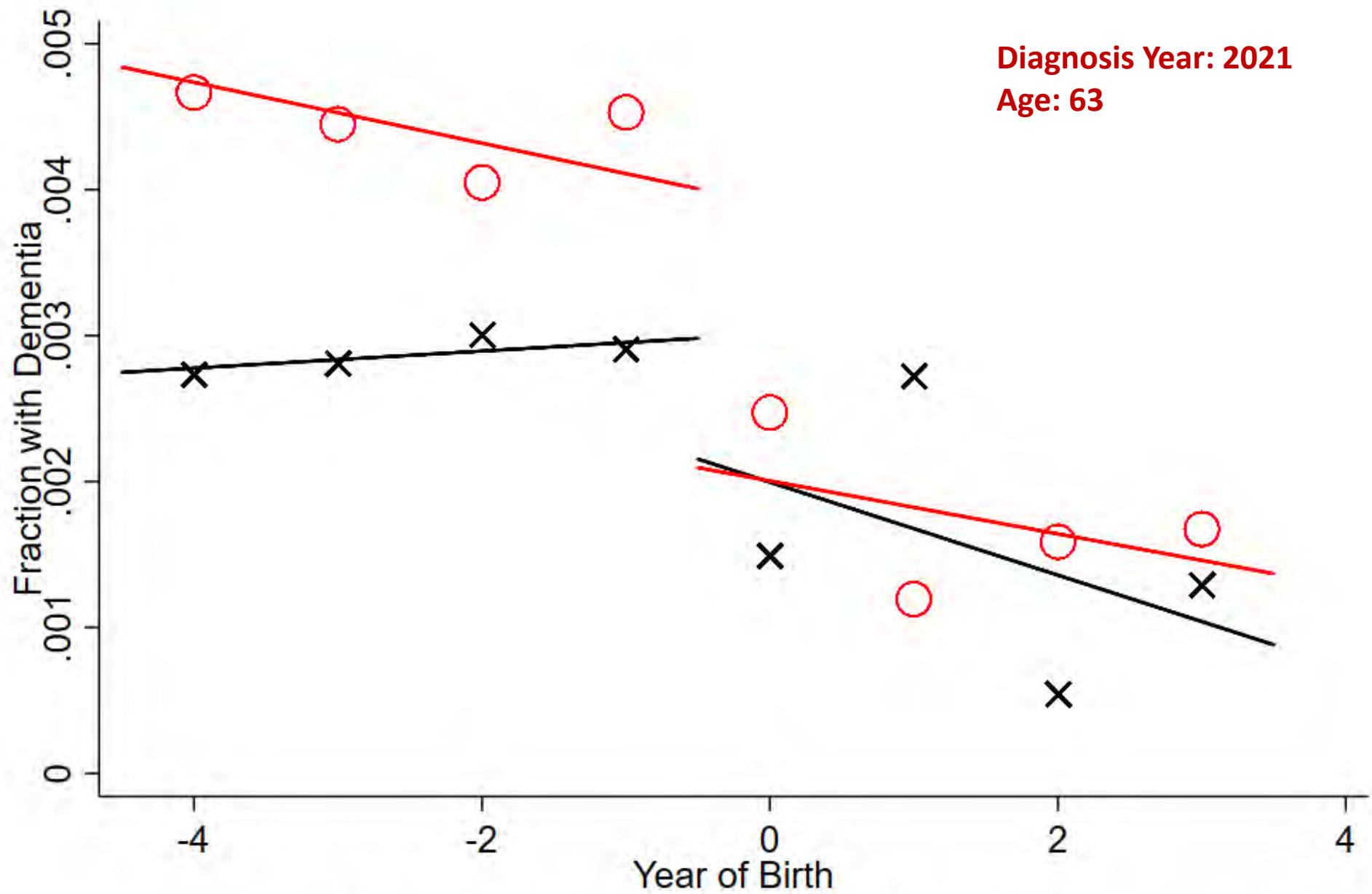
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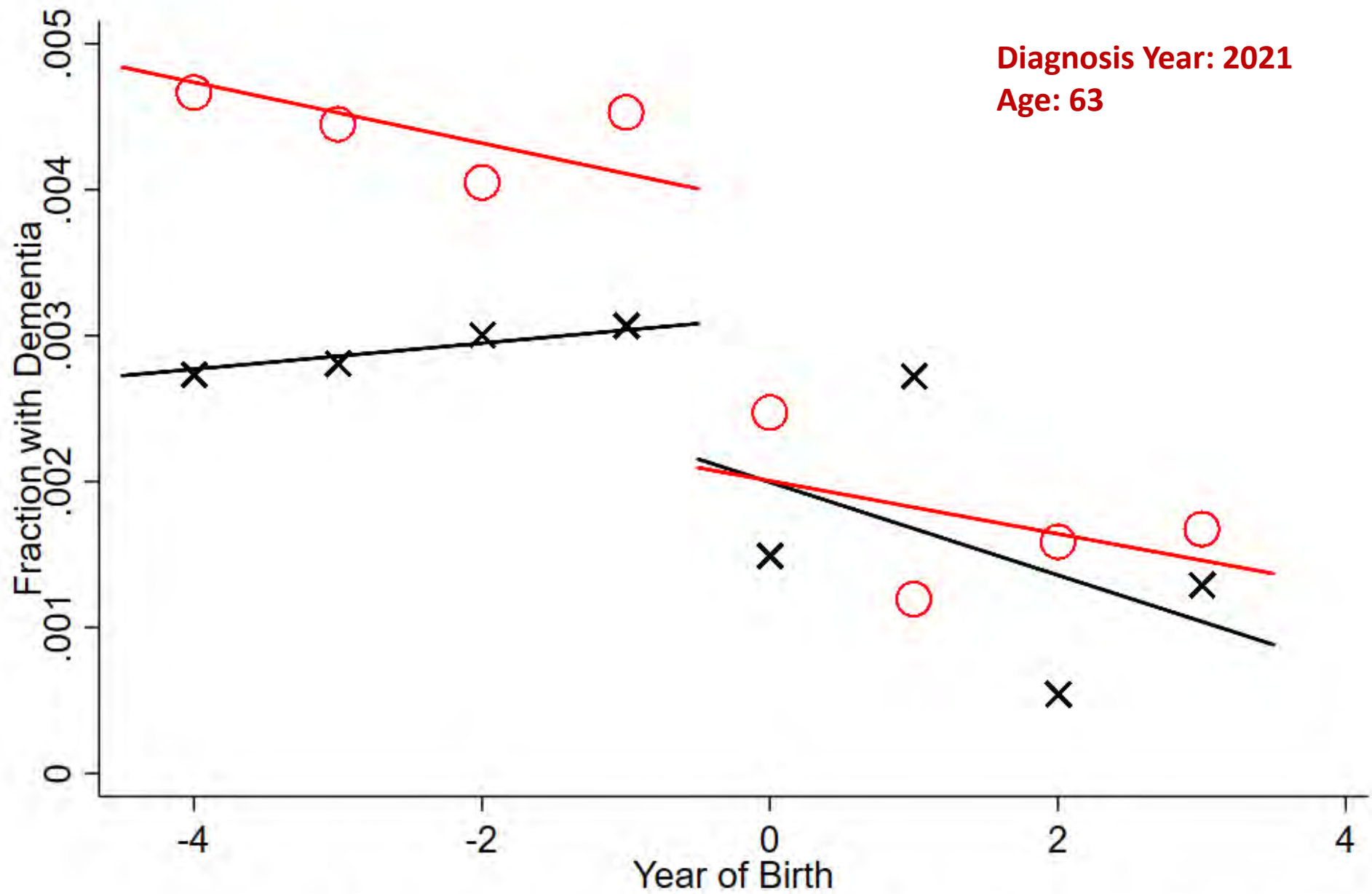
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

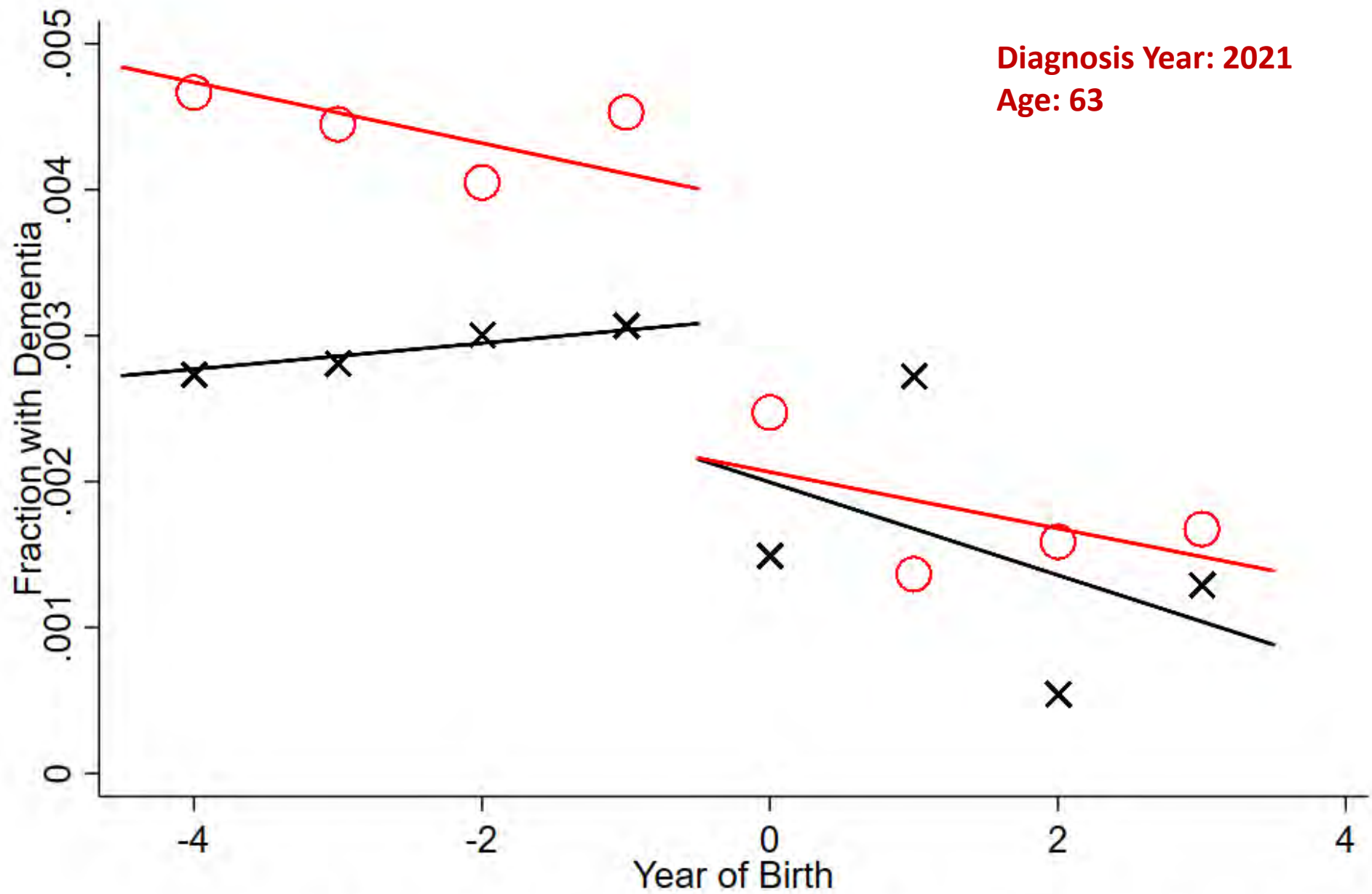


X Bottom Half Composite Genetic Risk O Top Half Composite Genetic Risk

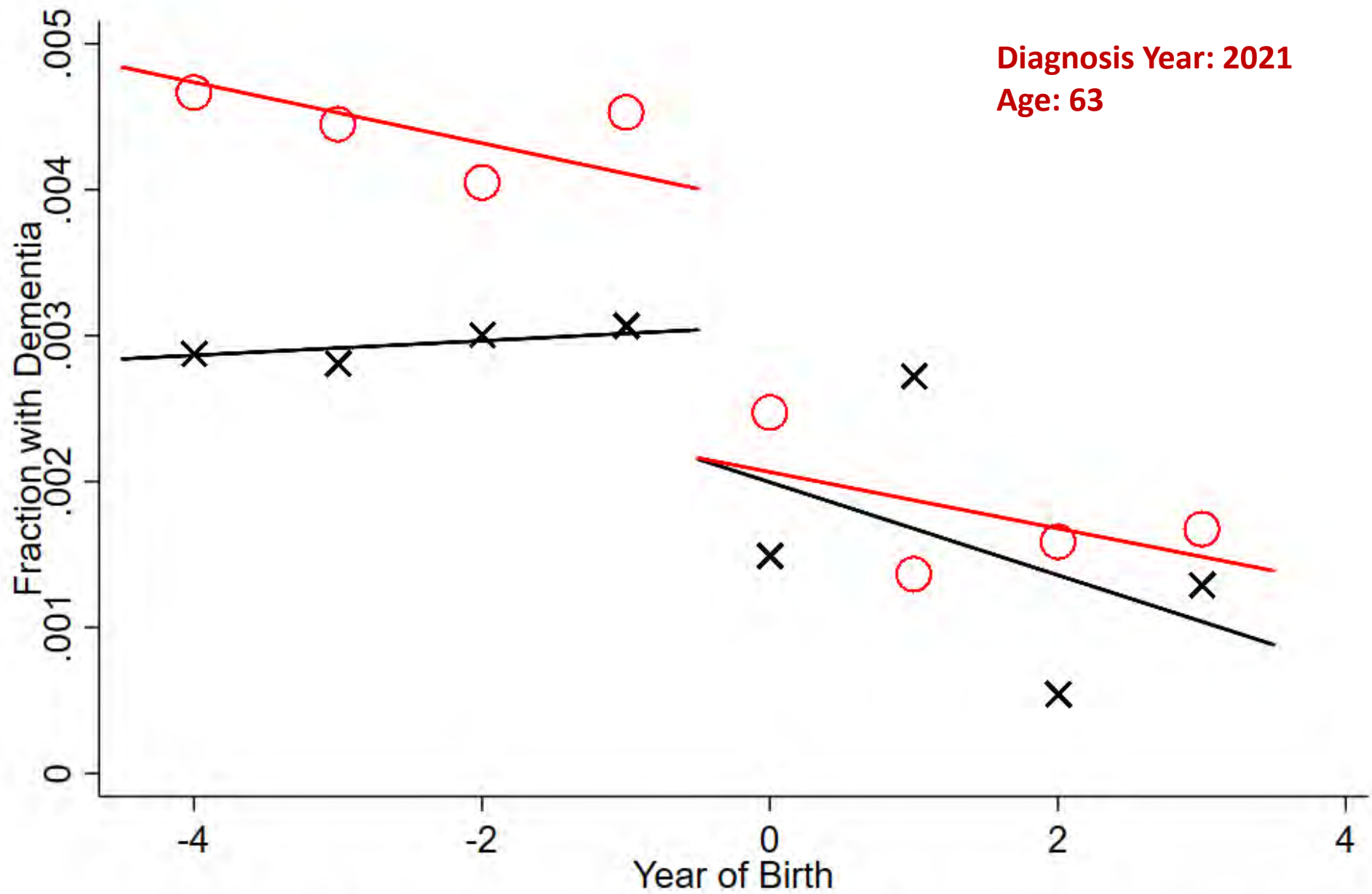


Diagnosis Year: 2021
Age: 63

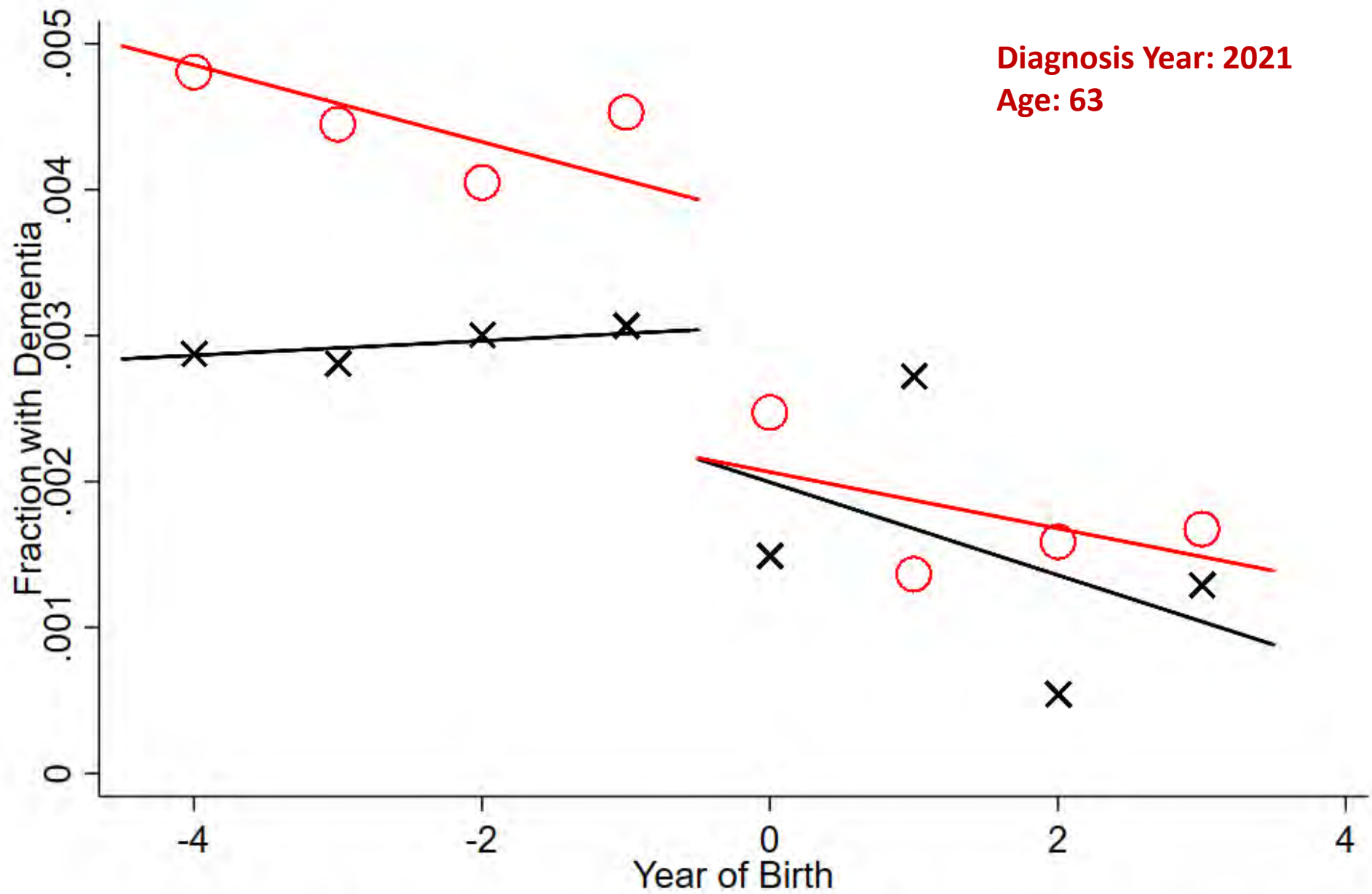
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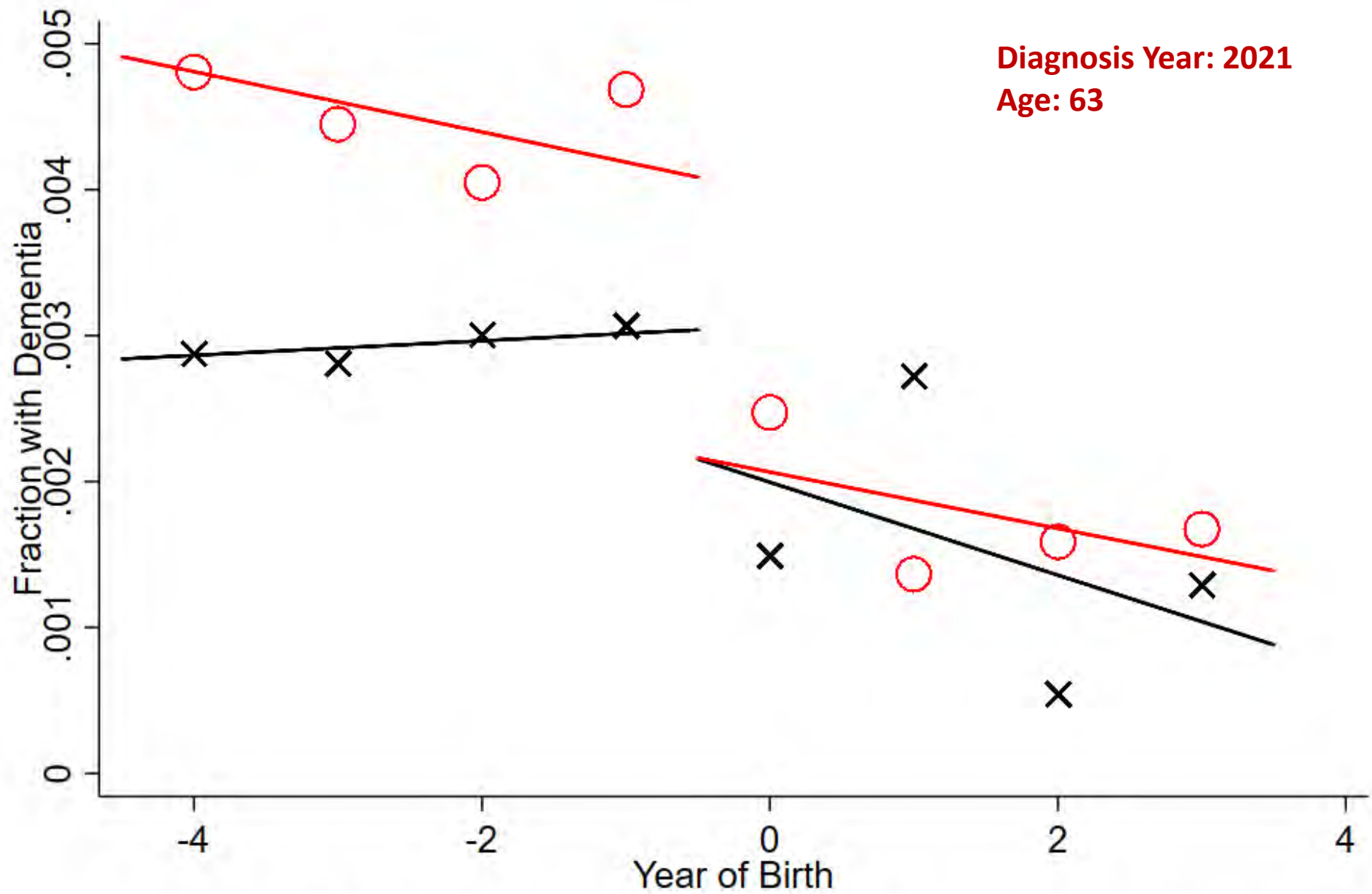


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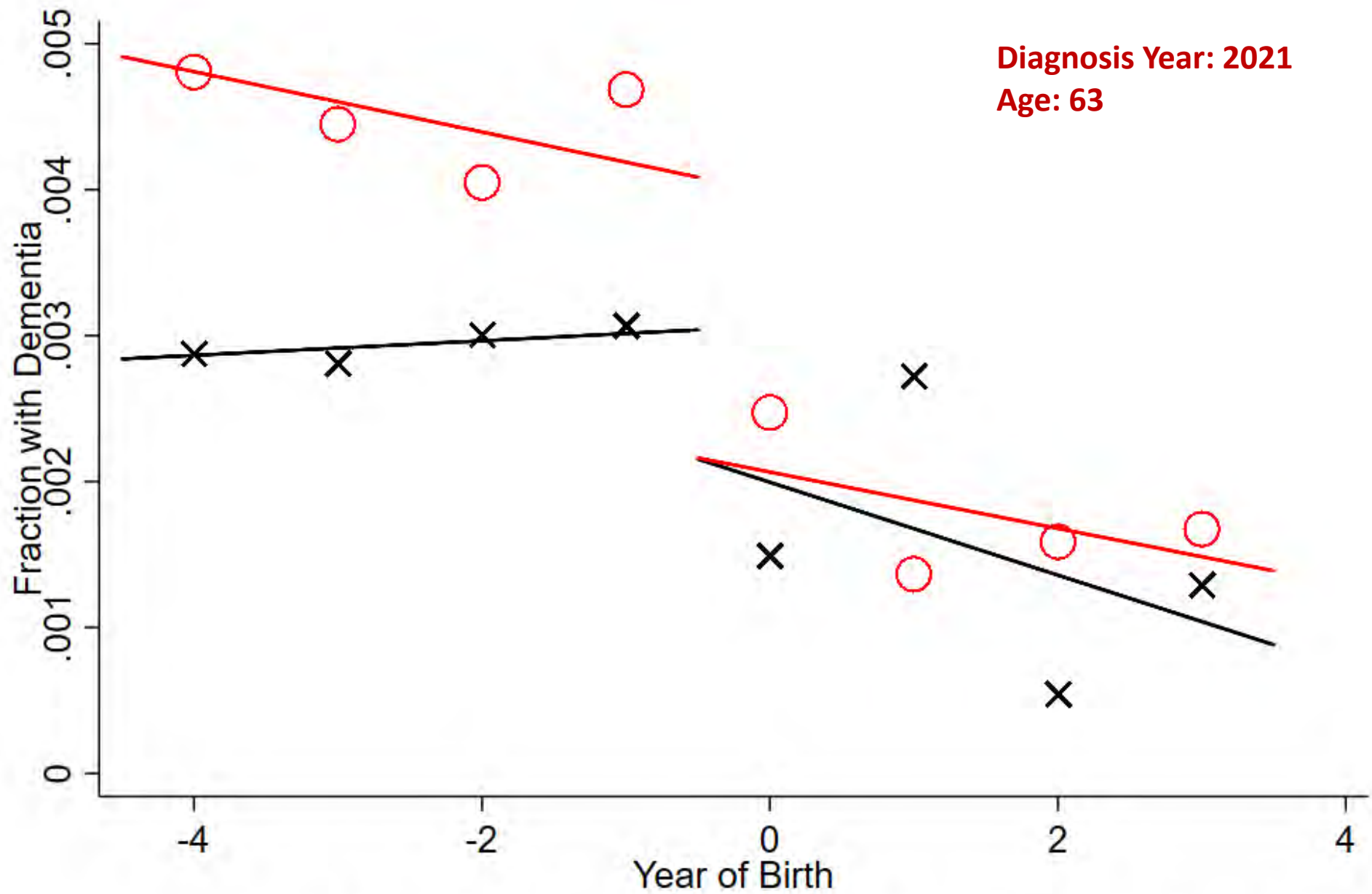


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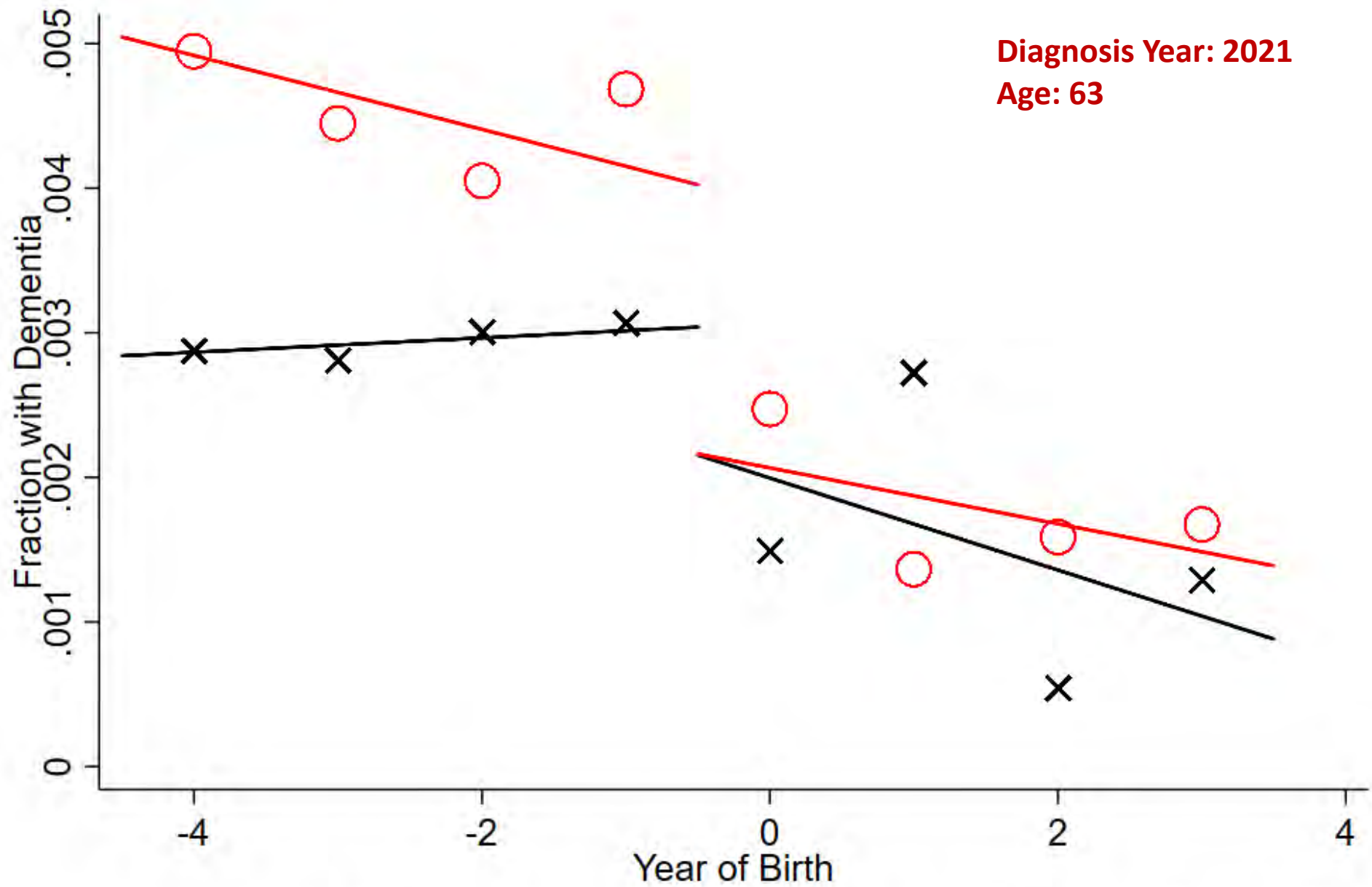




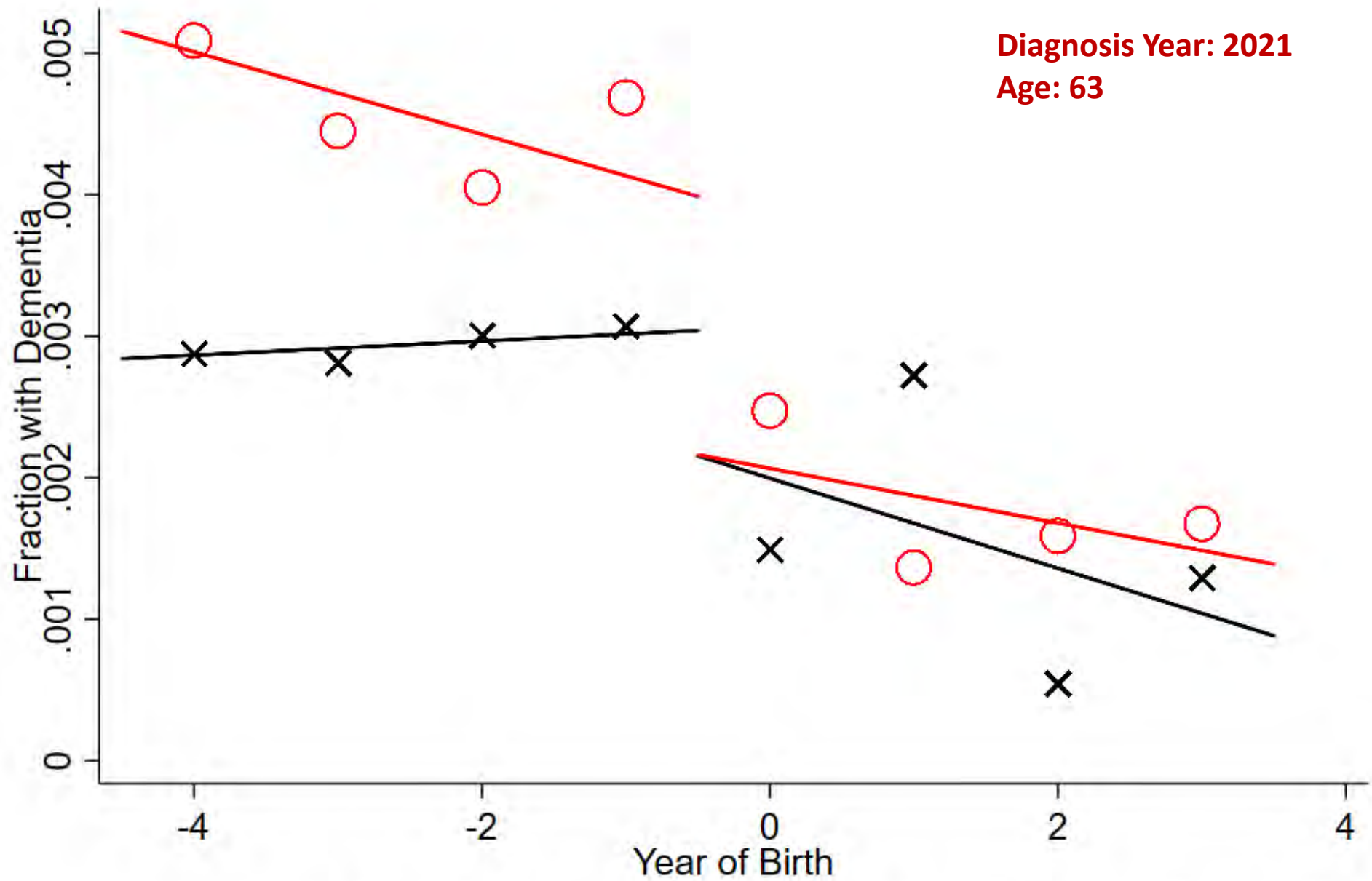
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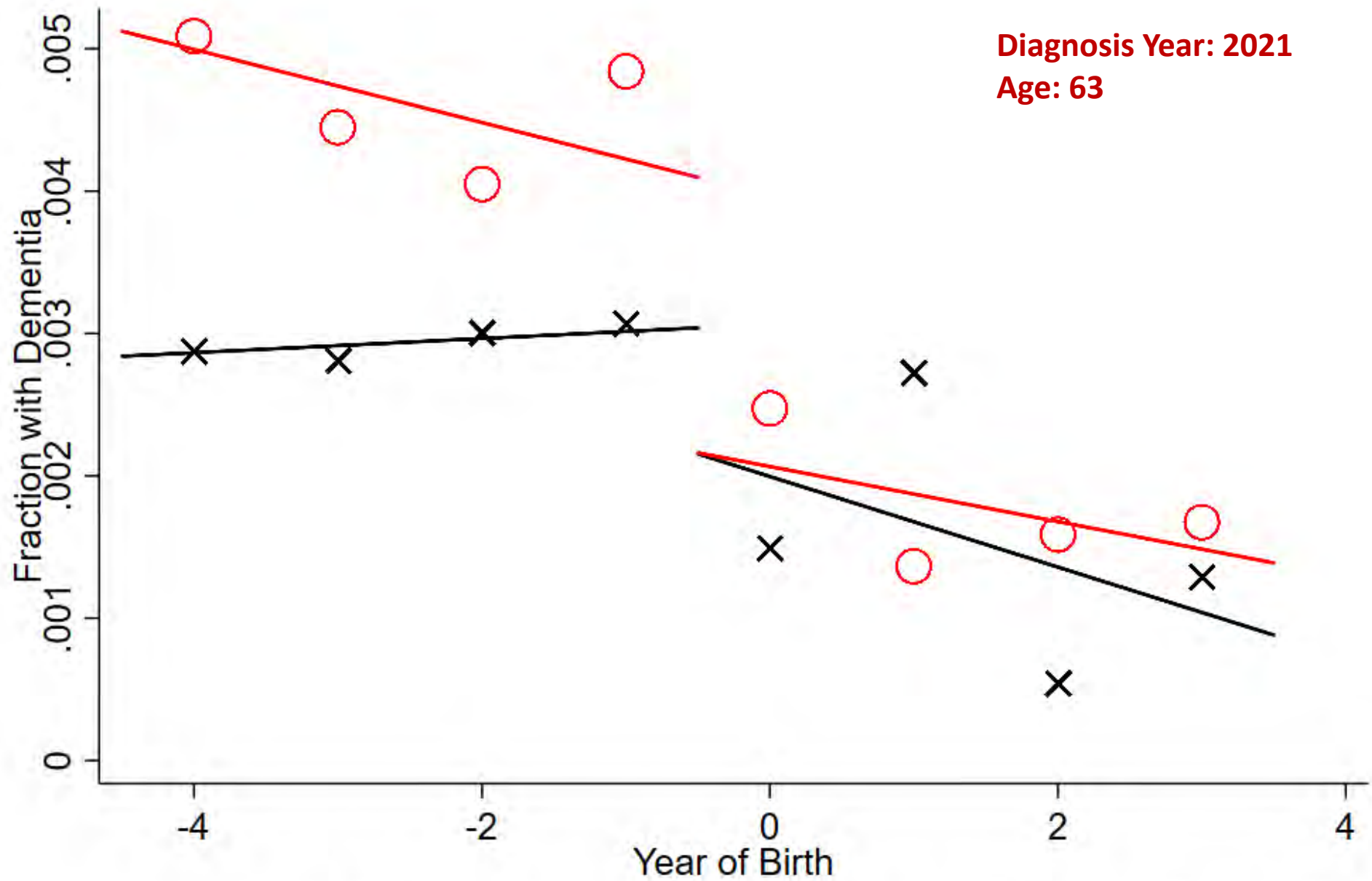
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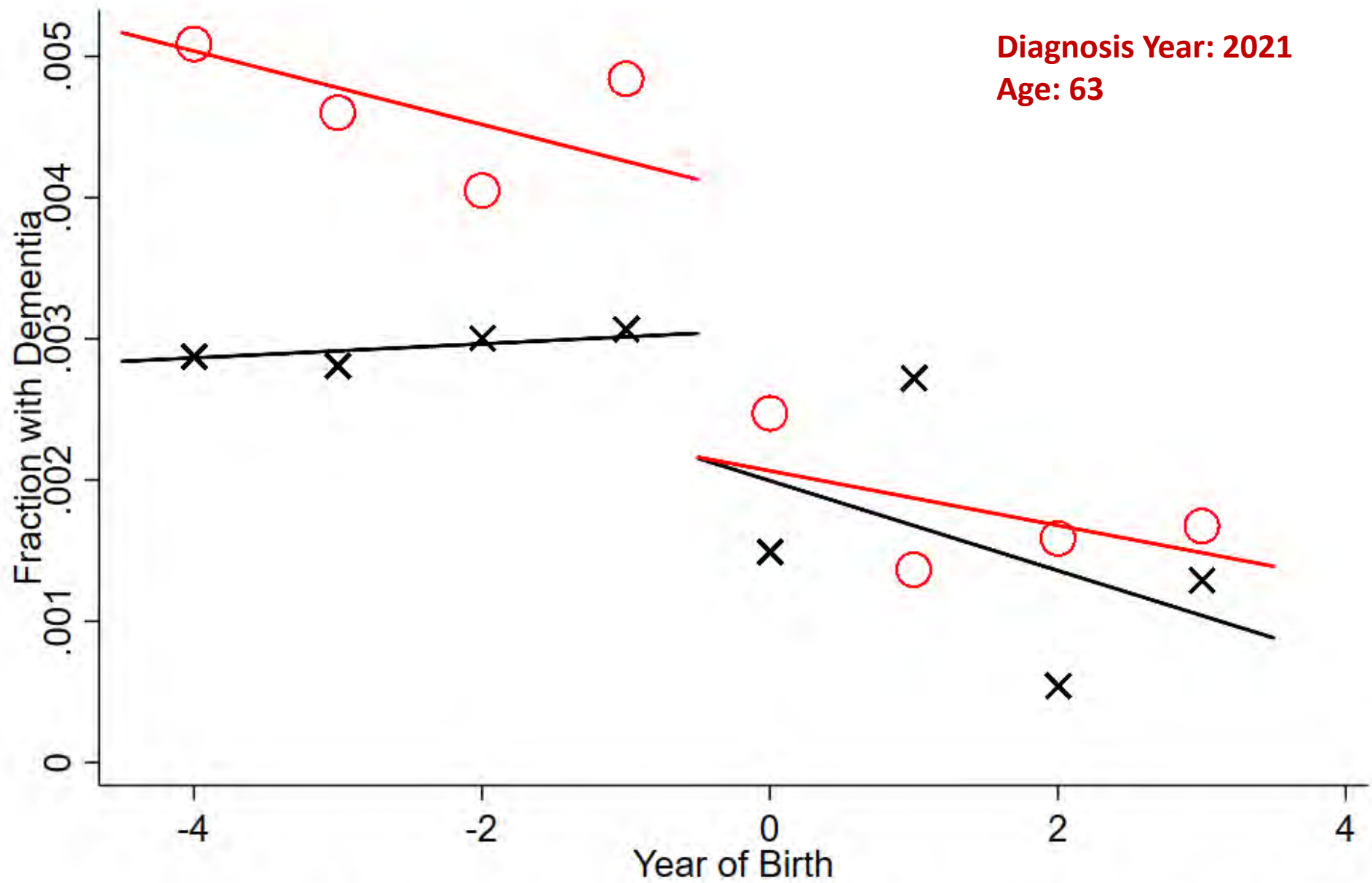
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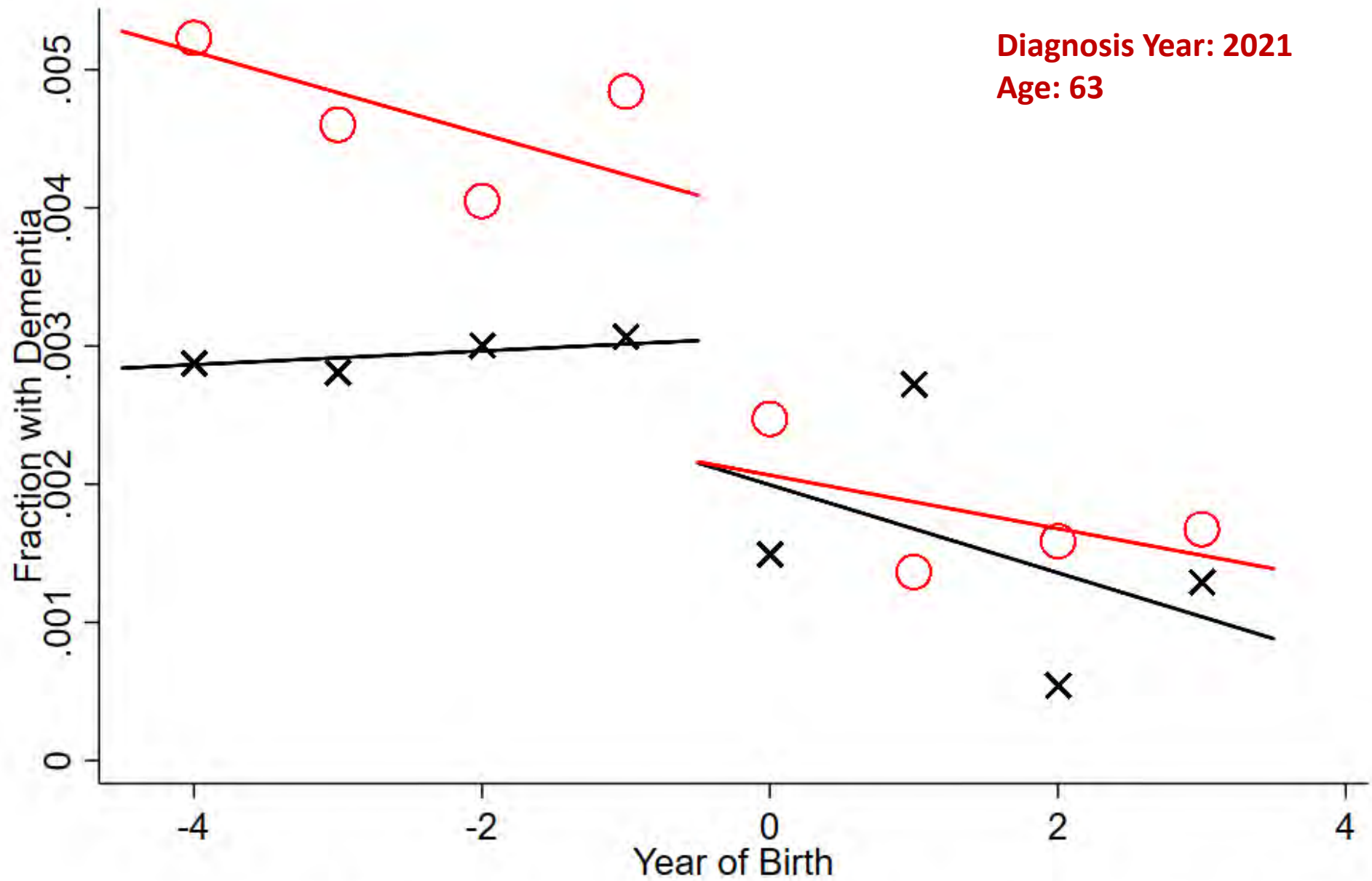
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

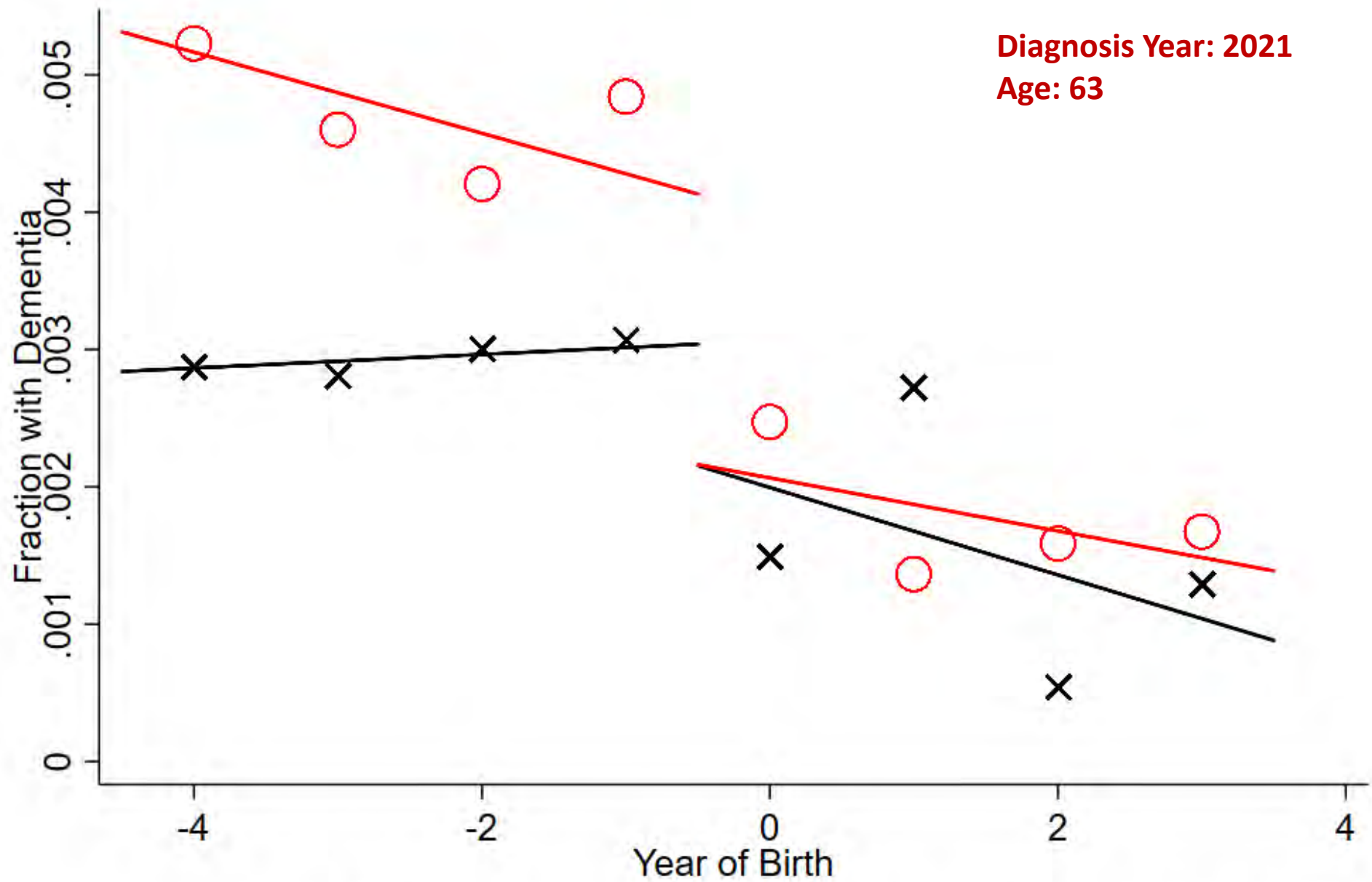


× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

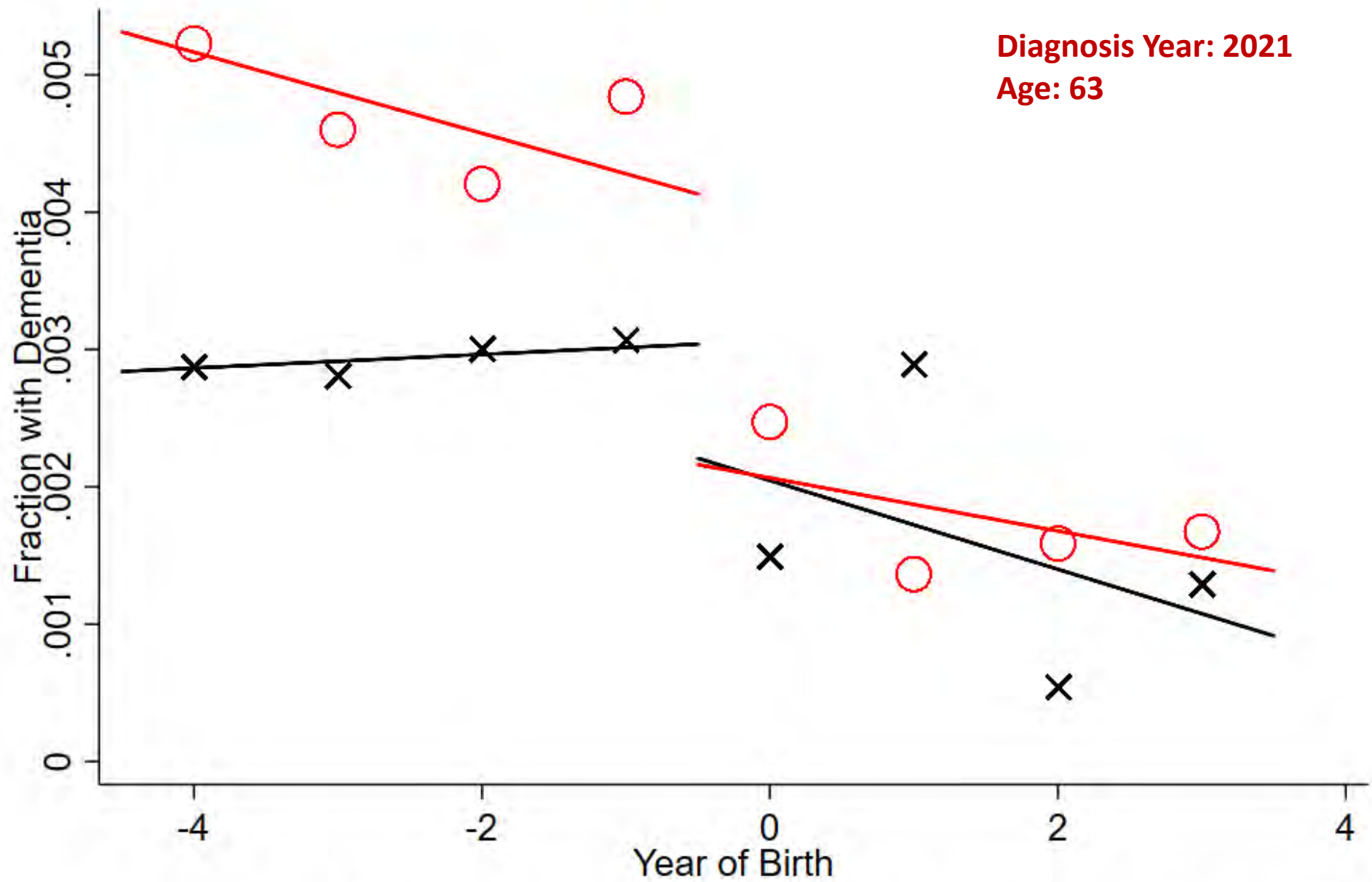


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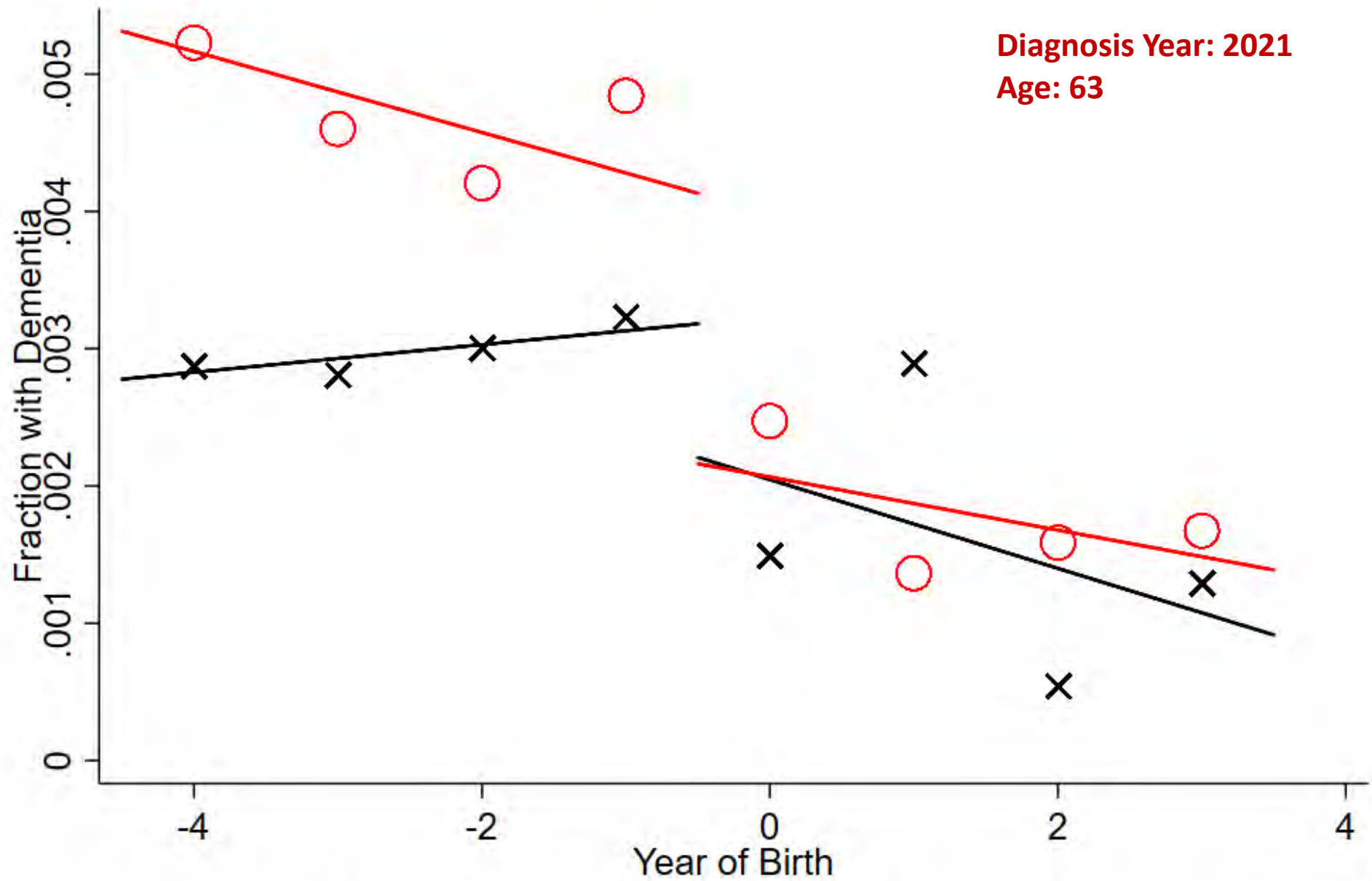




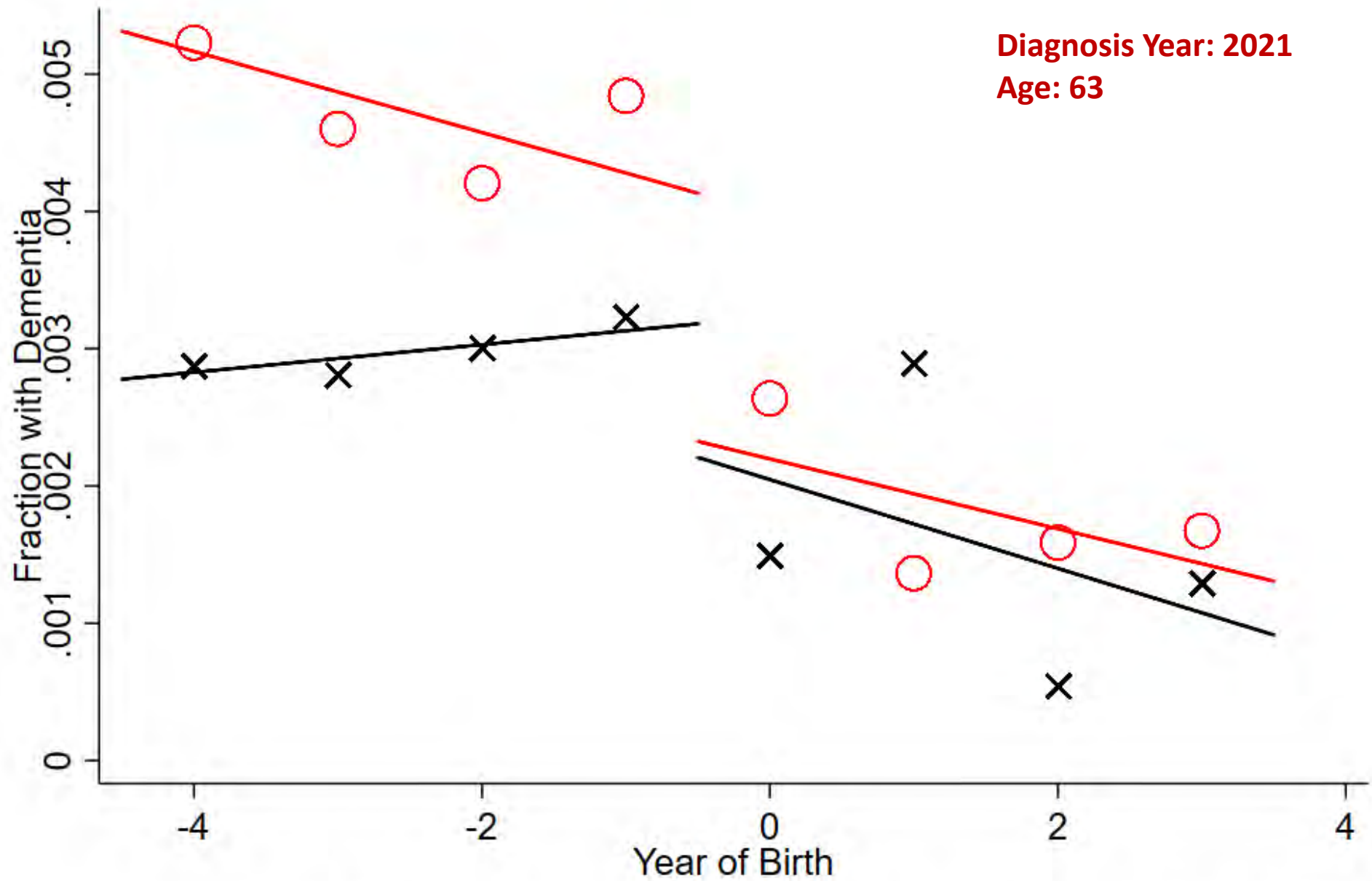
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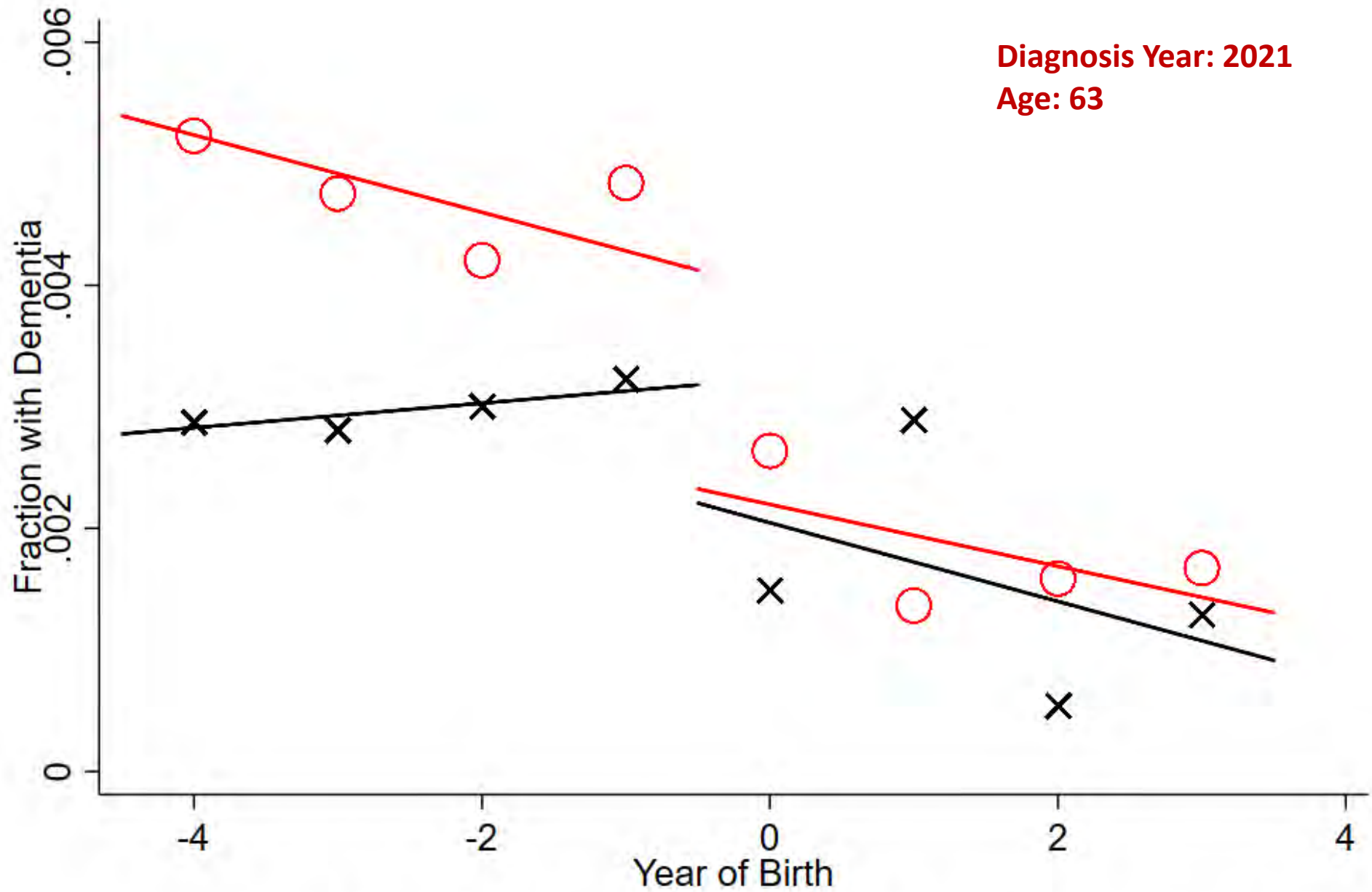
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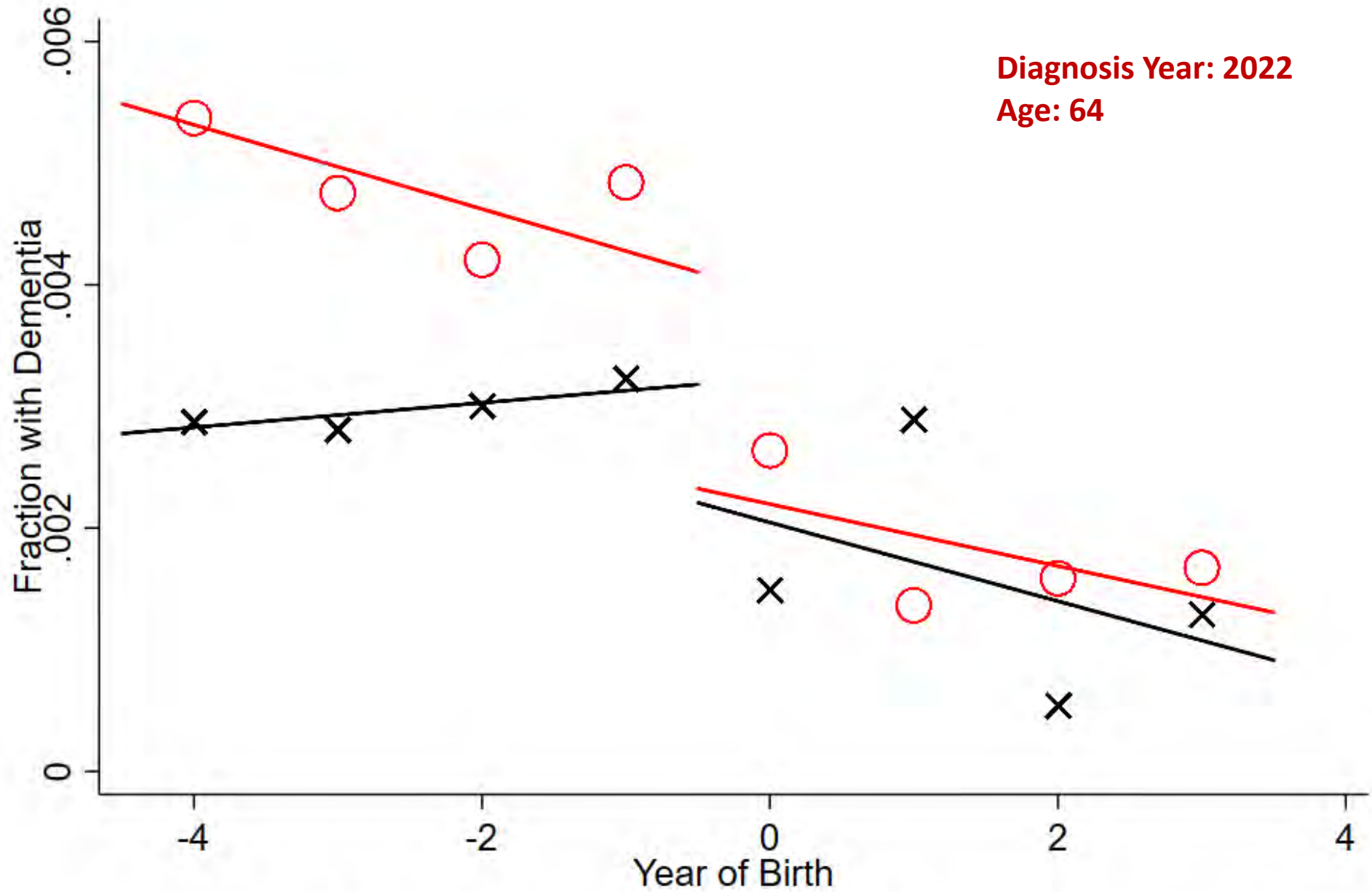
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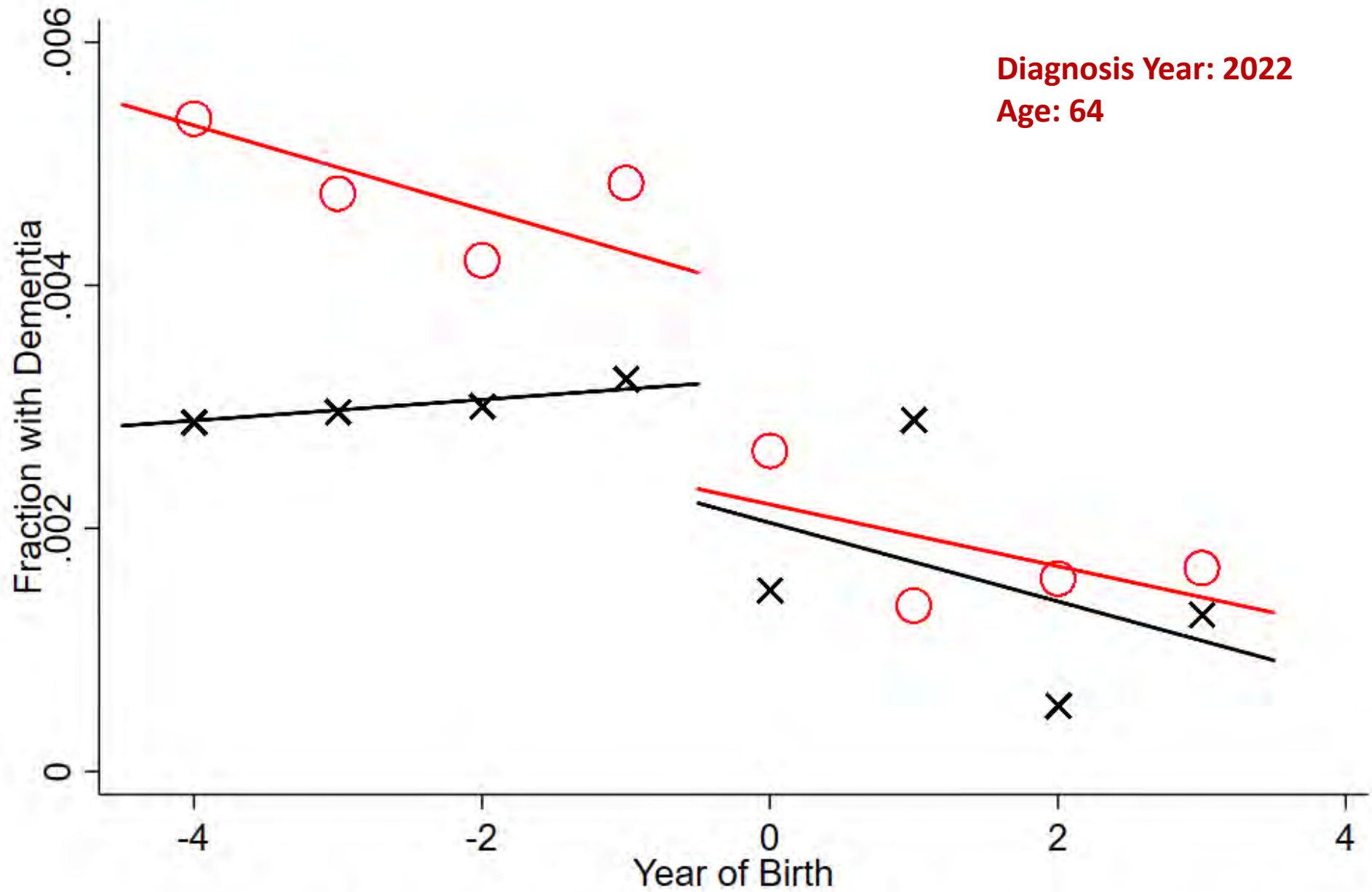
× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk



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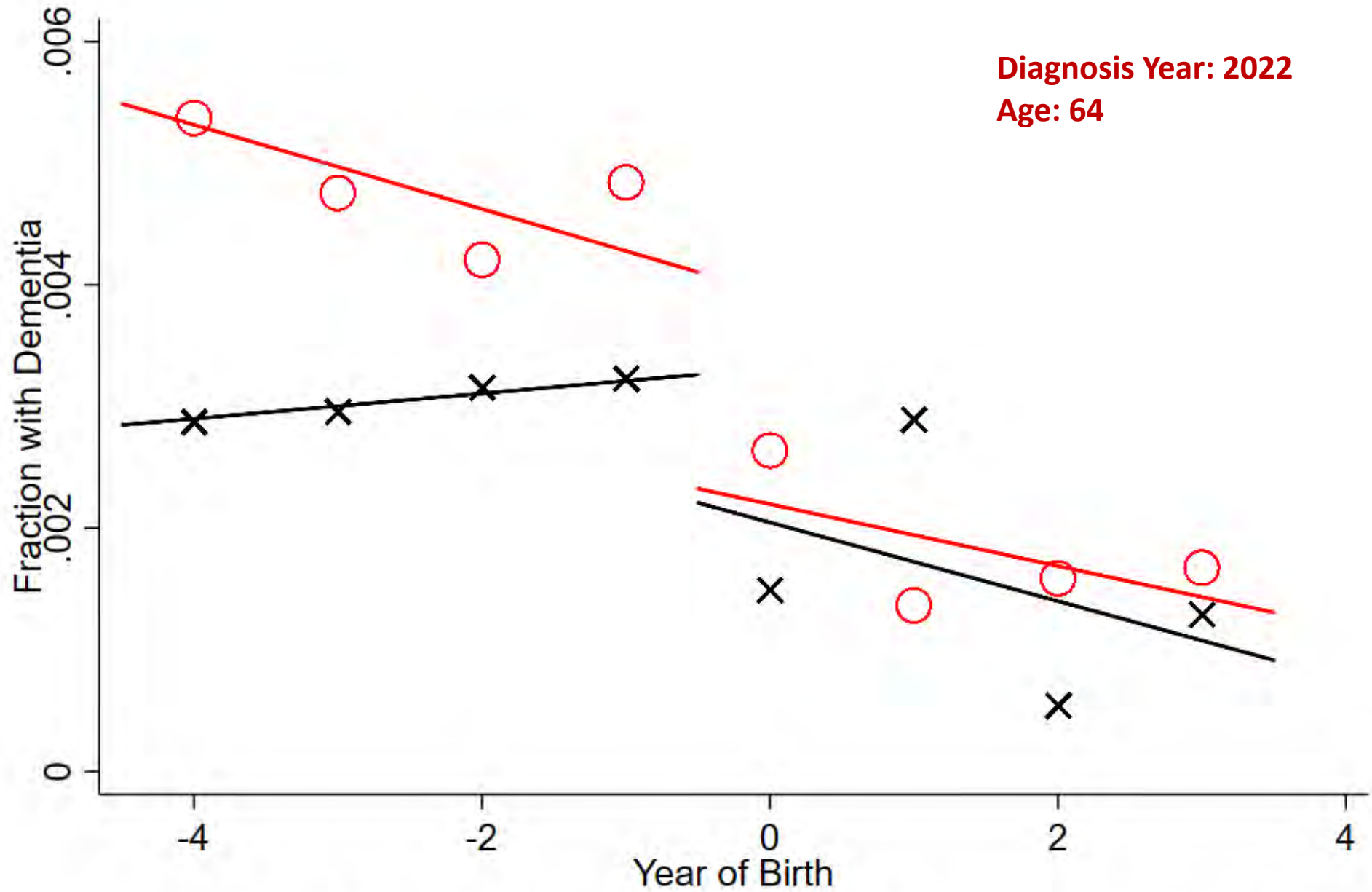


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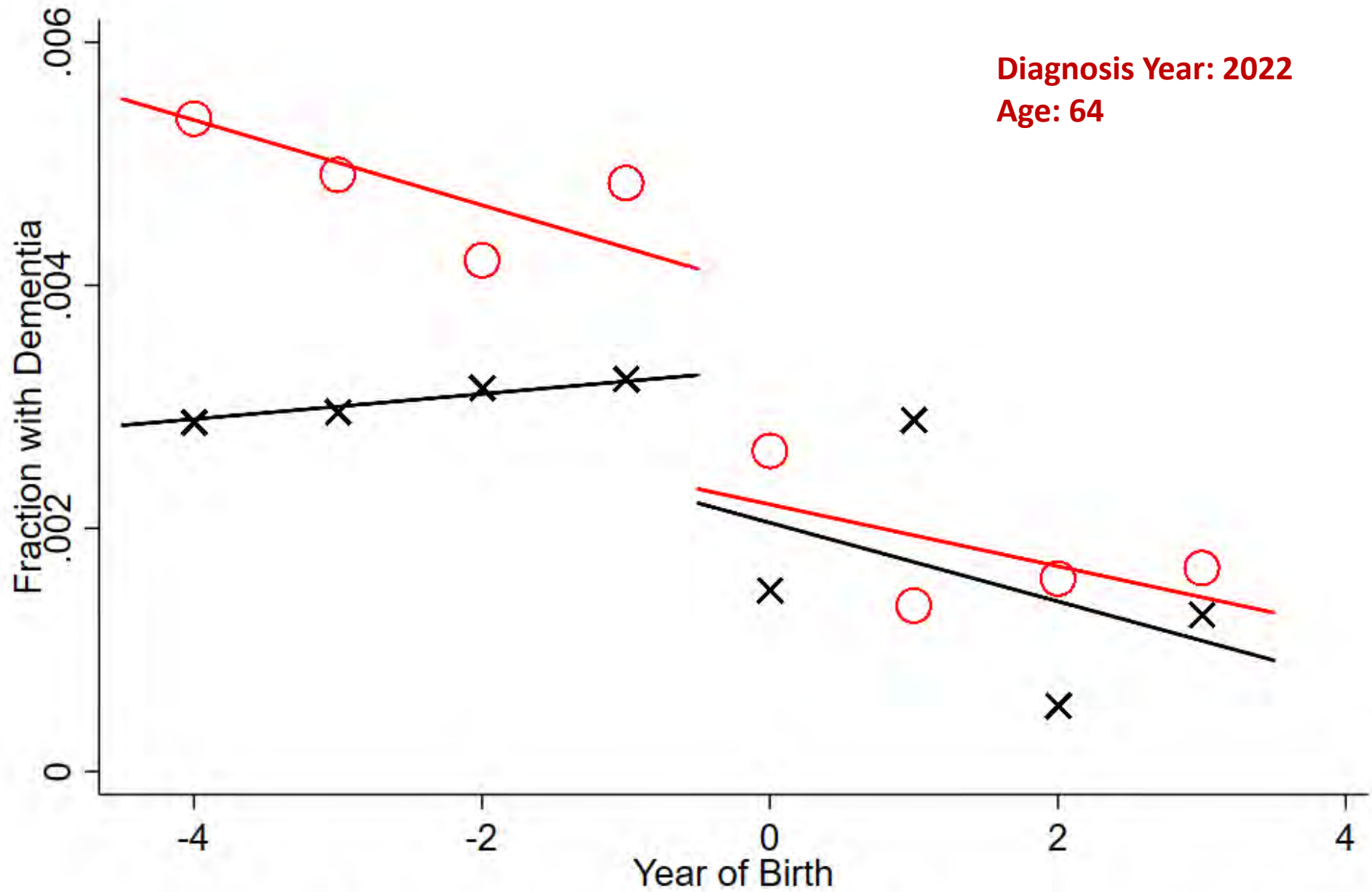


Diagnosis Year: 2022
Age: 64

X Bottom Half Composite Genetic Risk O Top Half Composite Genetic Risk

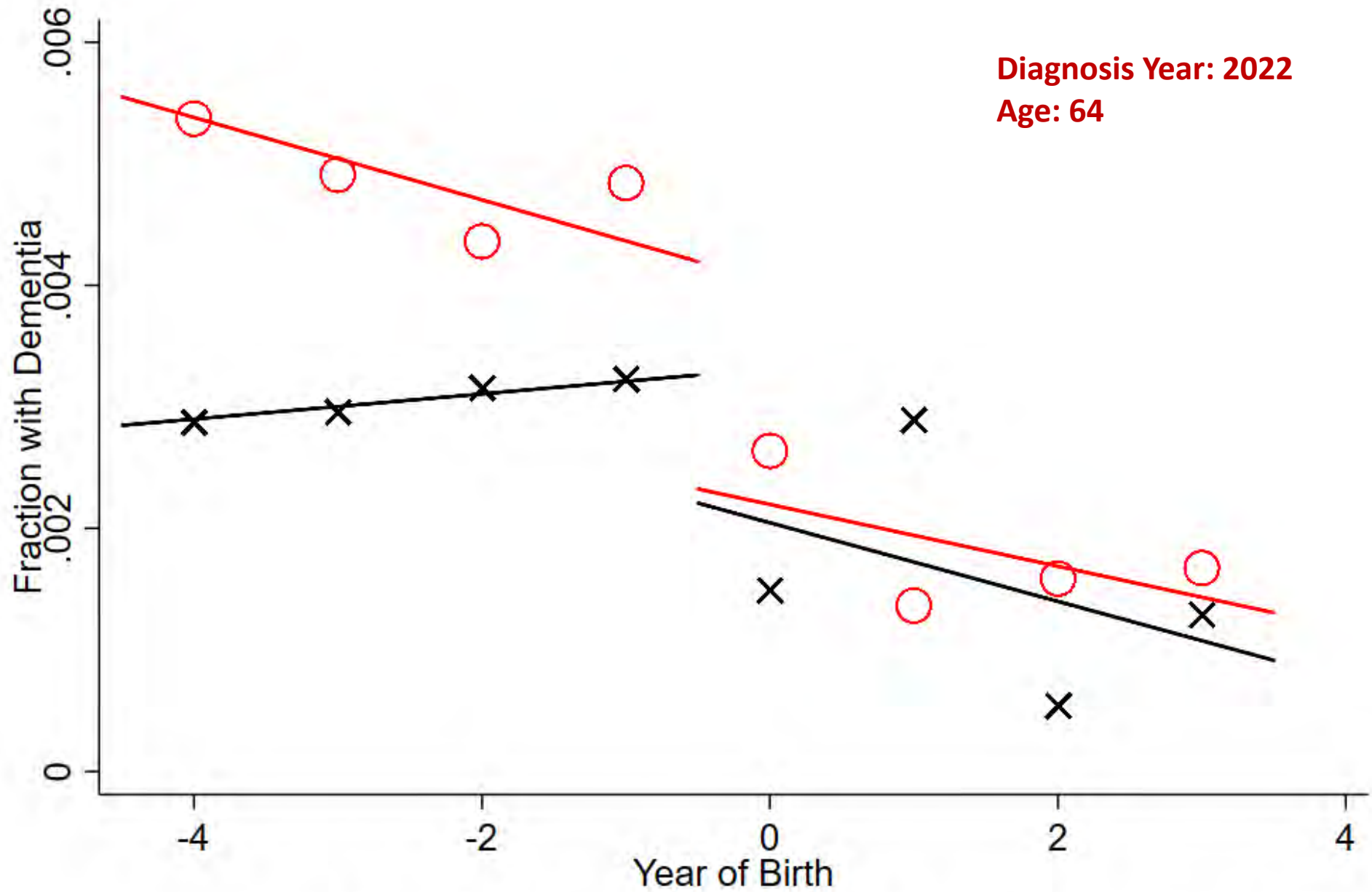


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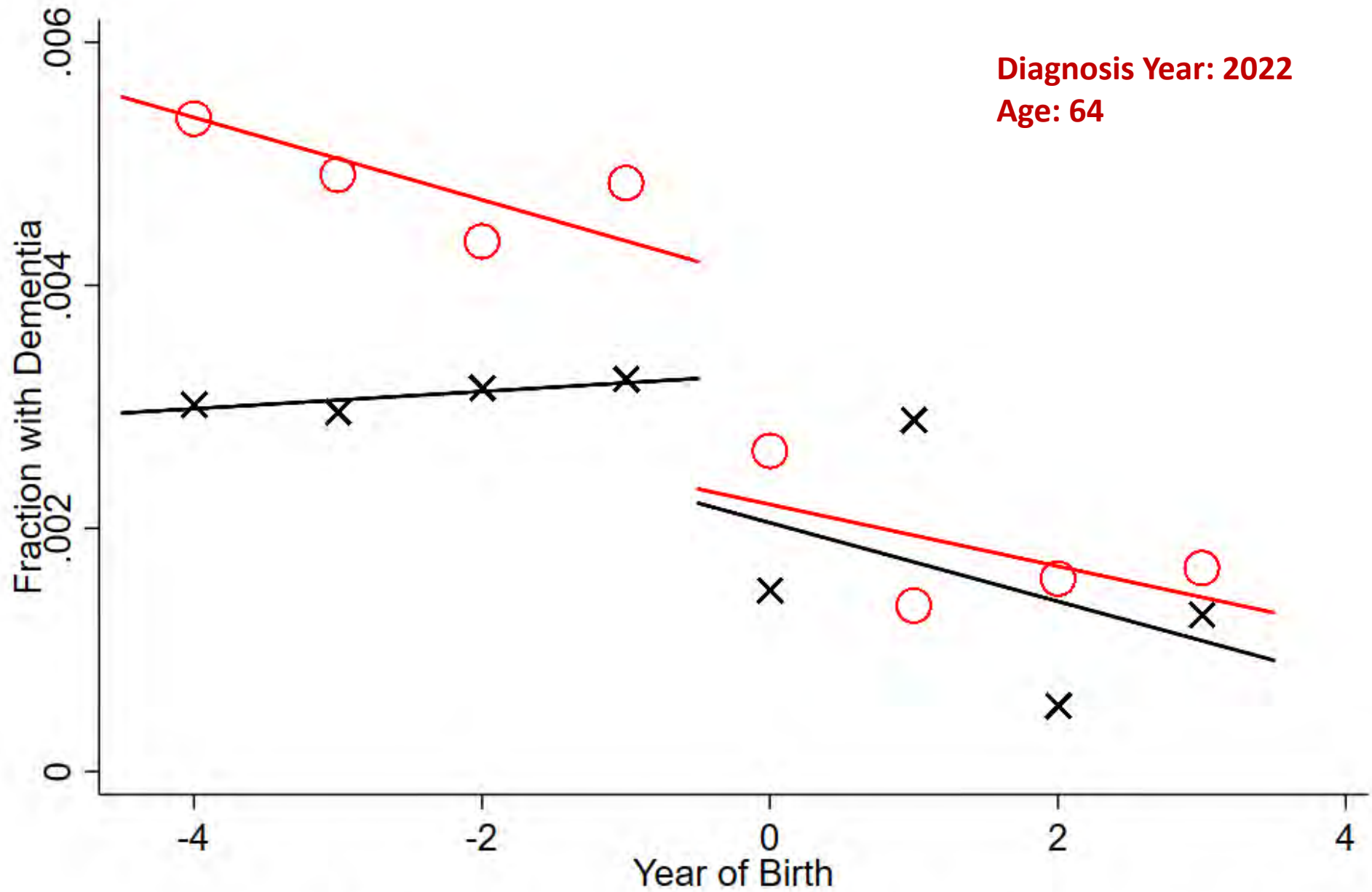


Diagnosis Year: 2022
Age: 64

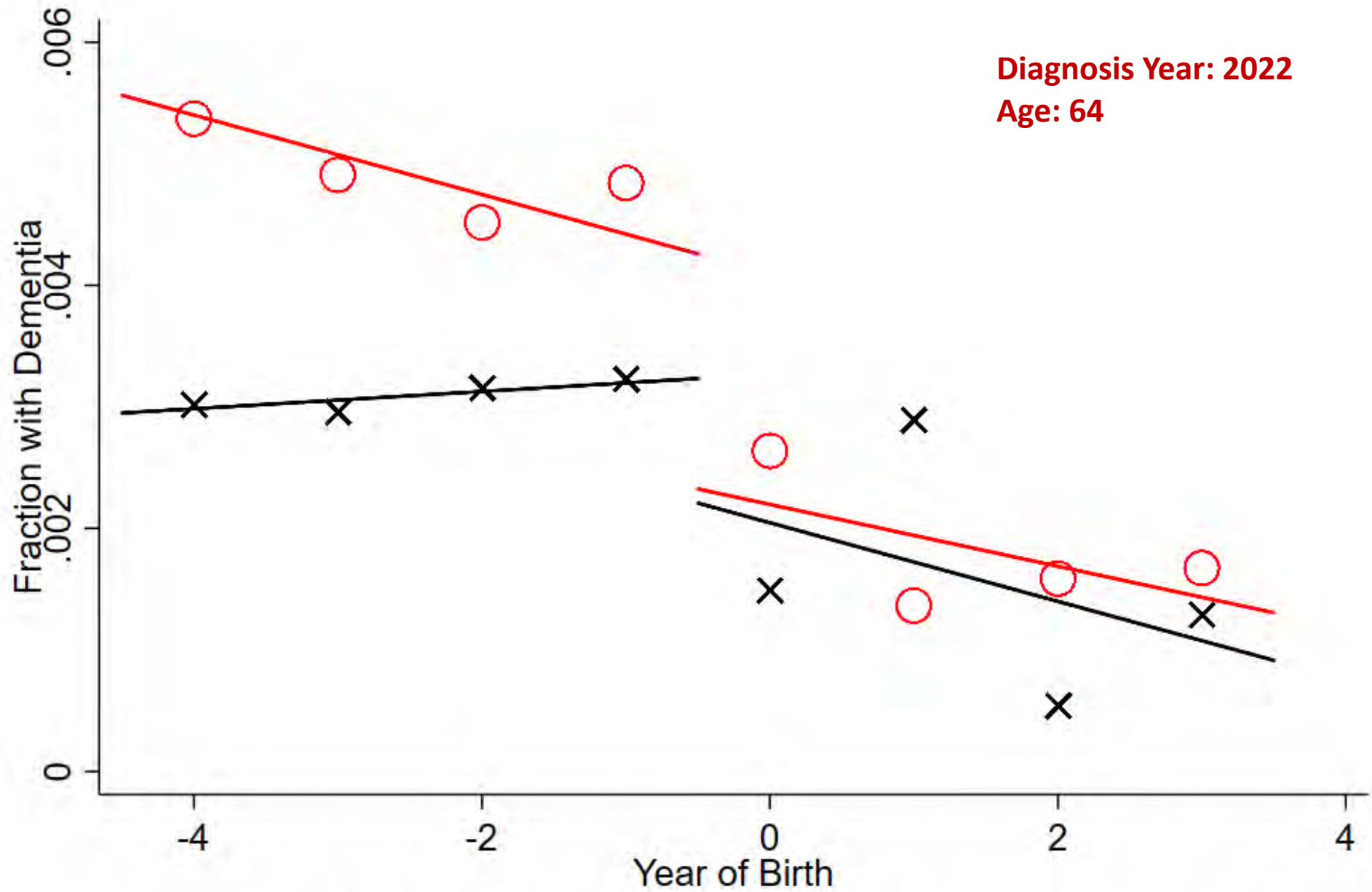
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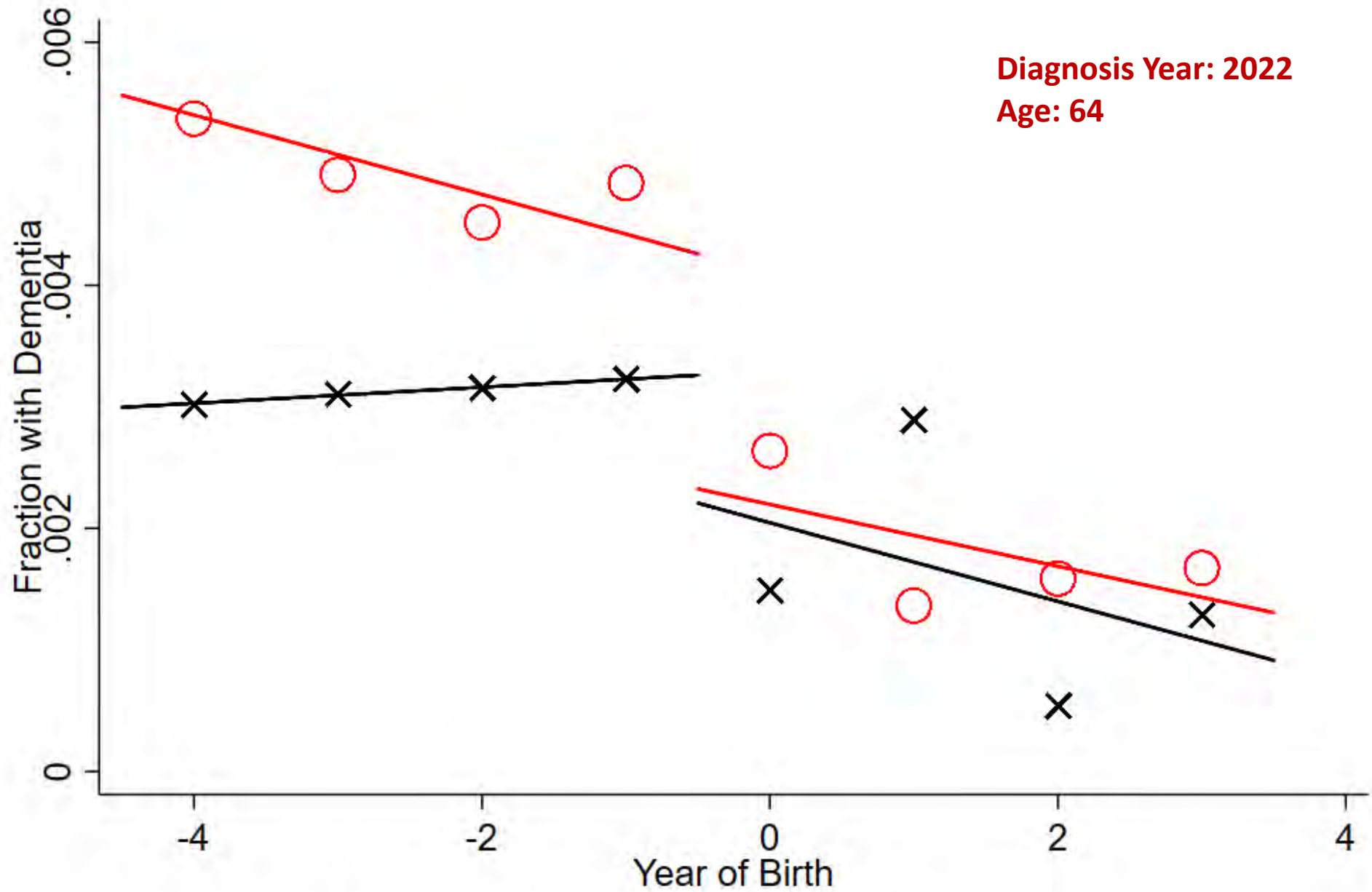
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× Bottom Half Composite Genetic Risk ○ Top Half Composite Genetic Risk

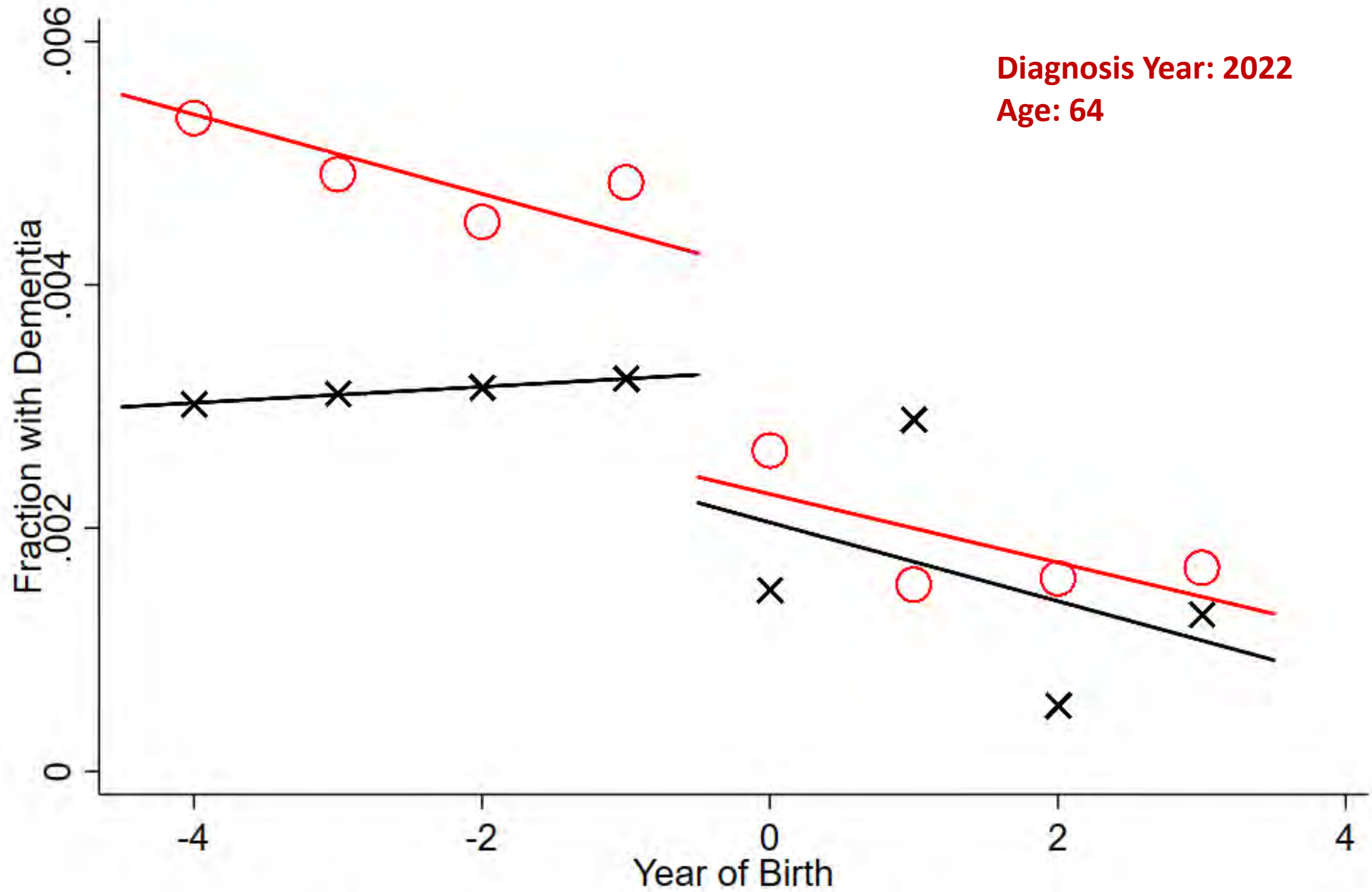


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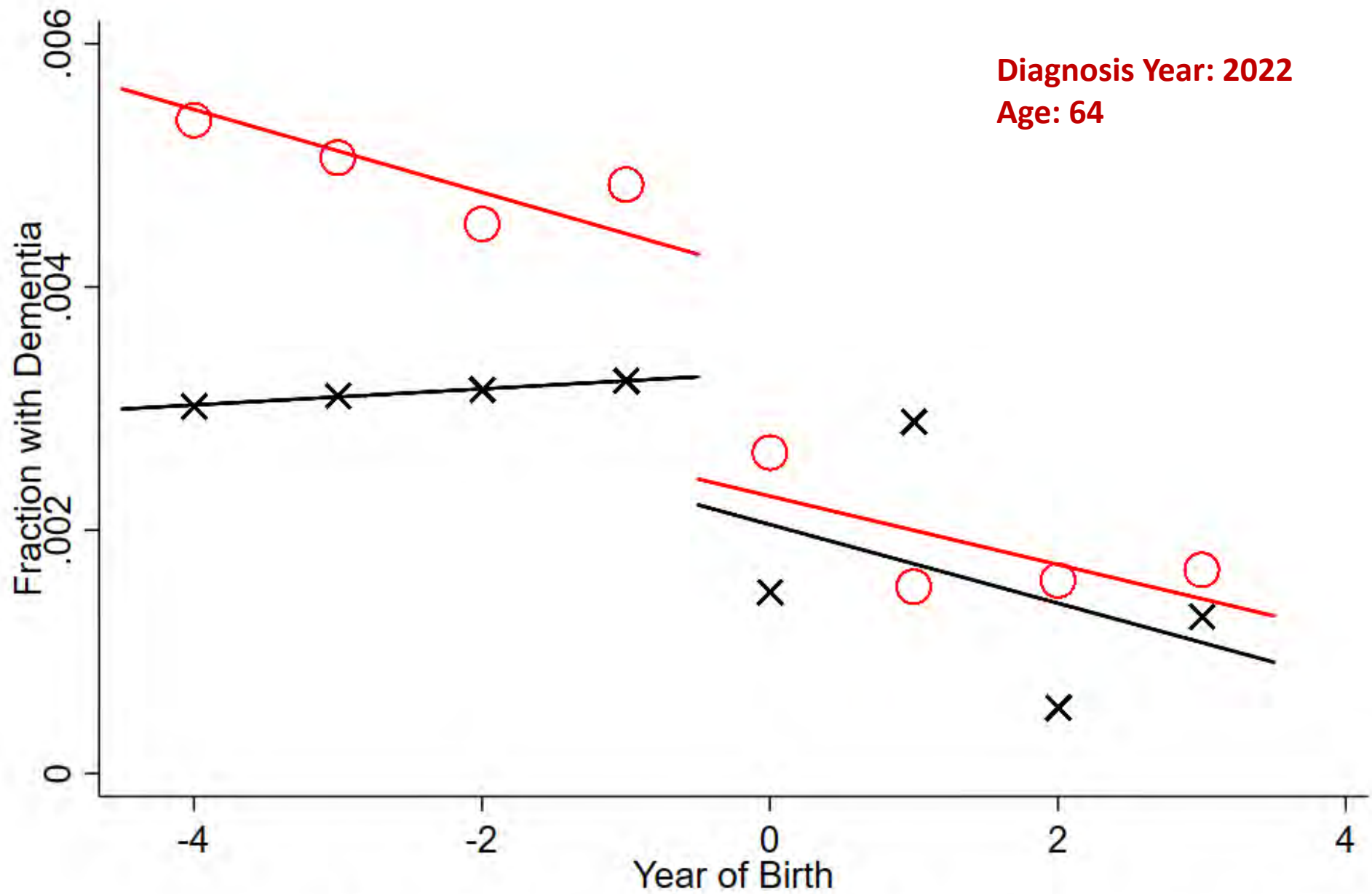
Diagnosis Year: 2022
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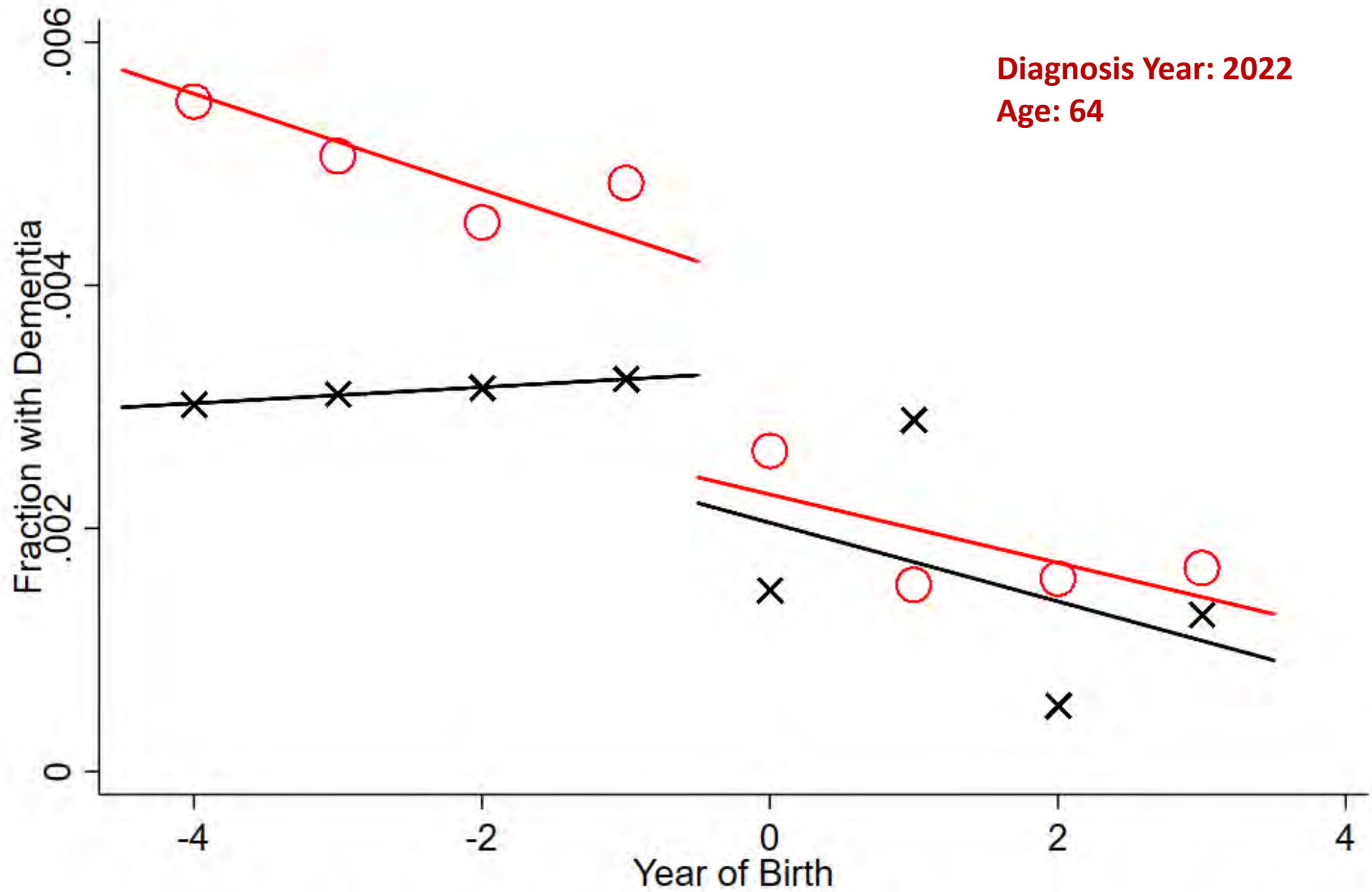


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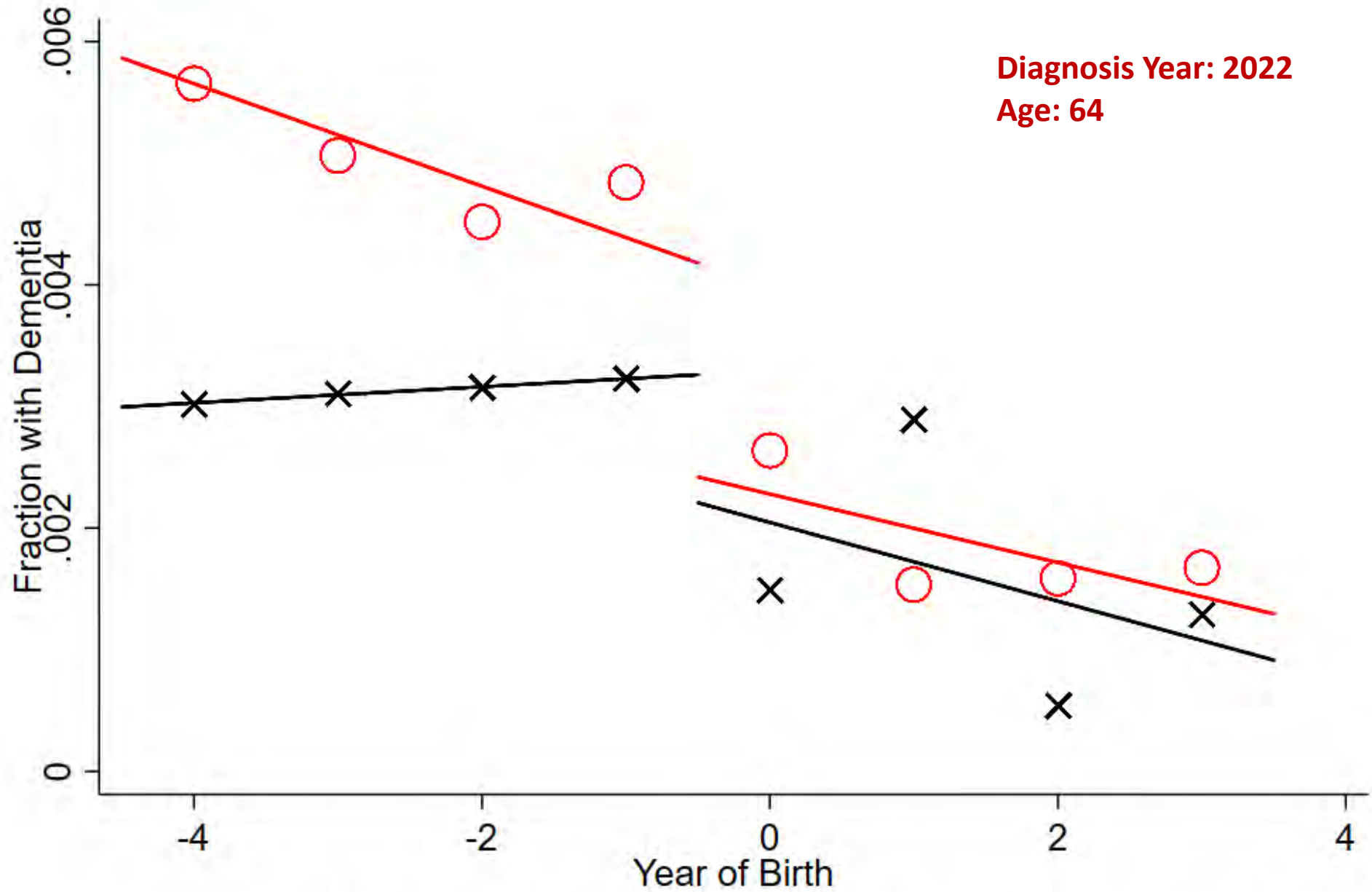
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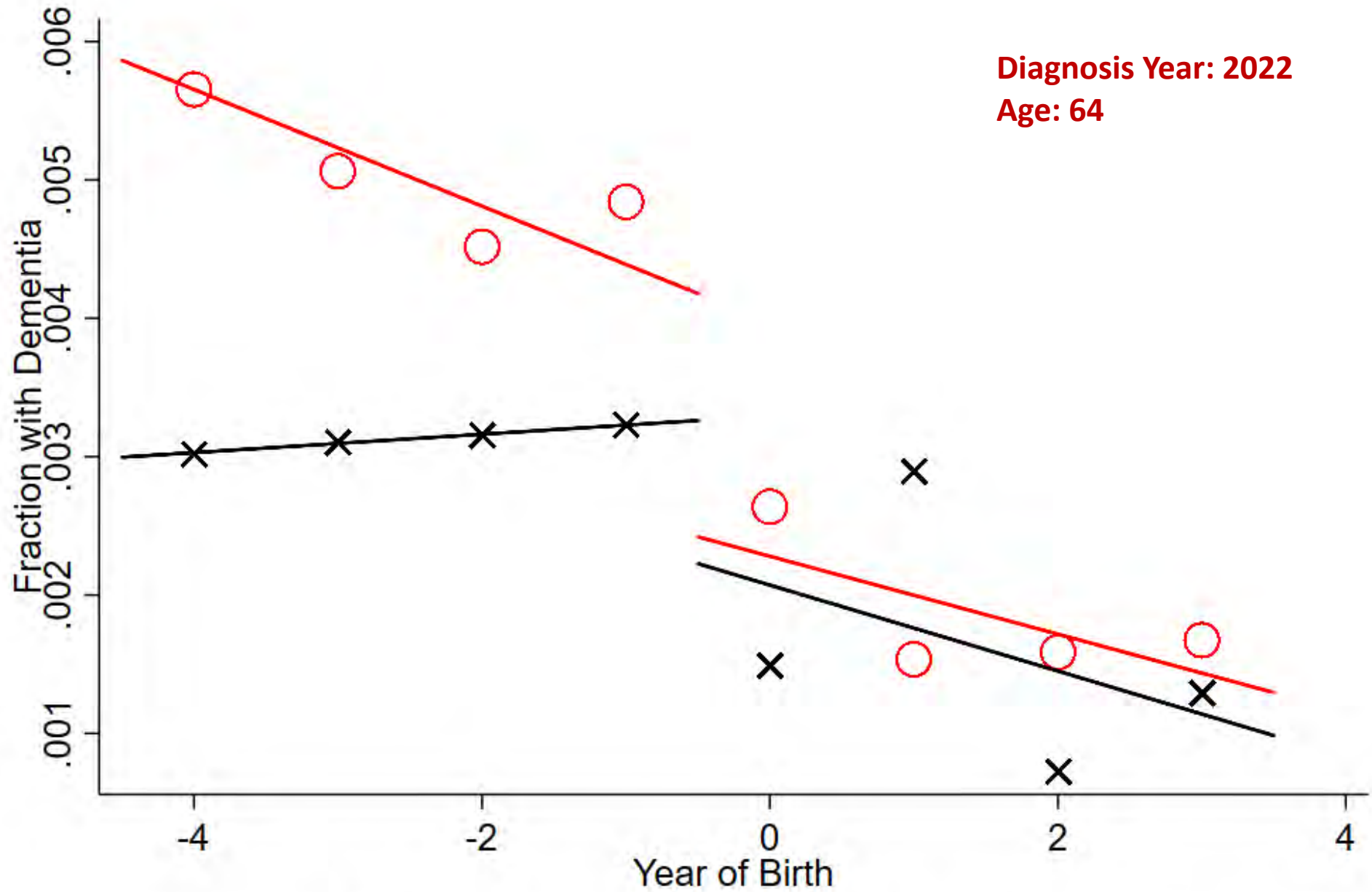
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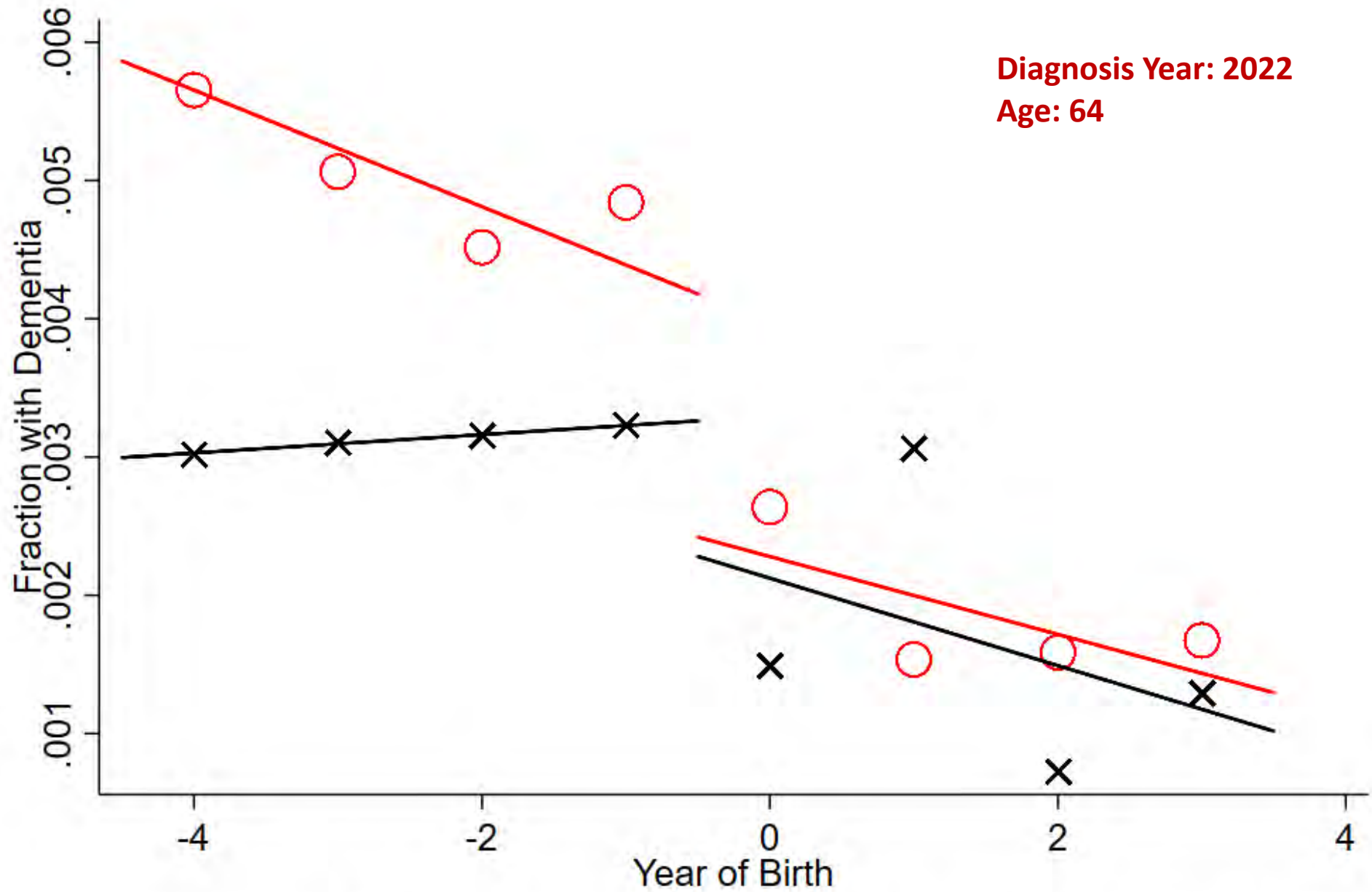
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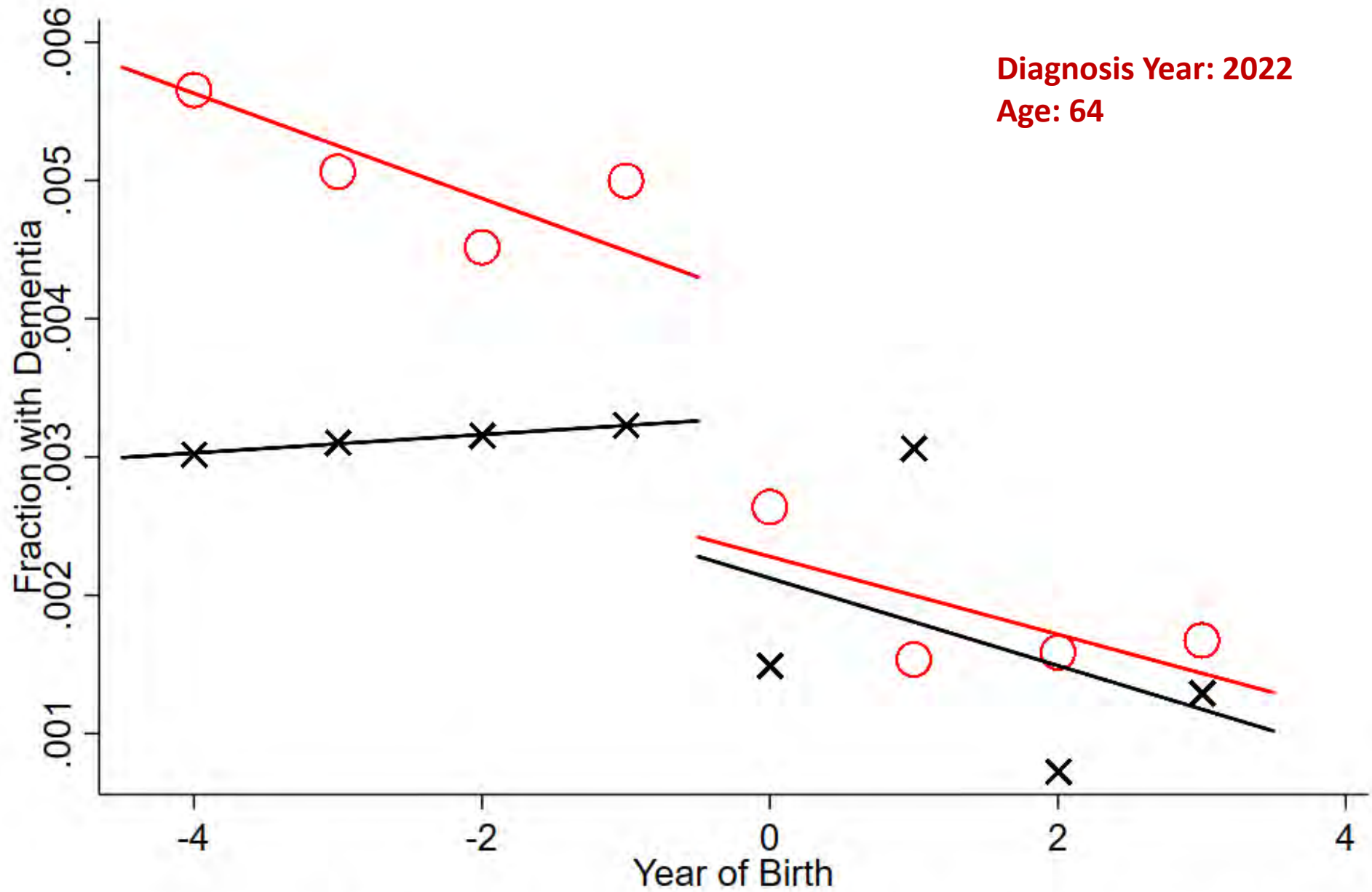
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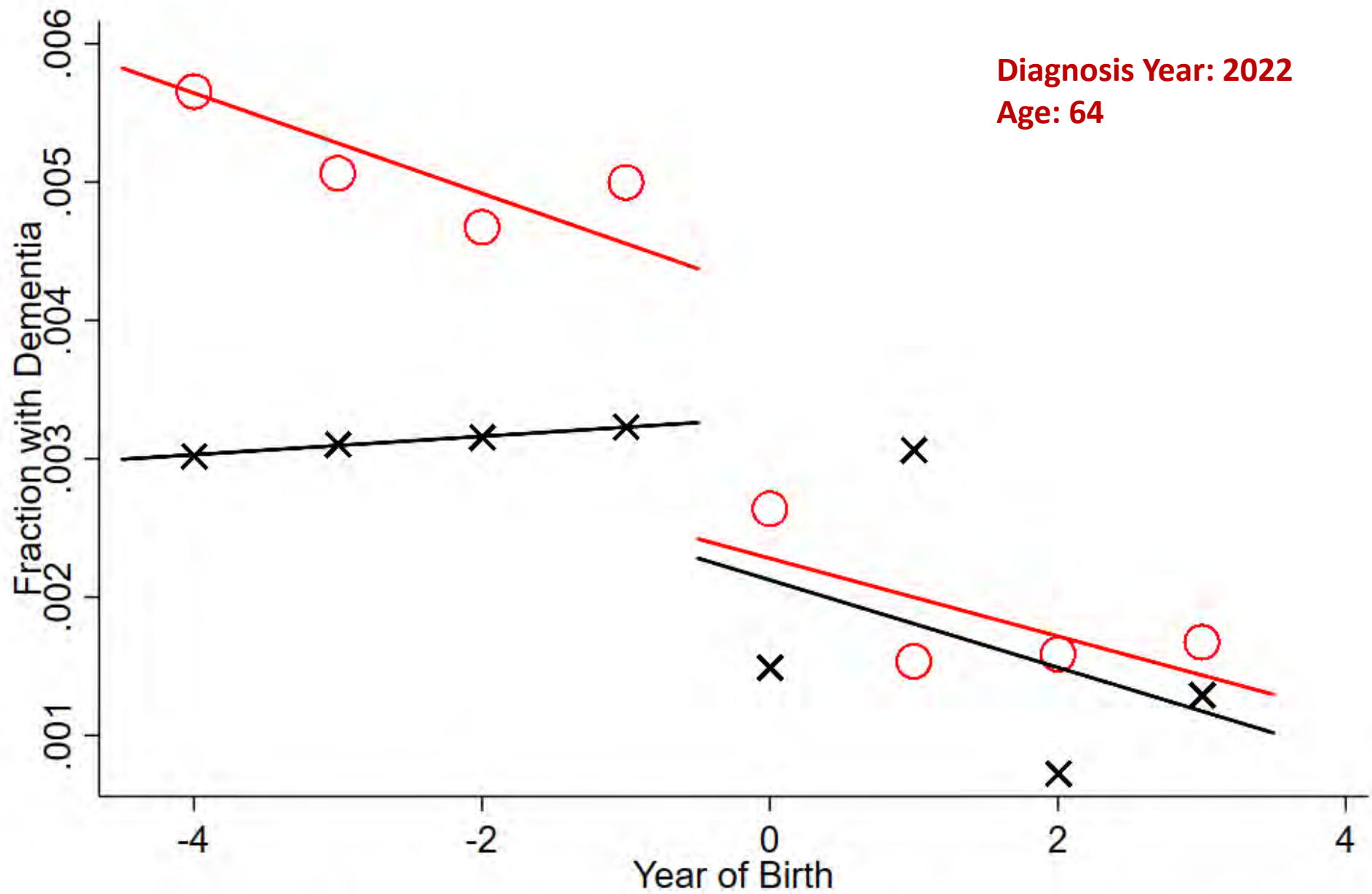
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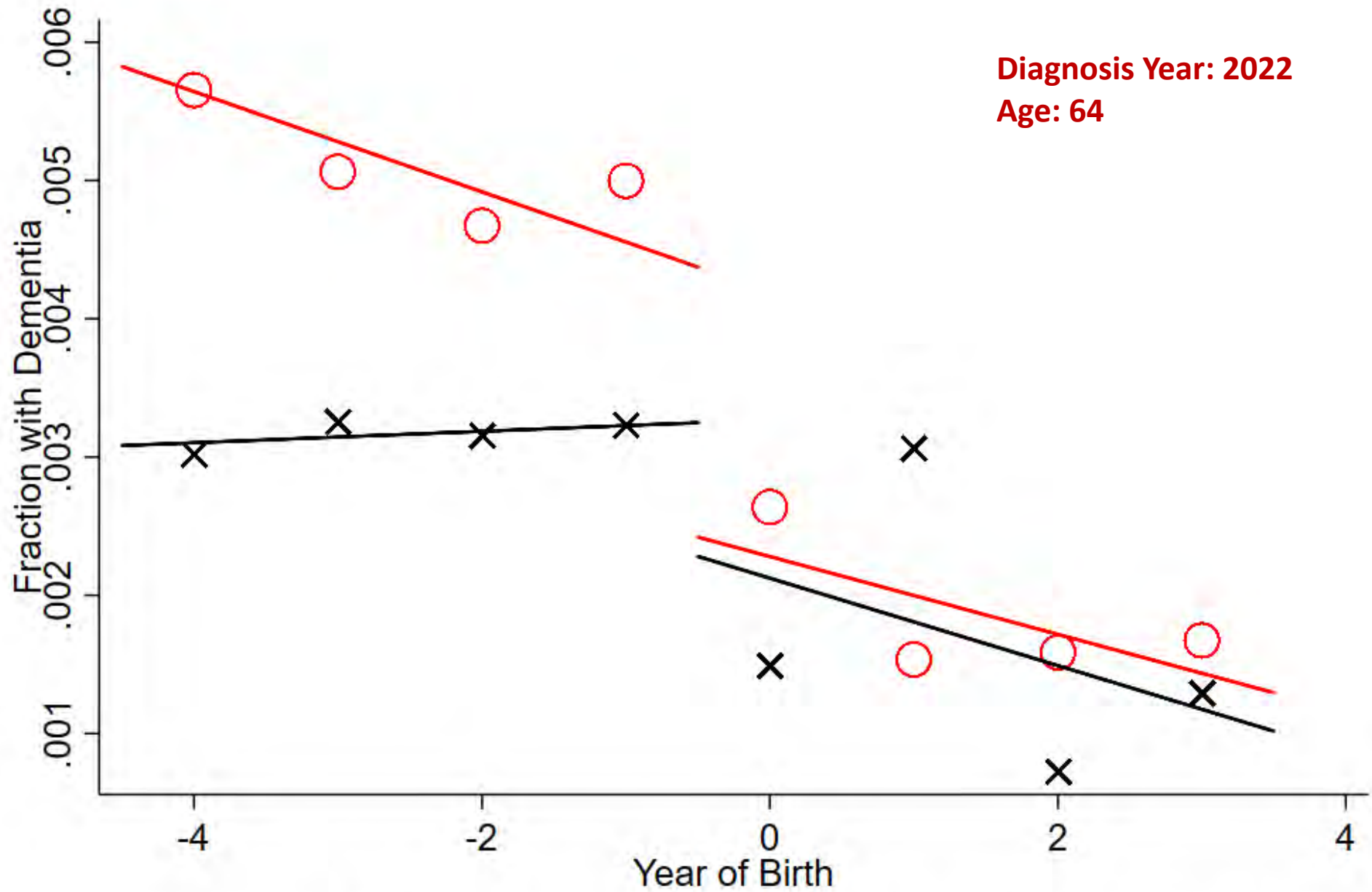
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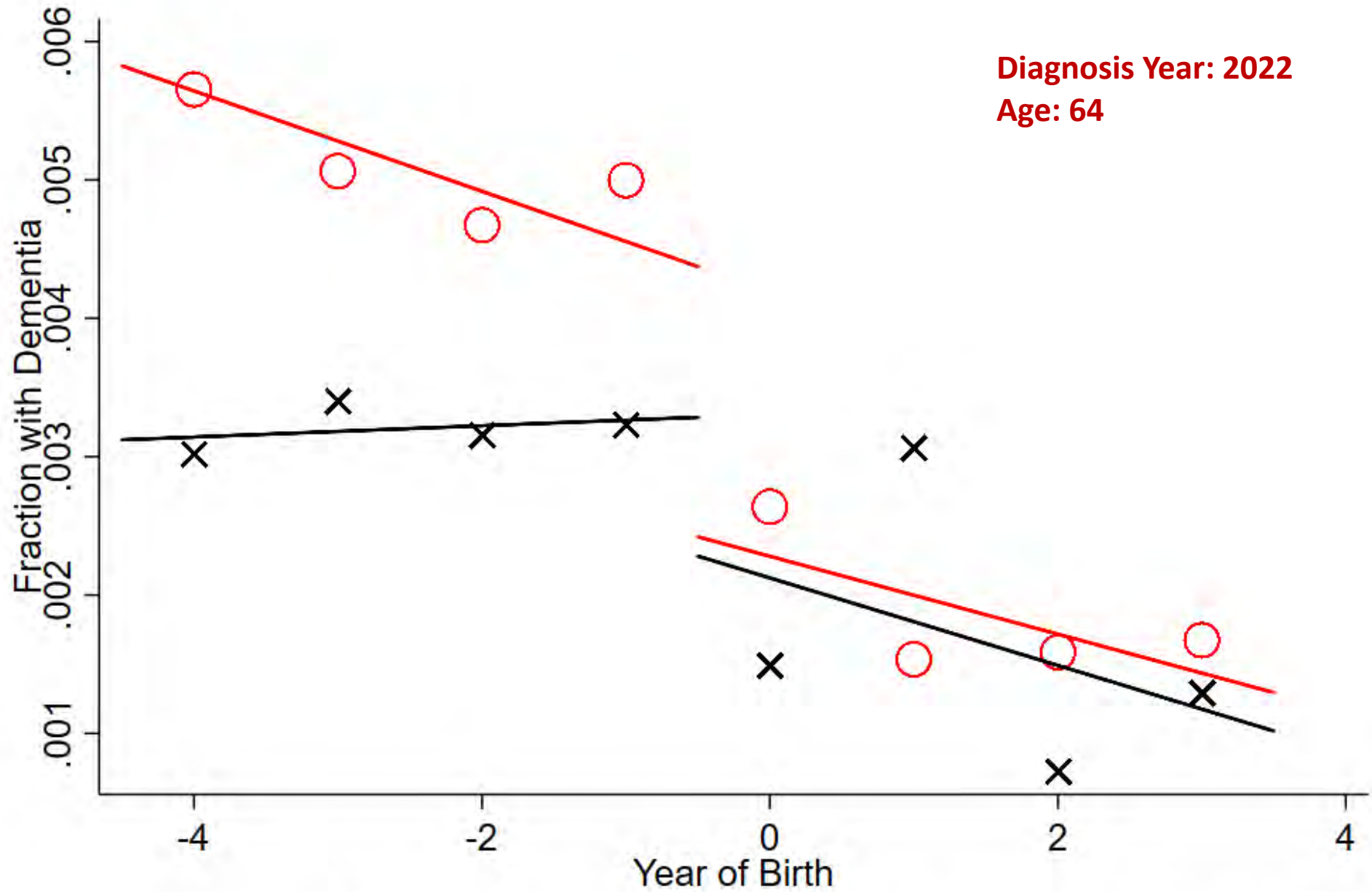
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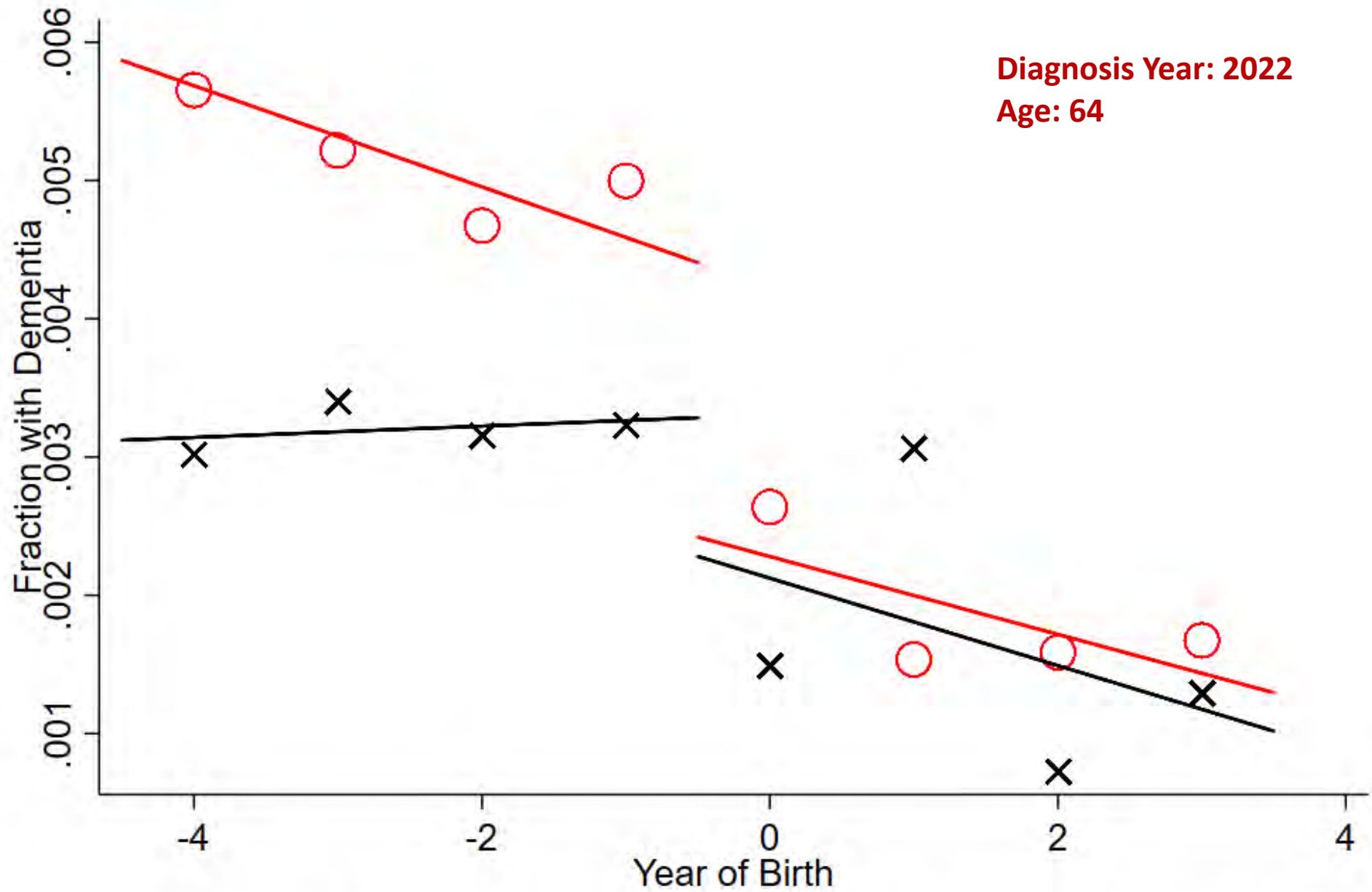
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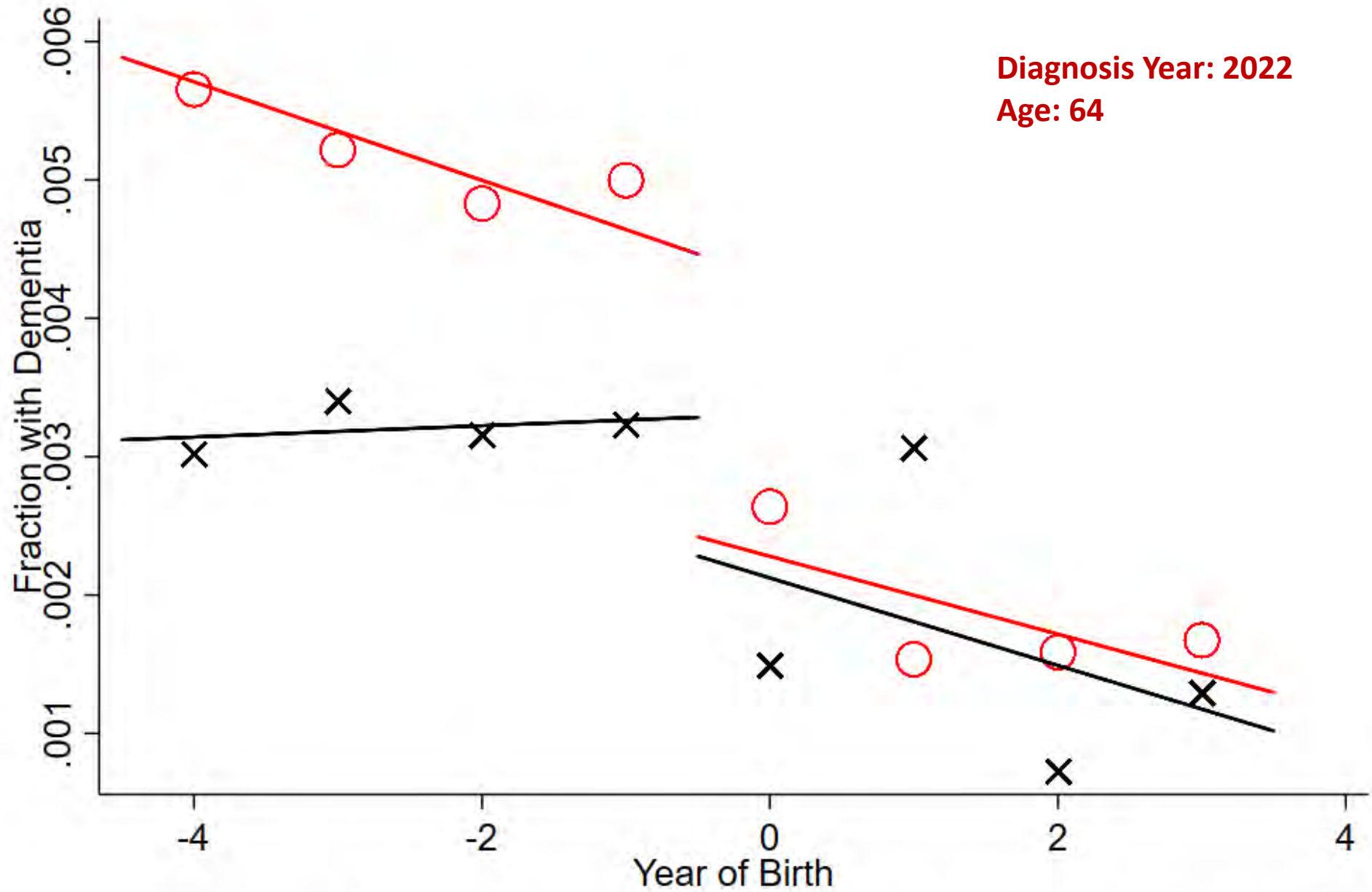
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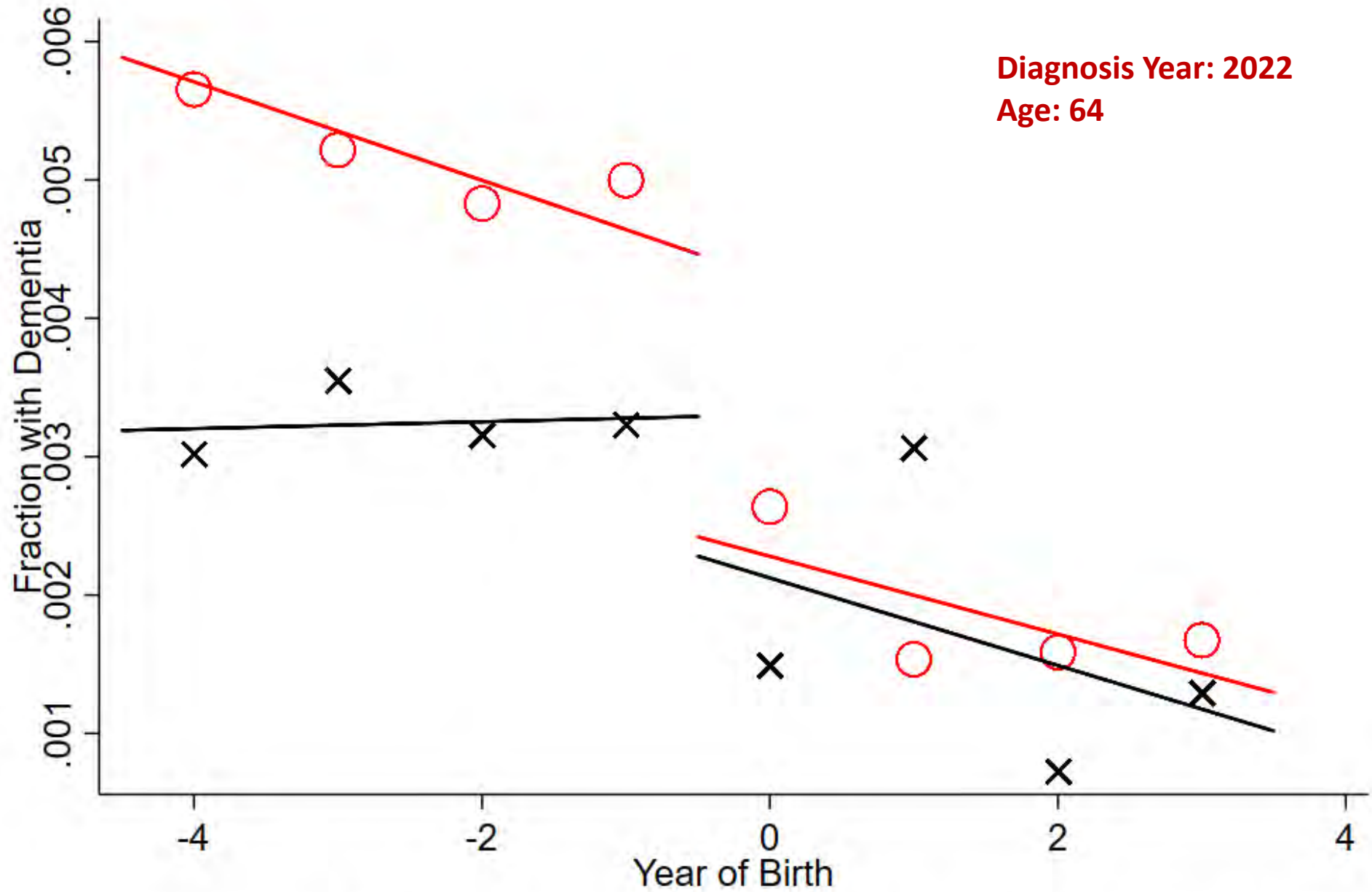
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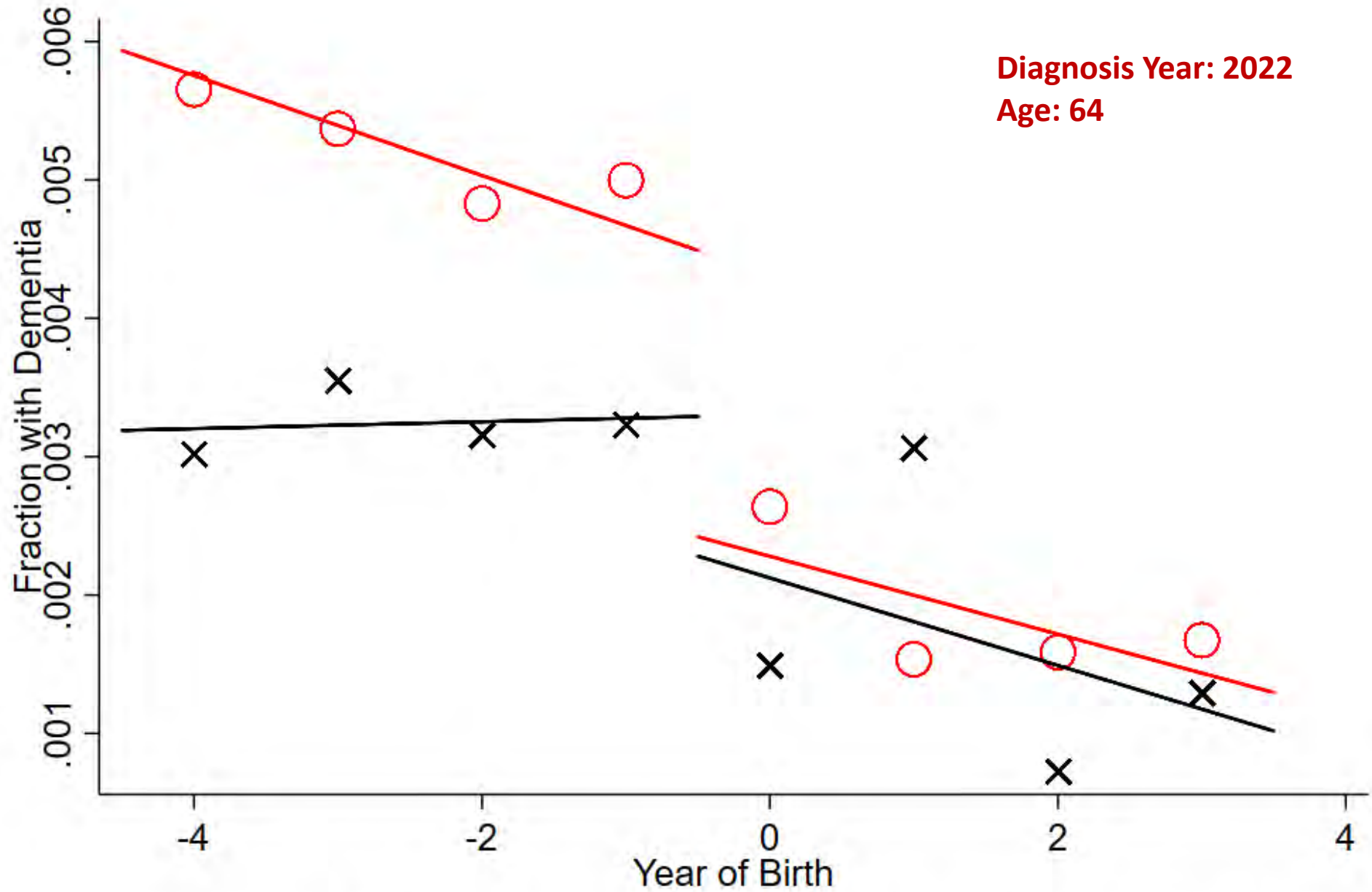
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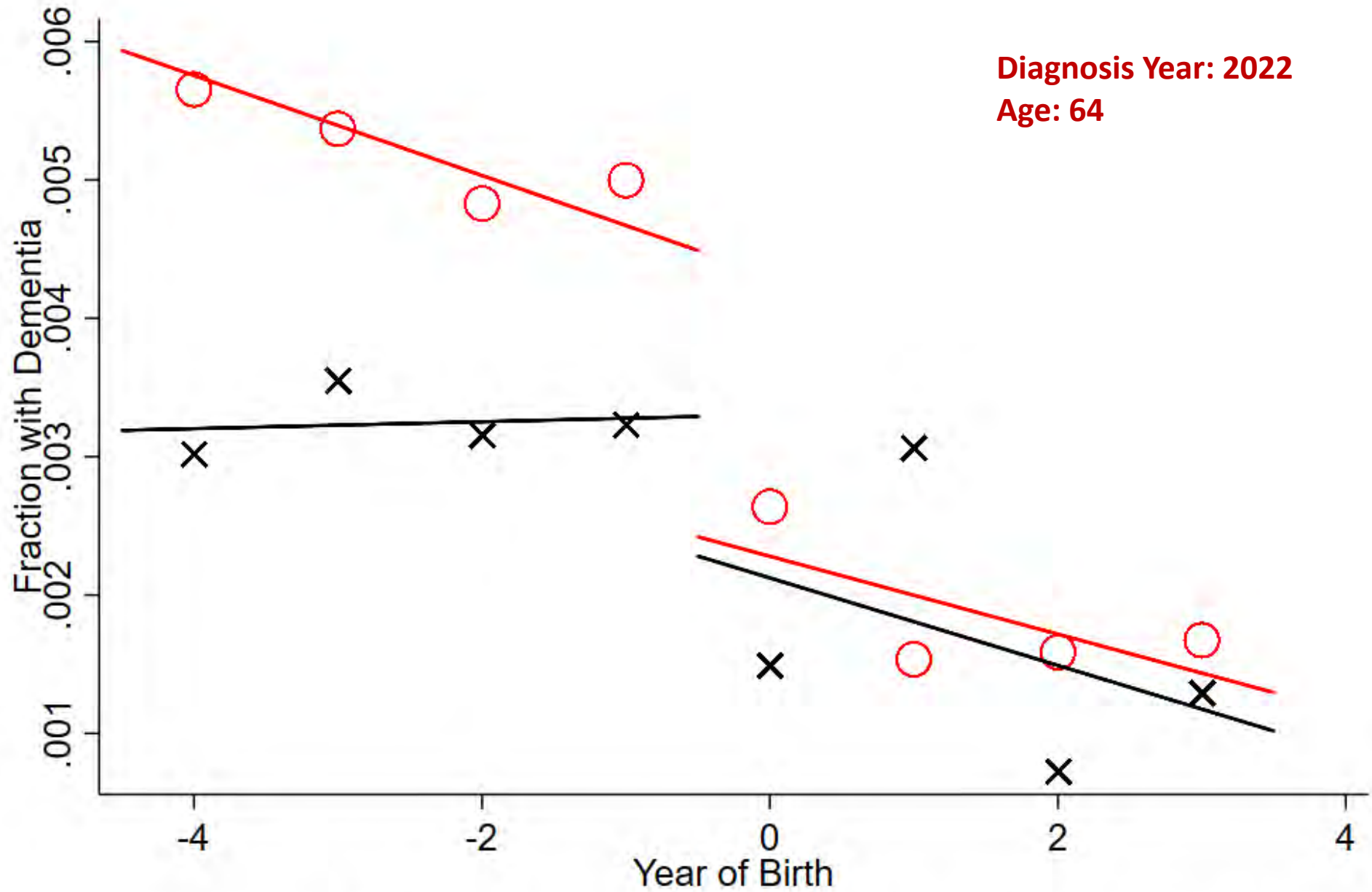
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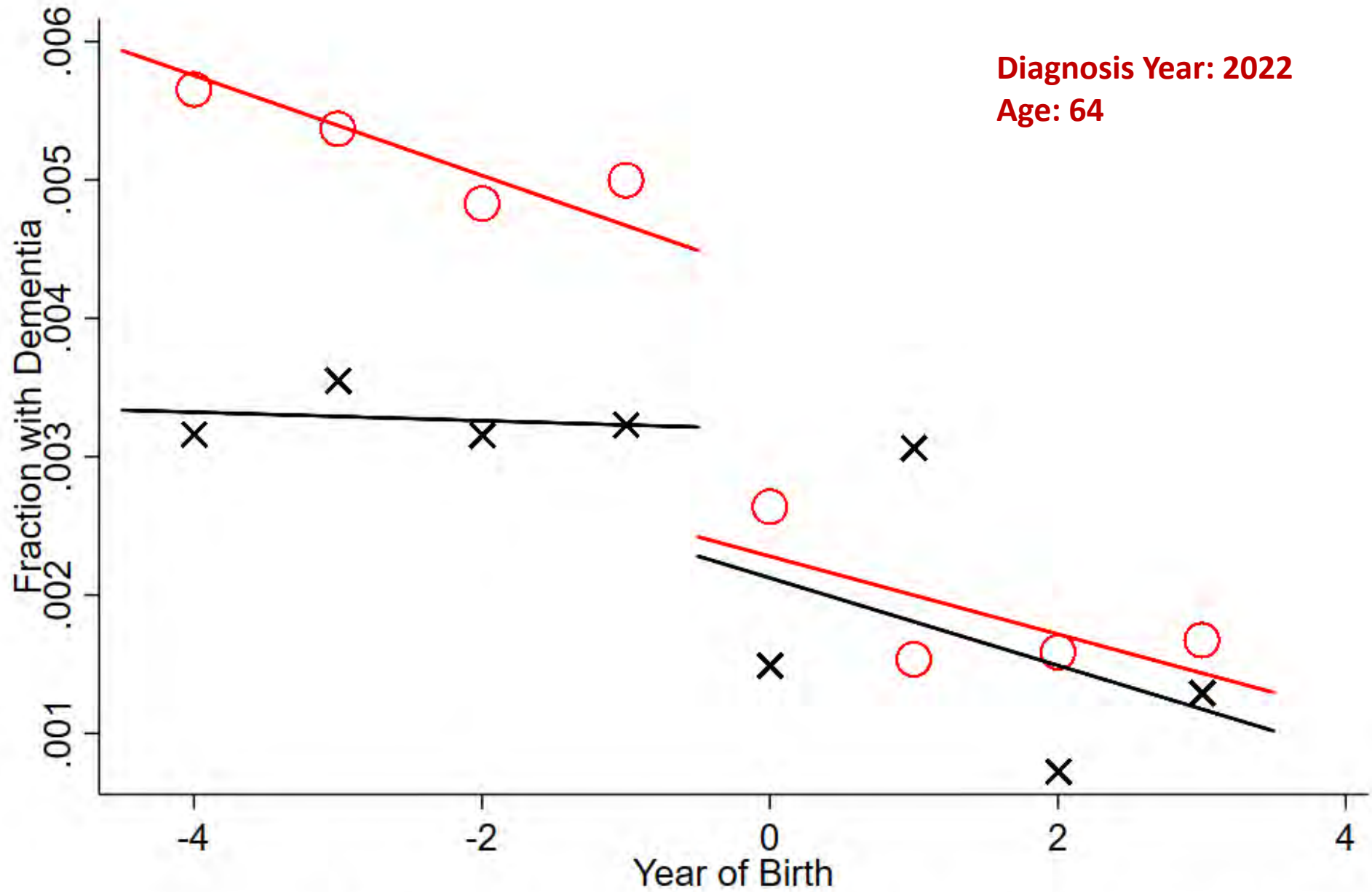
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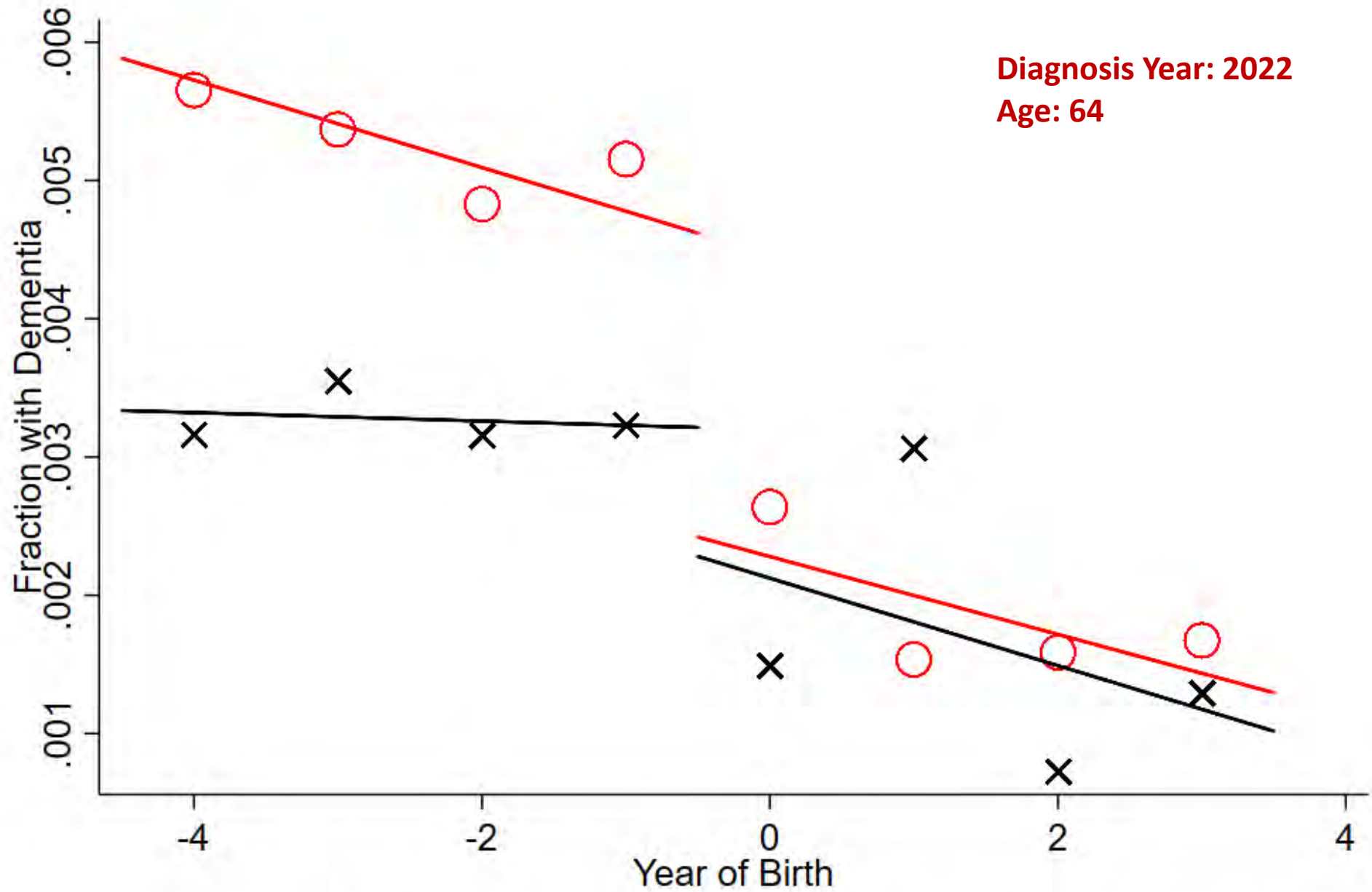
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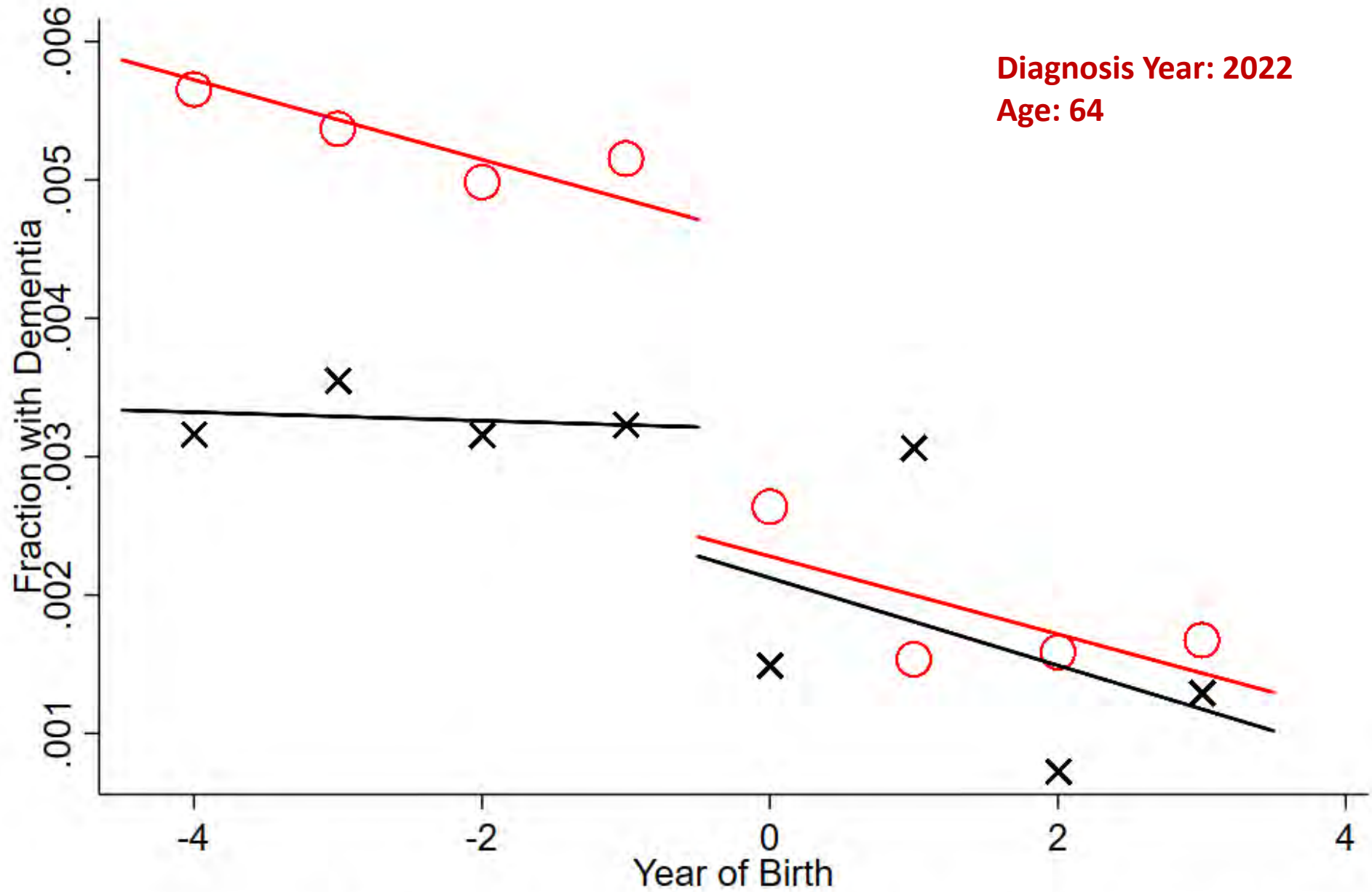
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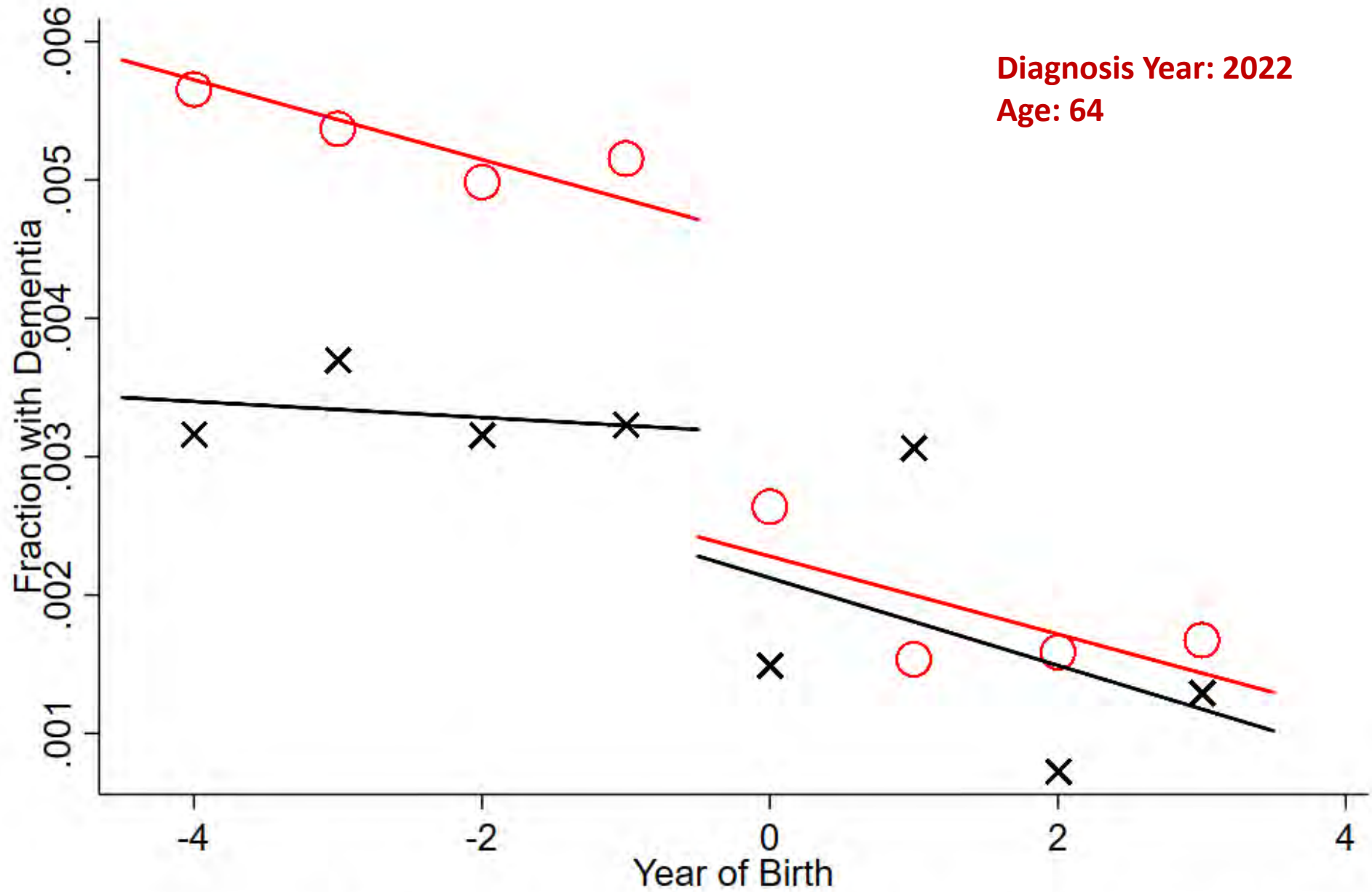
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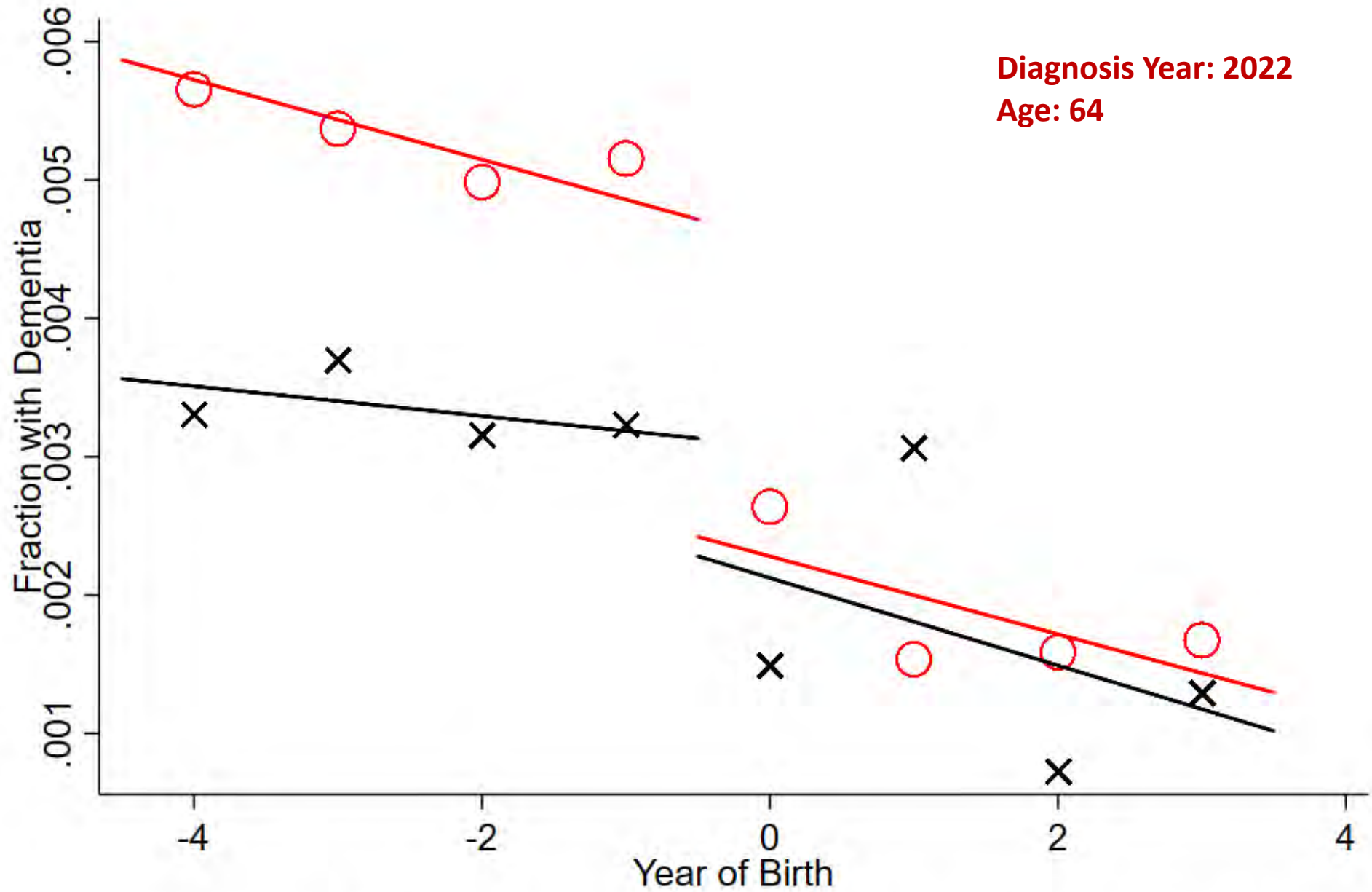
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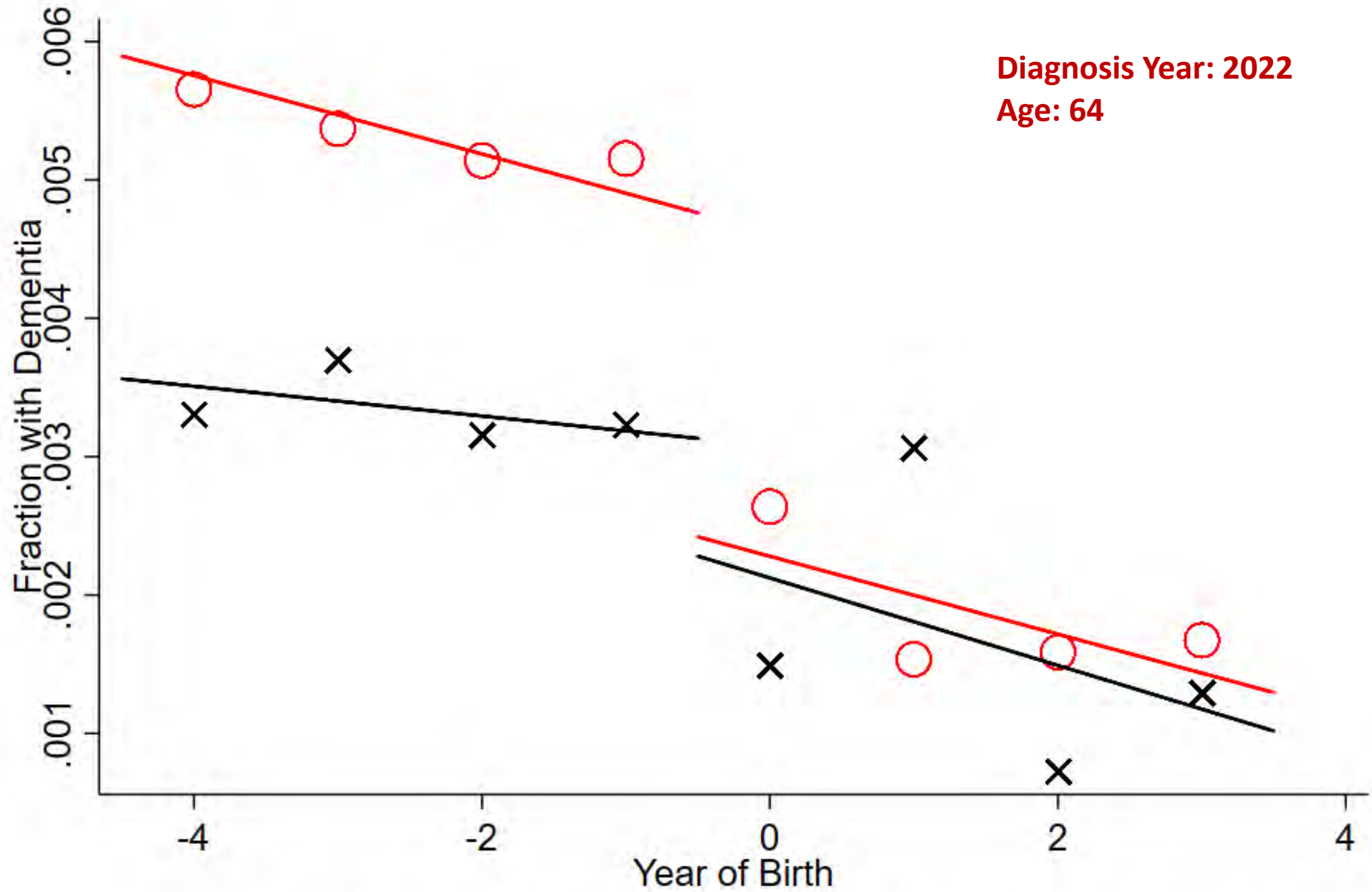
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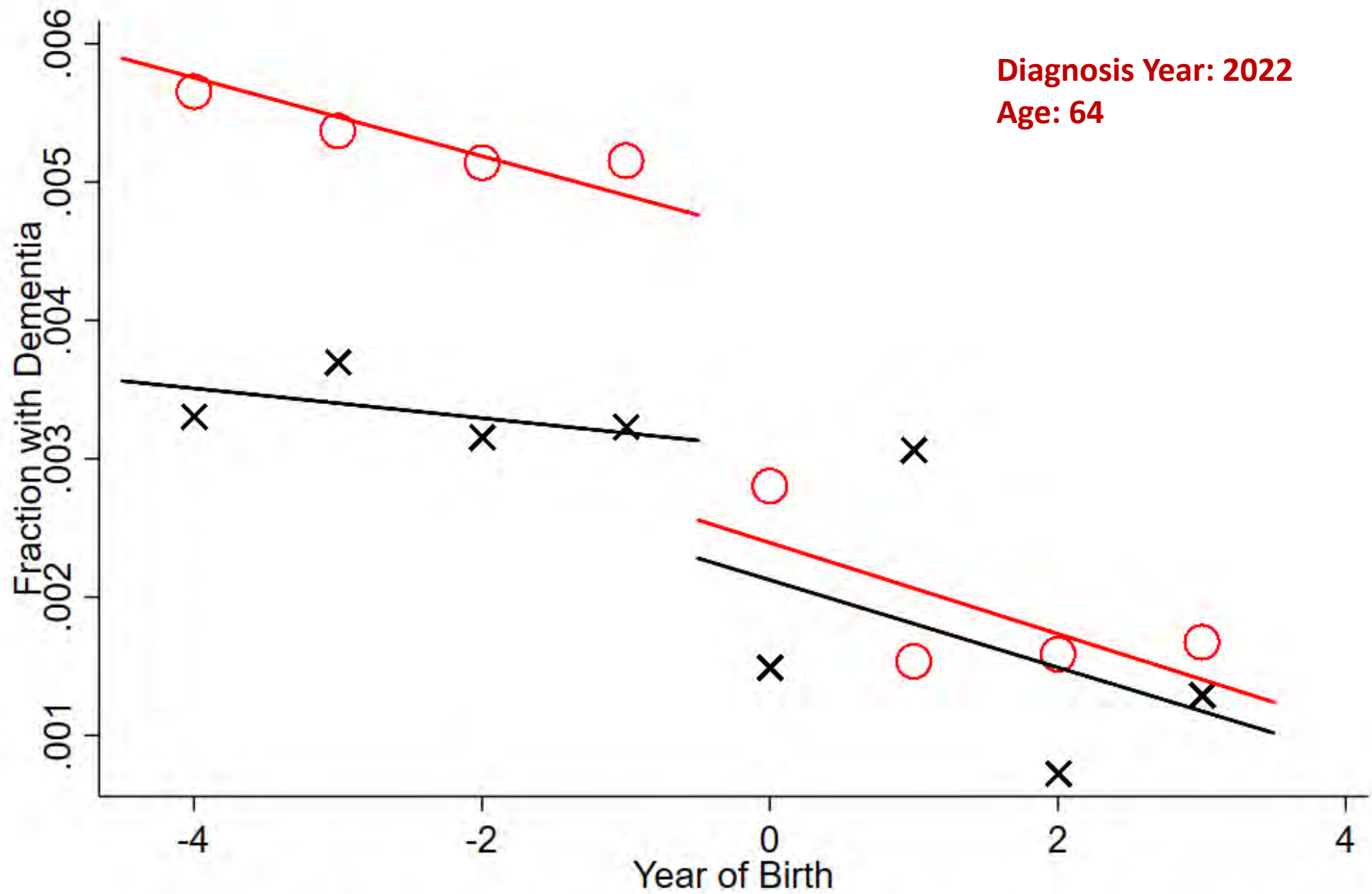
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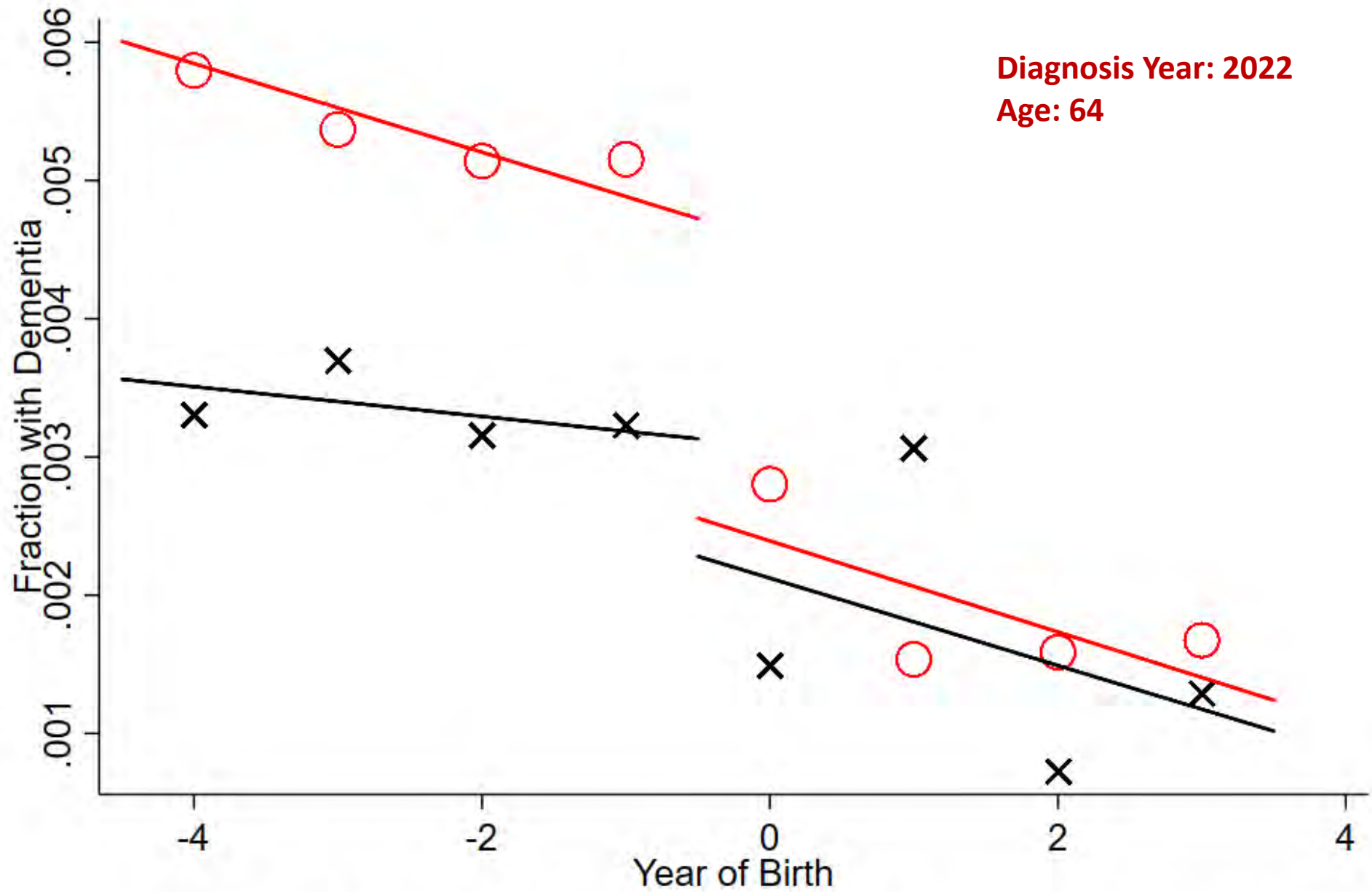
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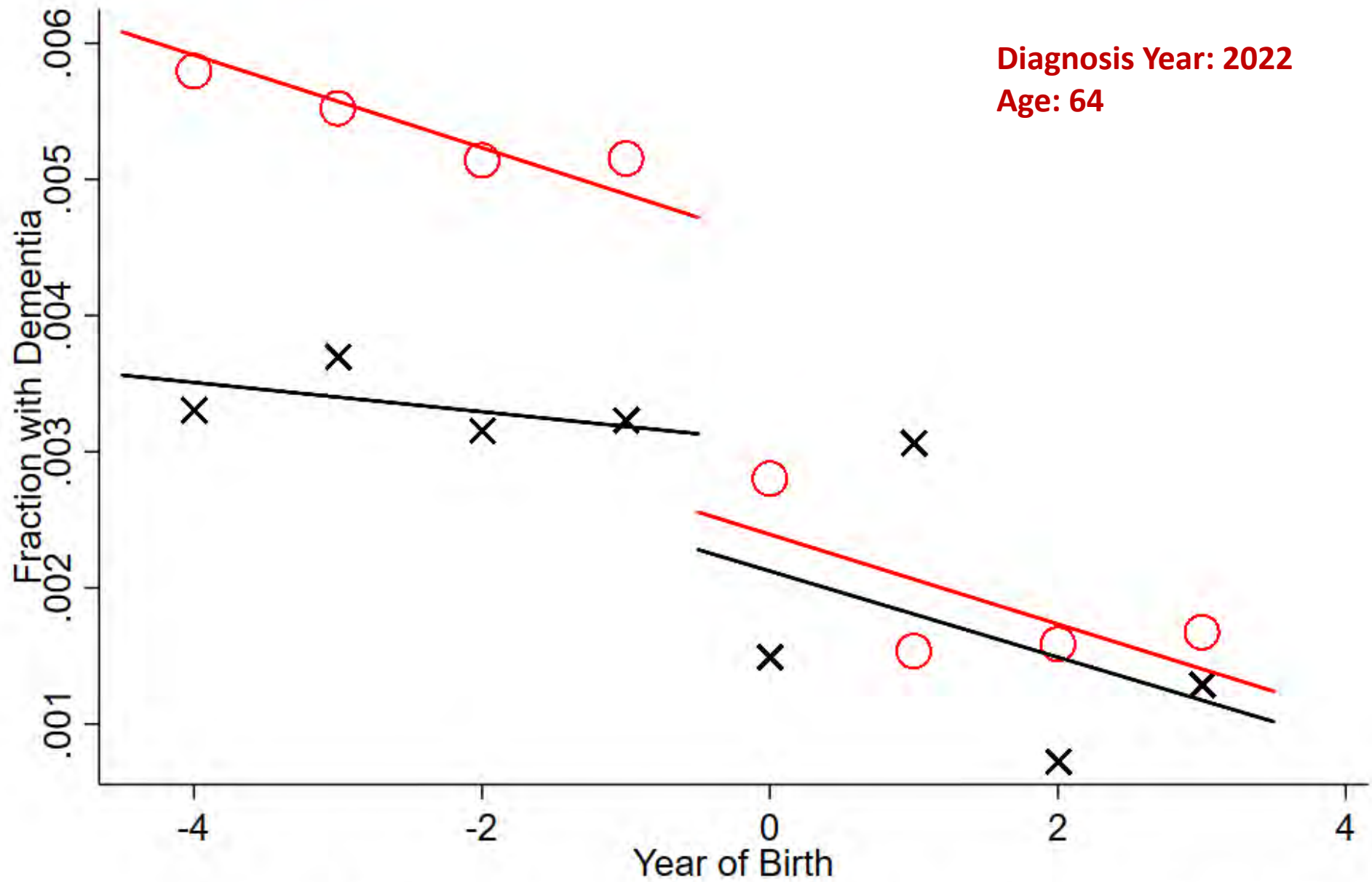
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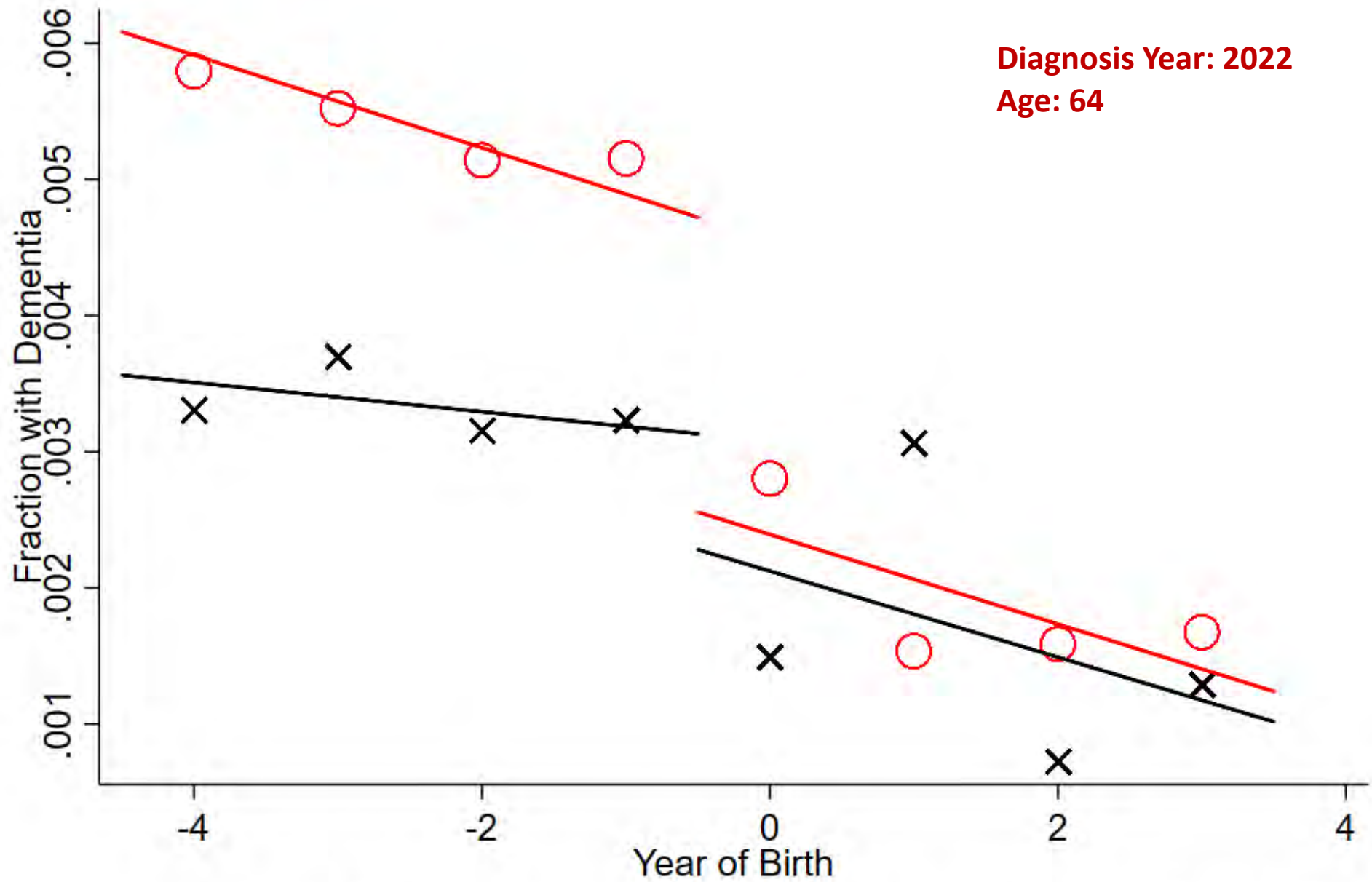
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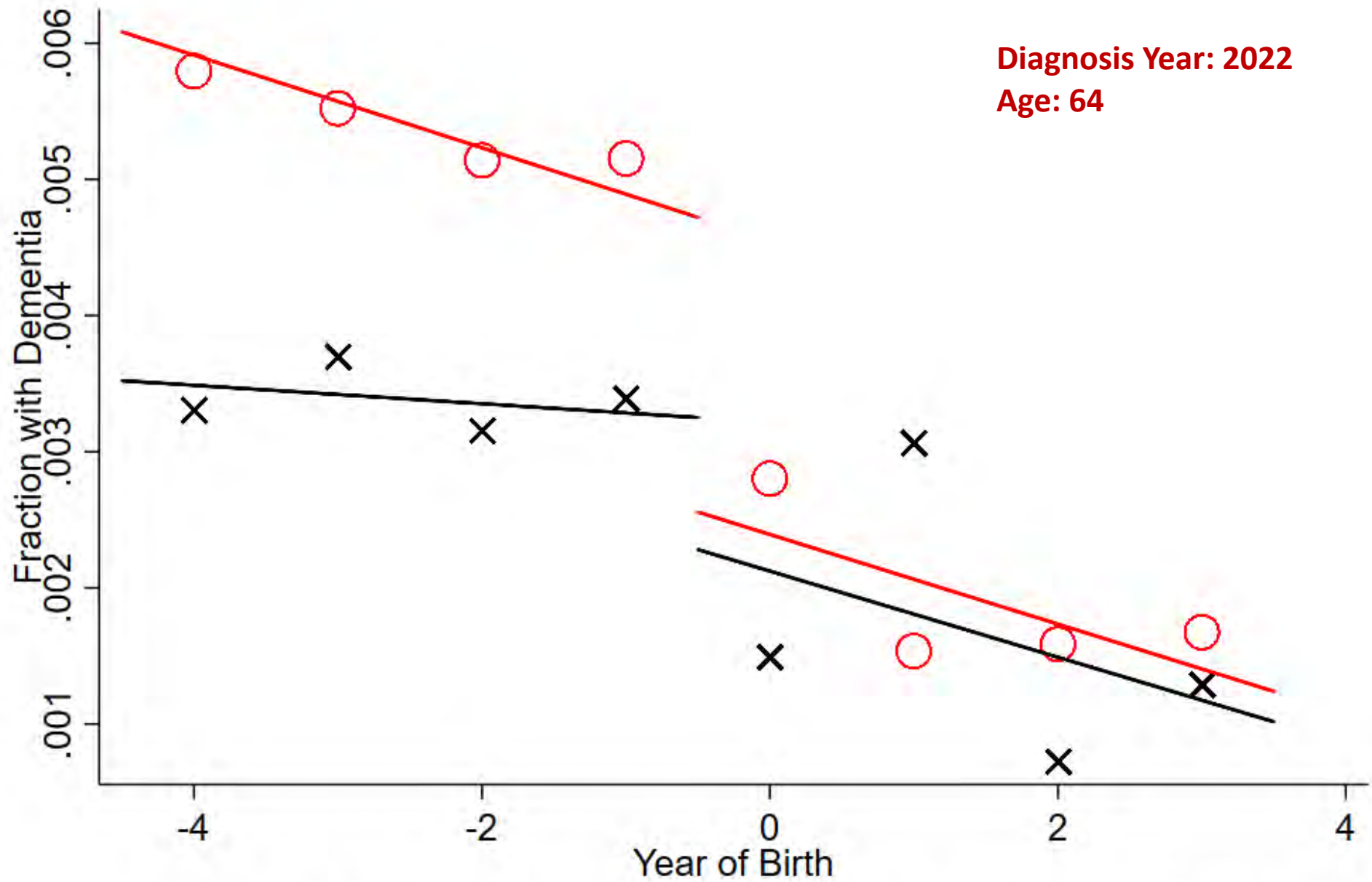
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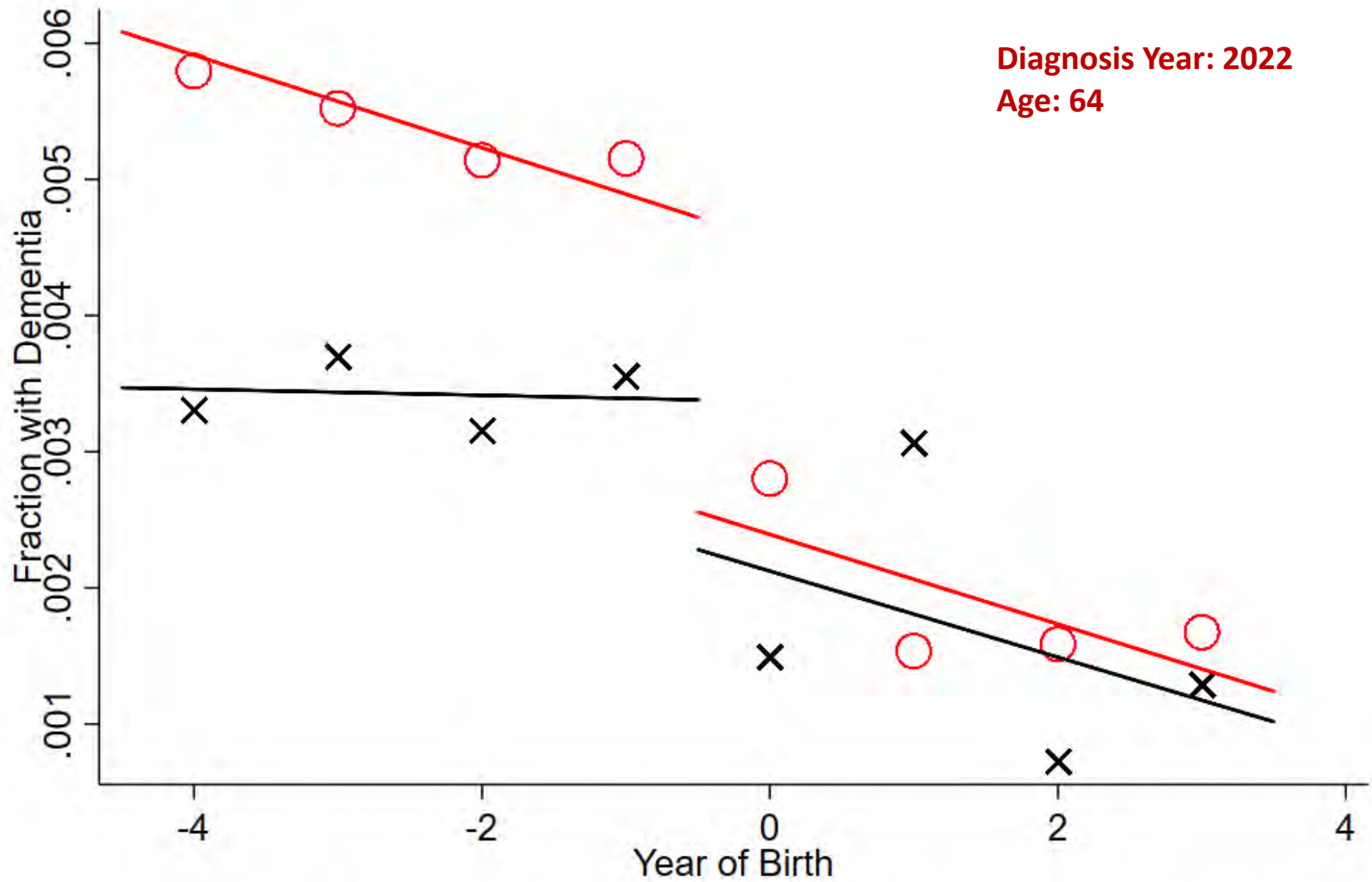


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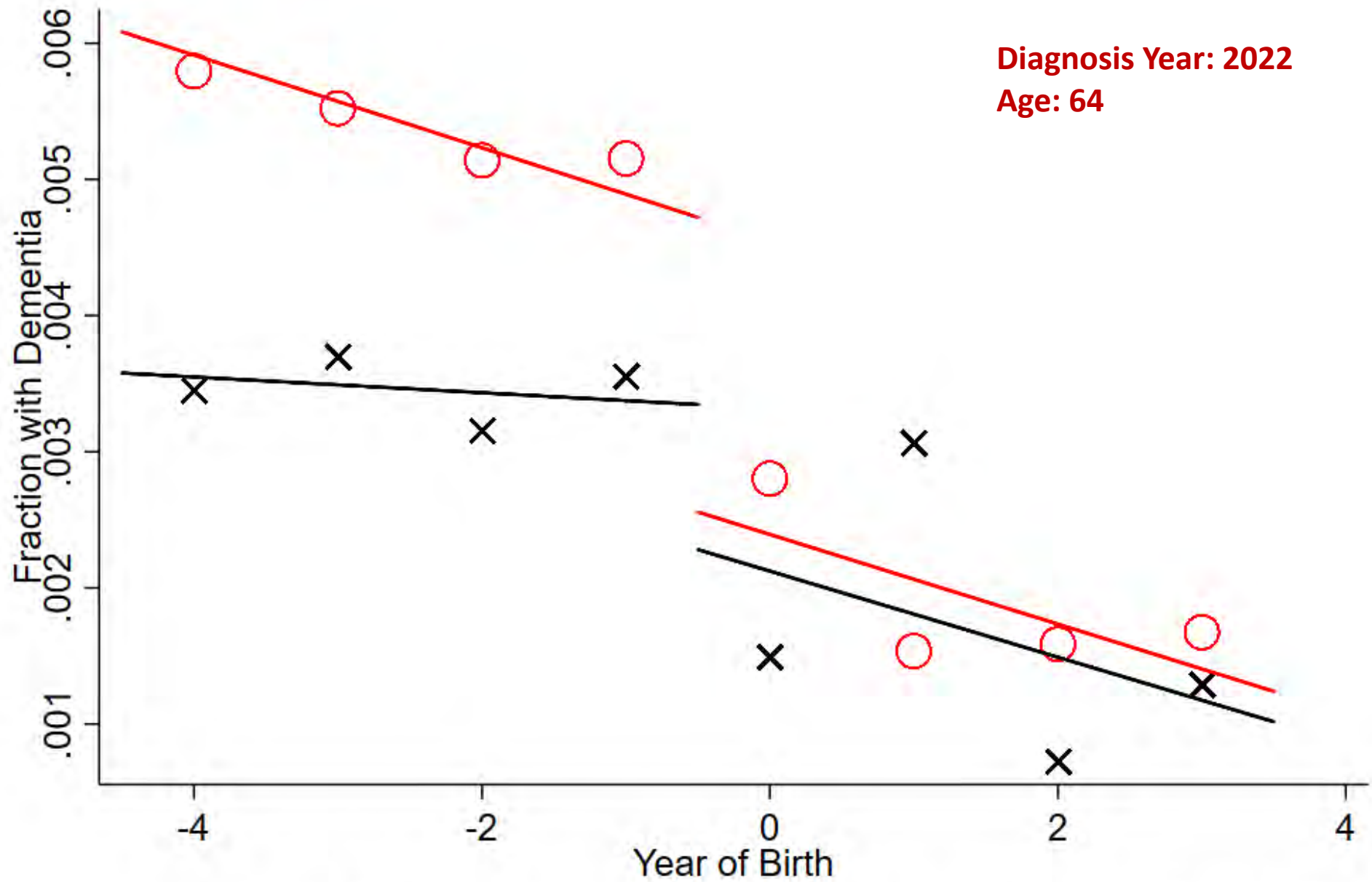


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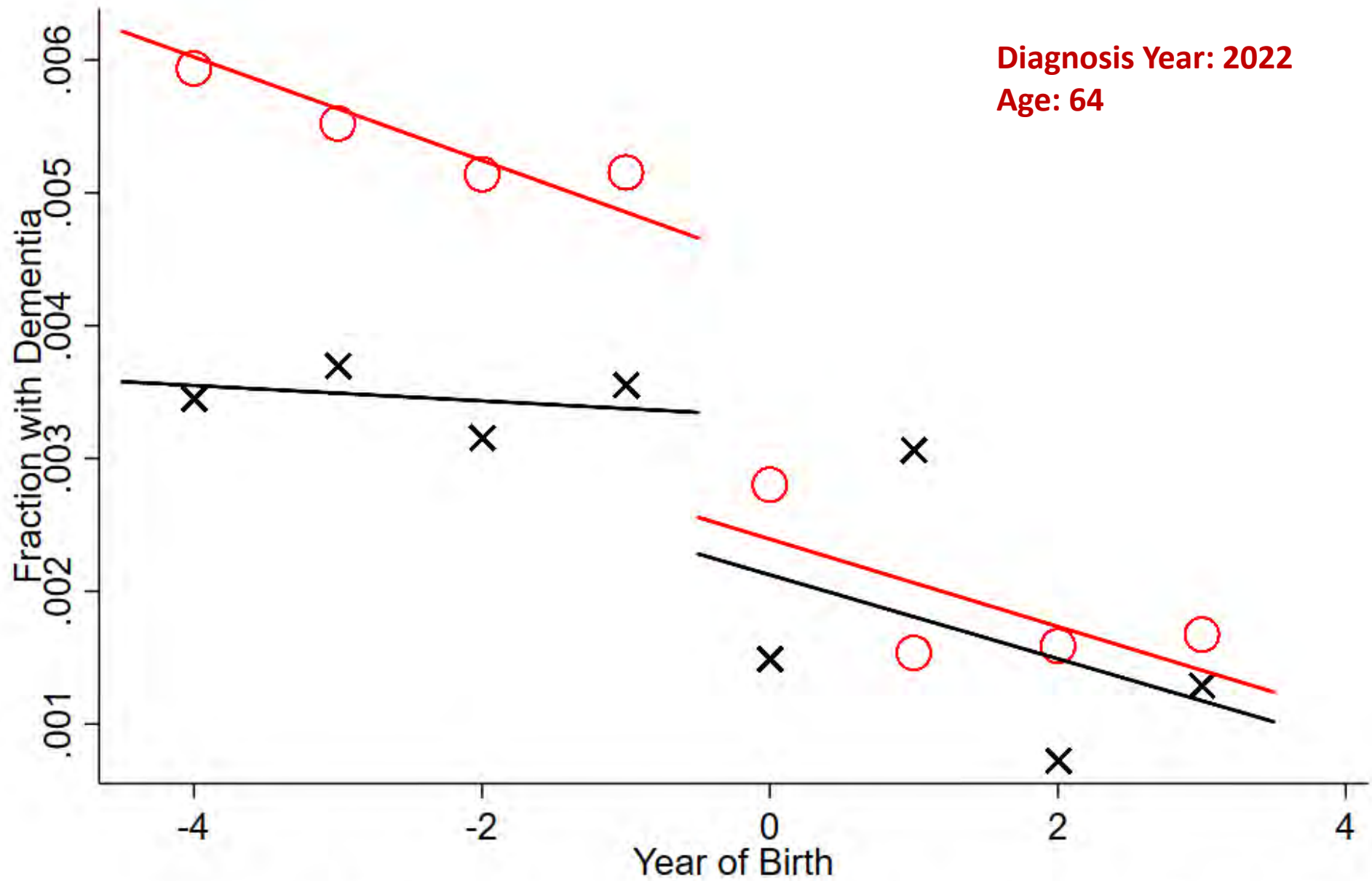
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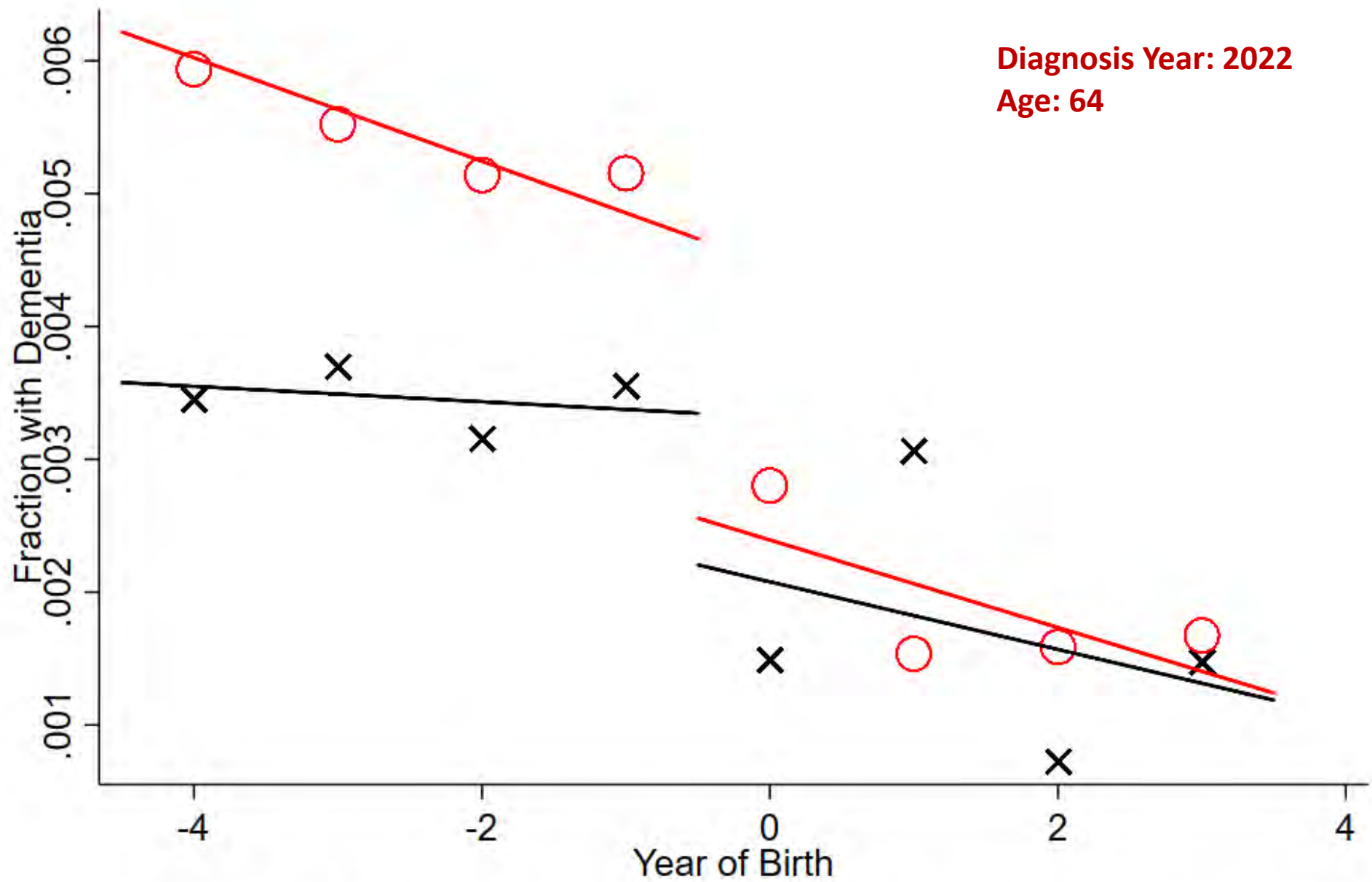
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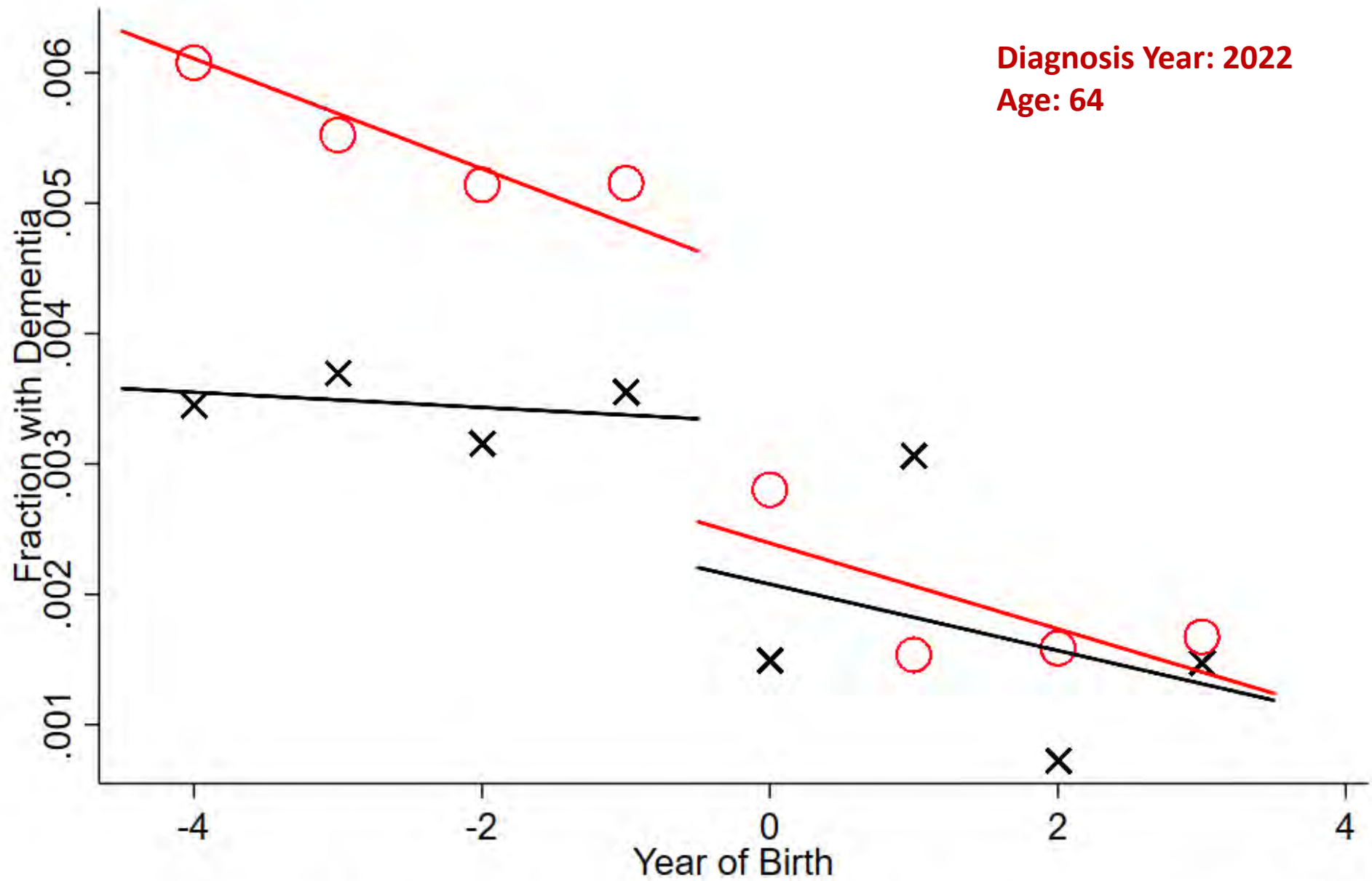
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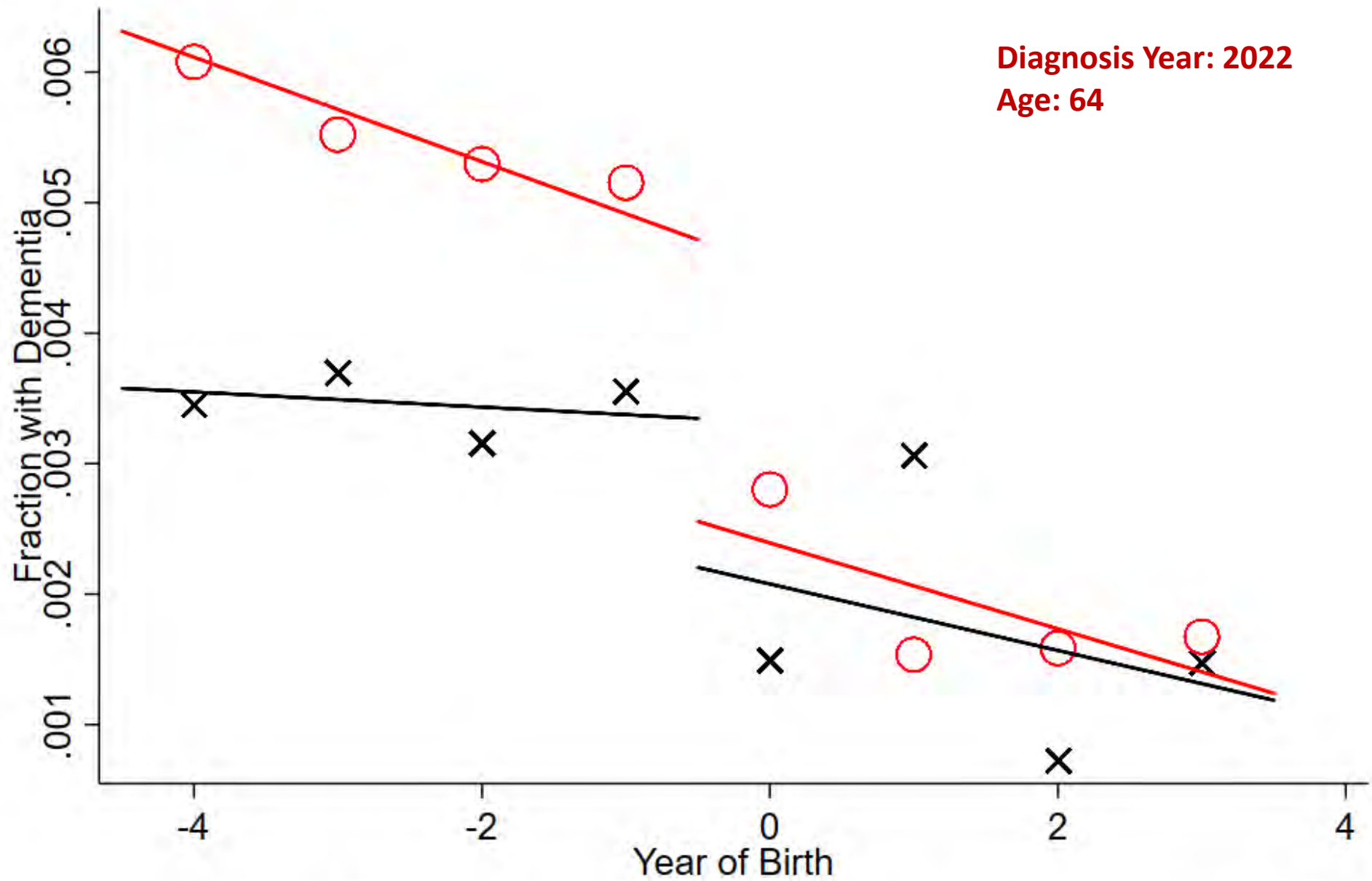
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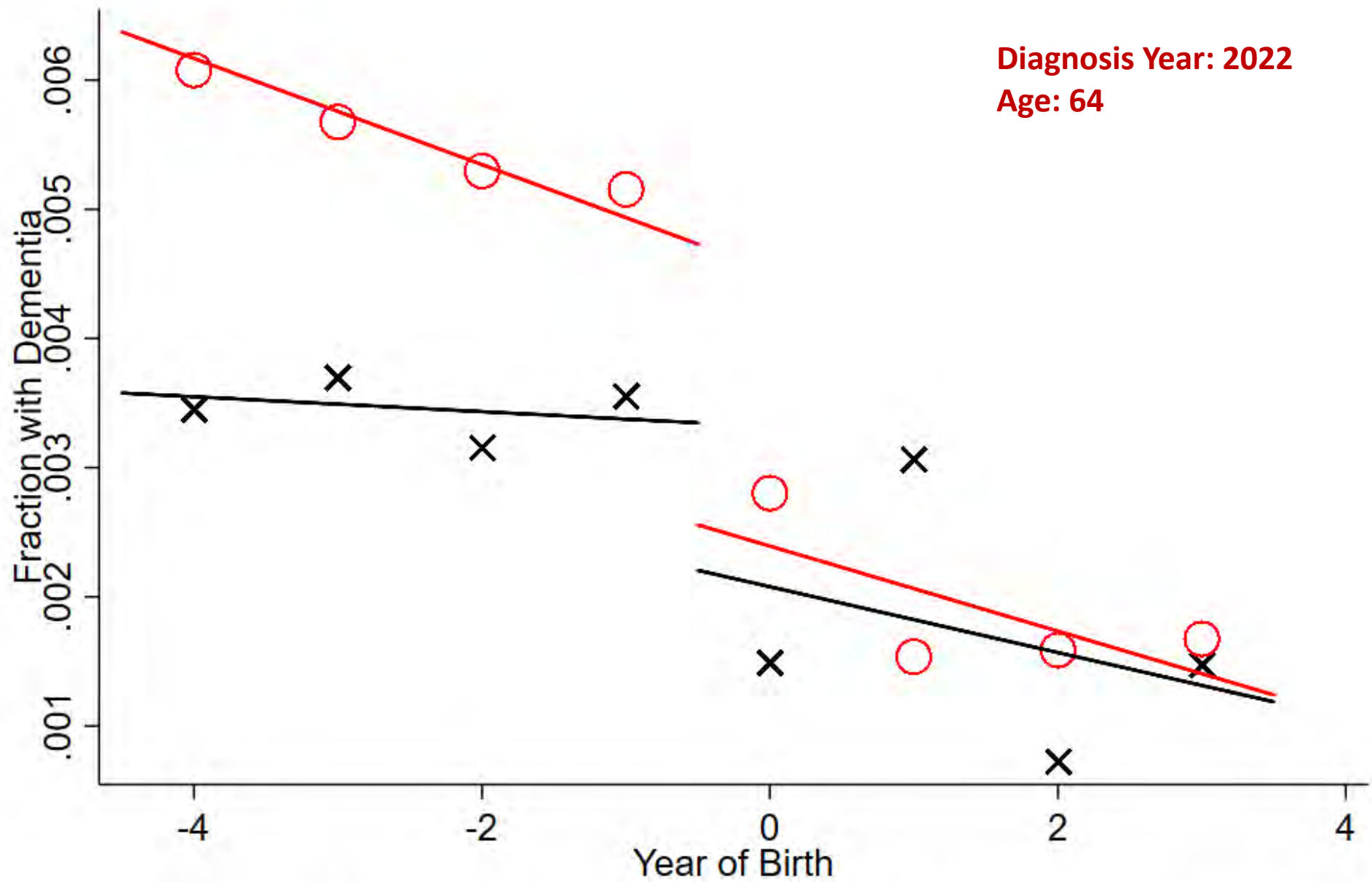
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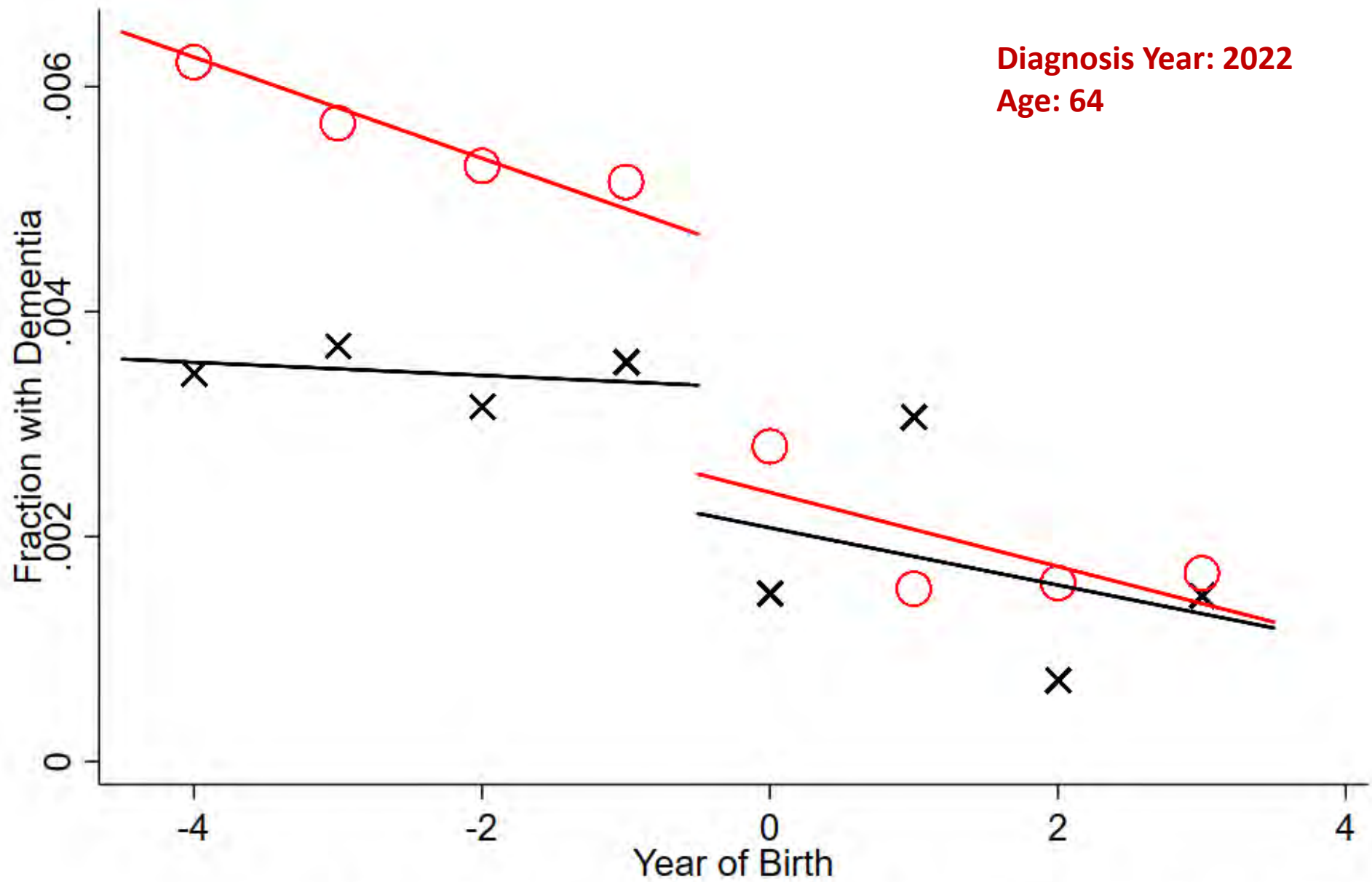
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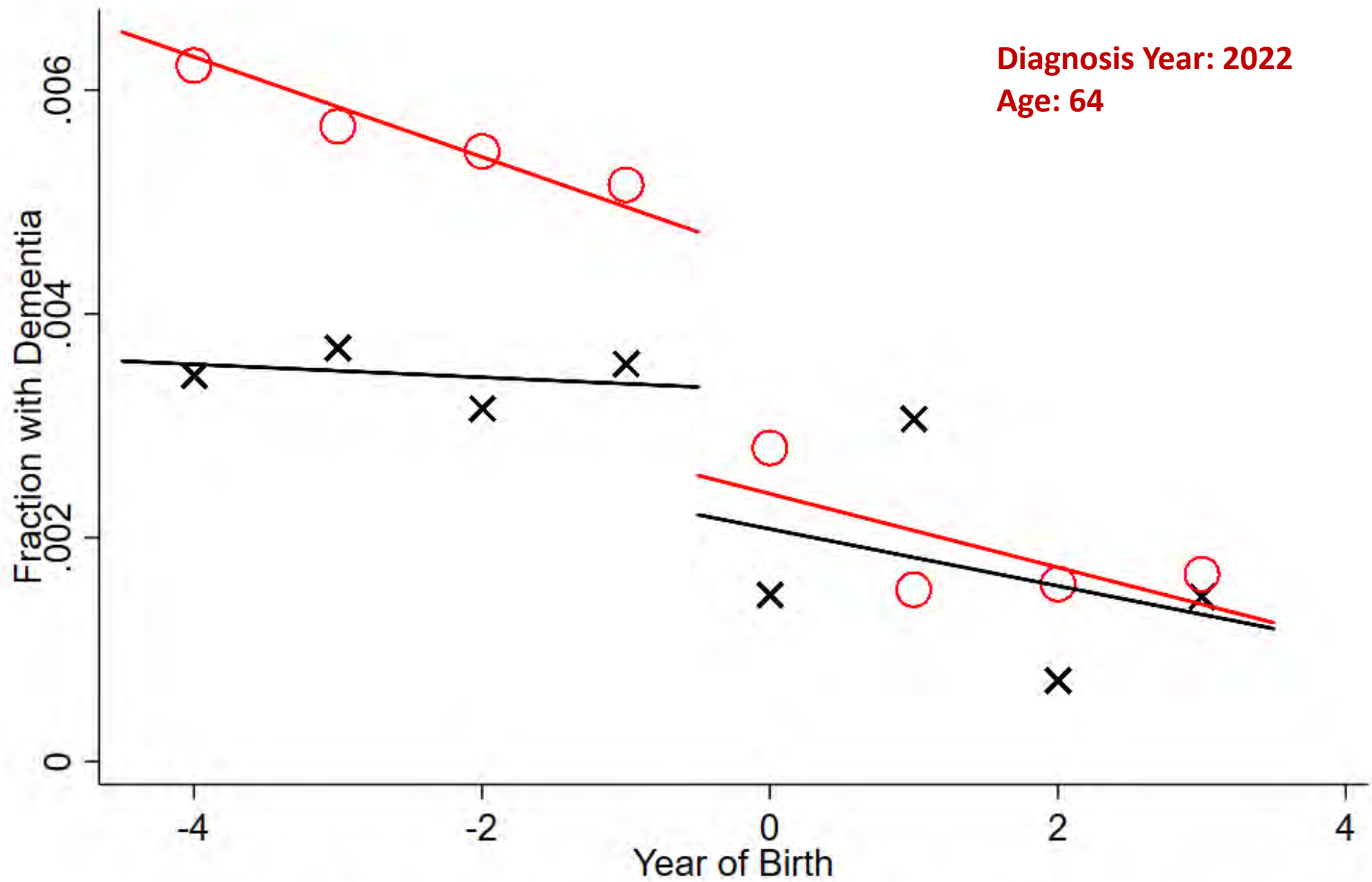
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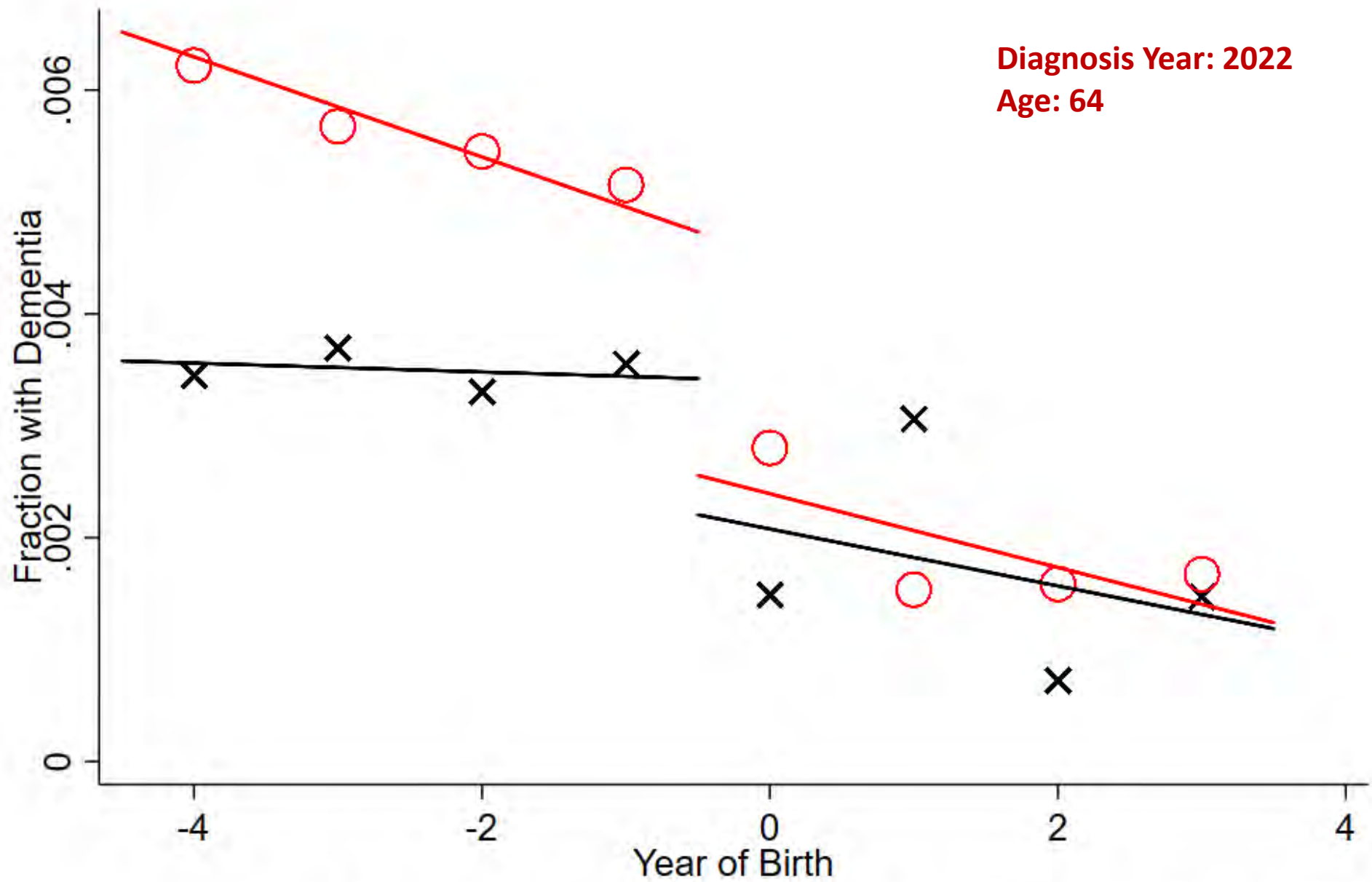
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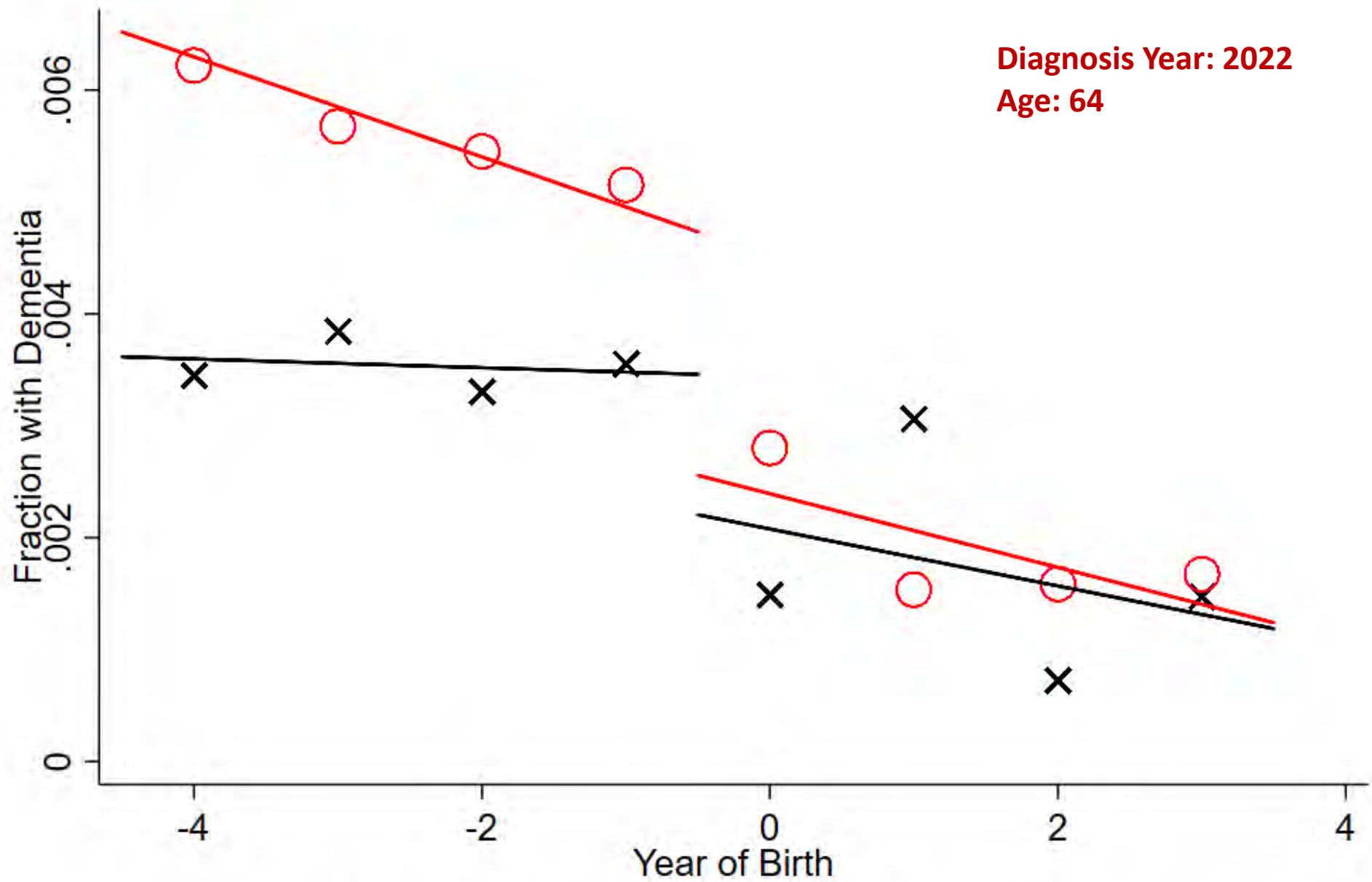
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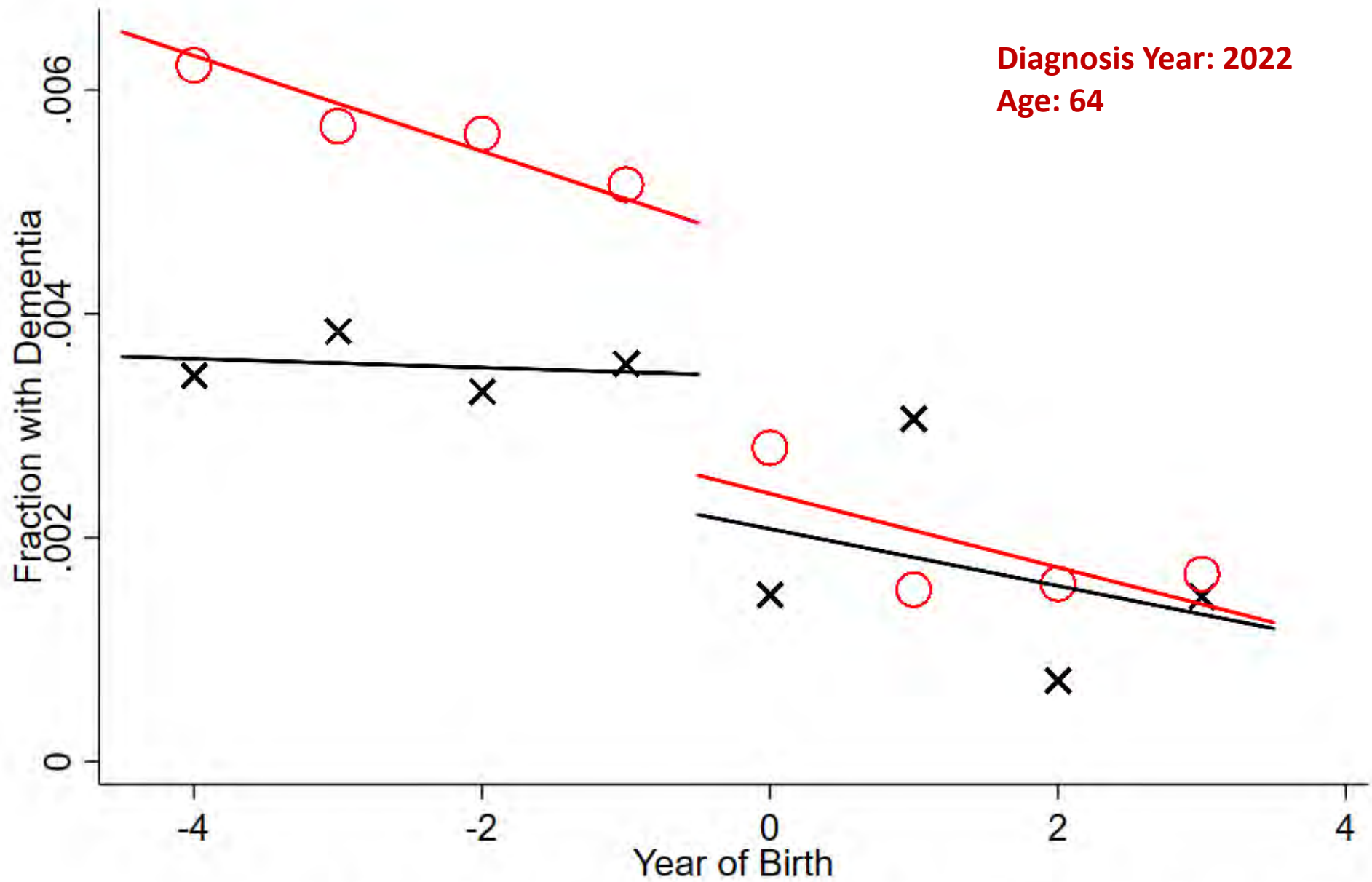


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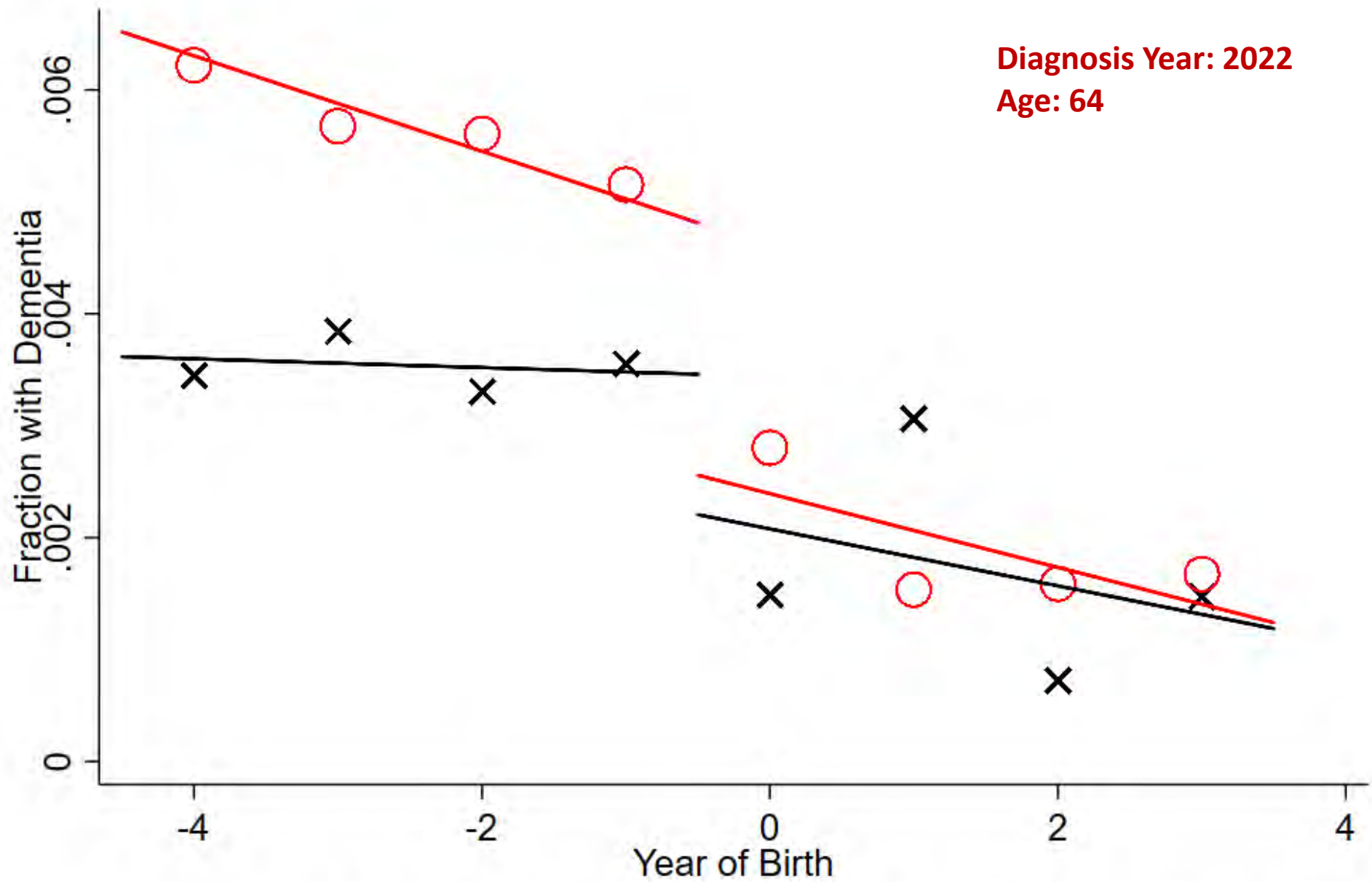


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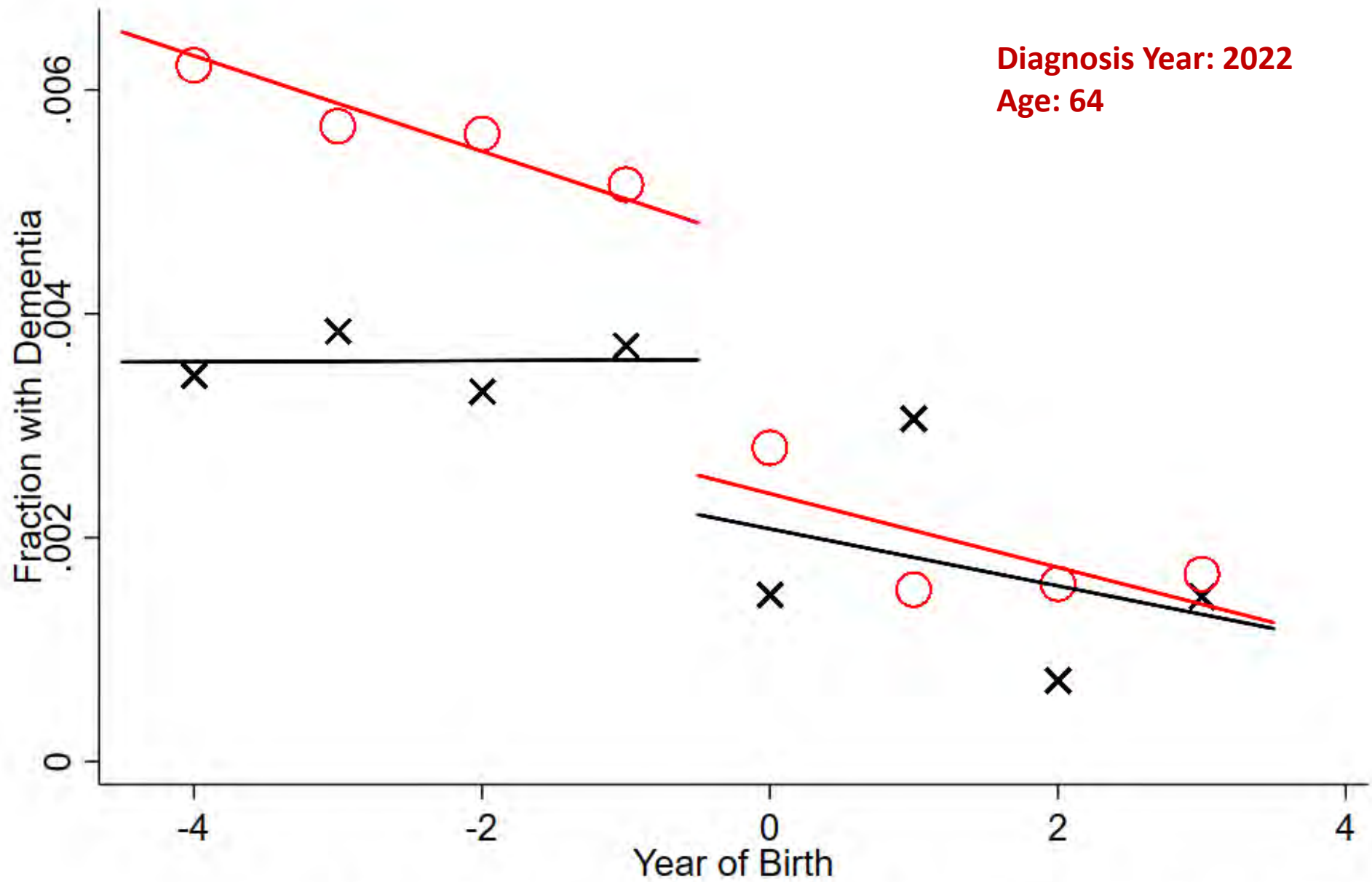
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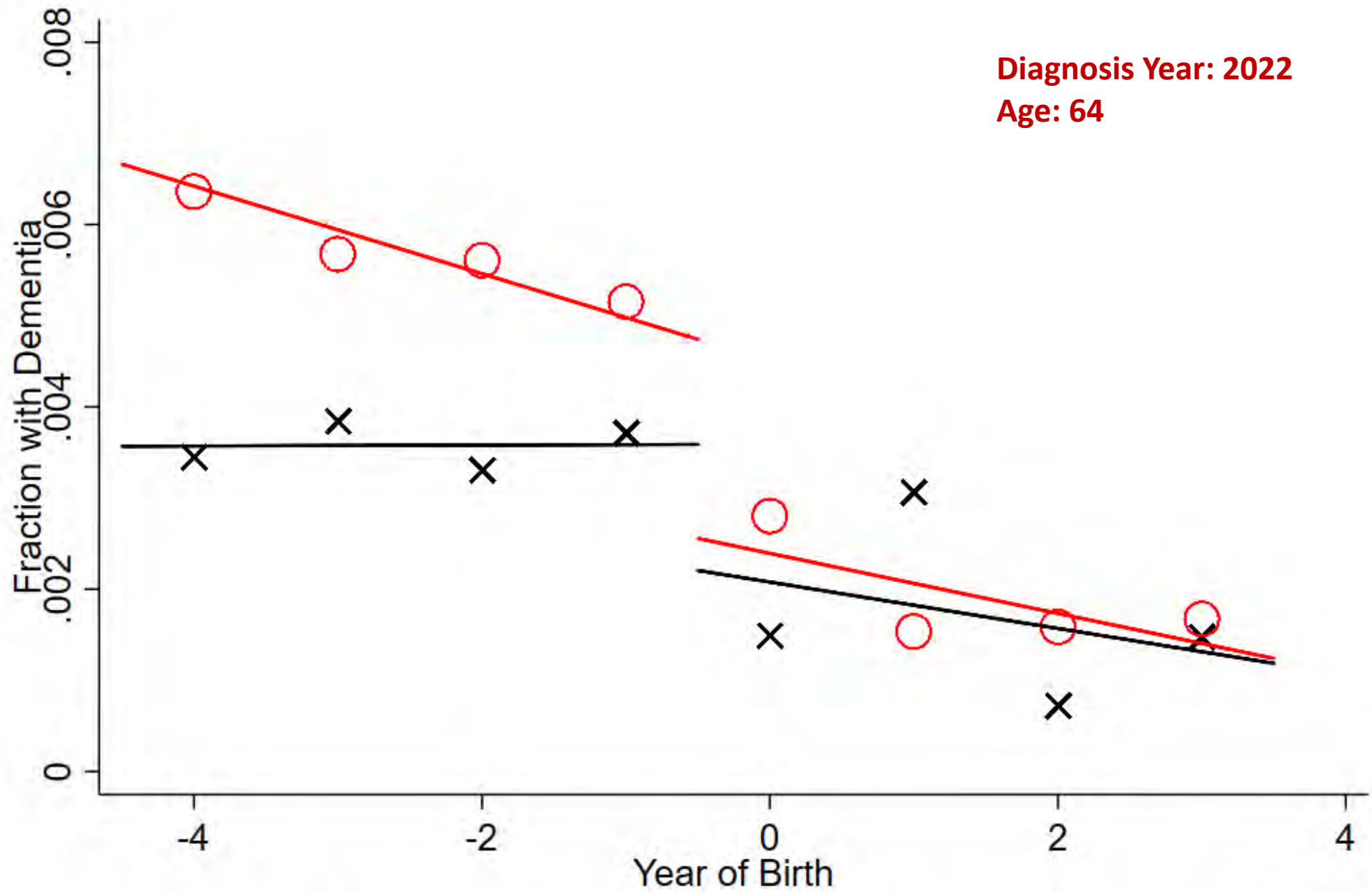
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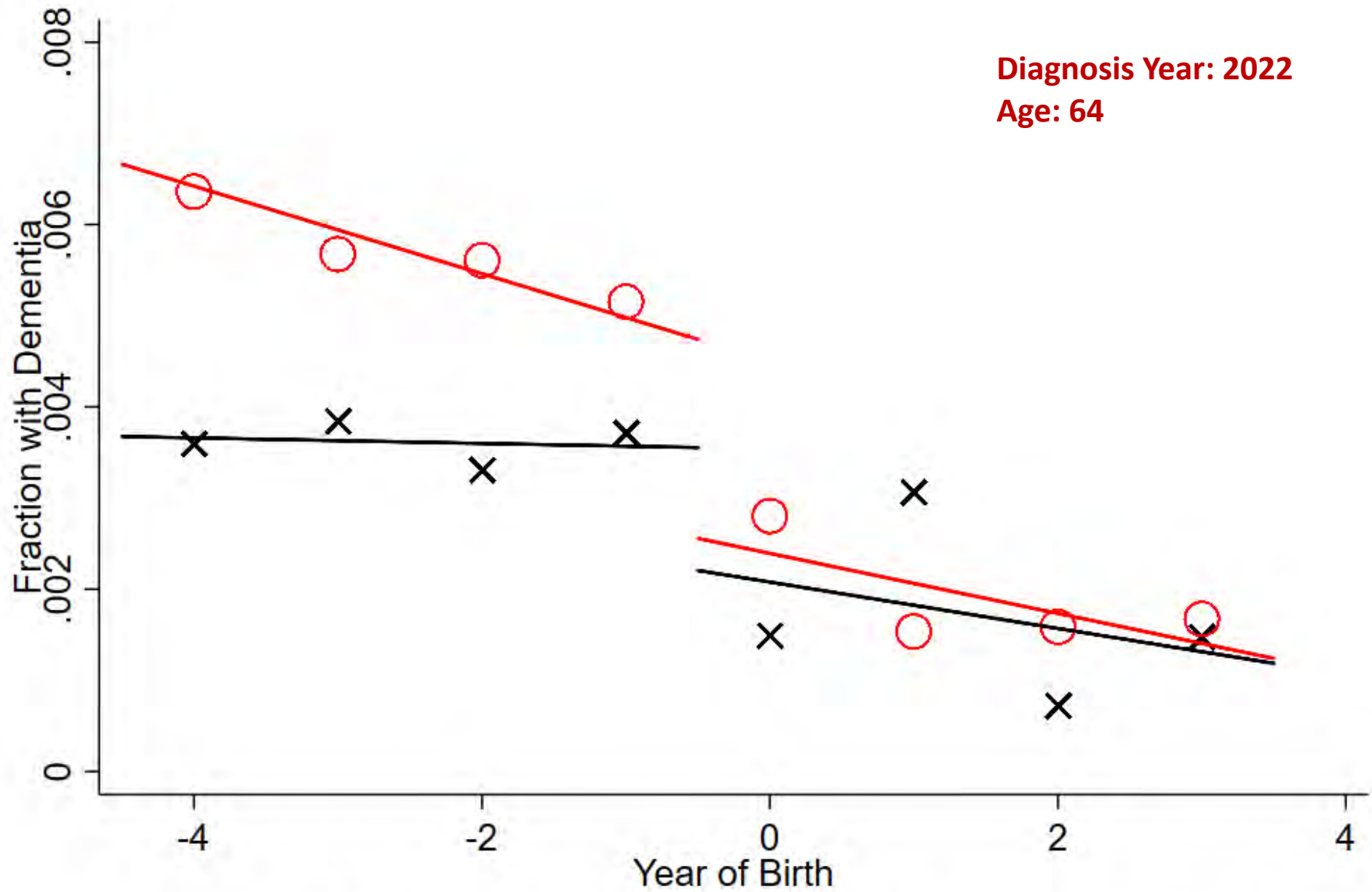
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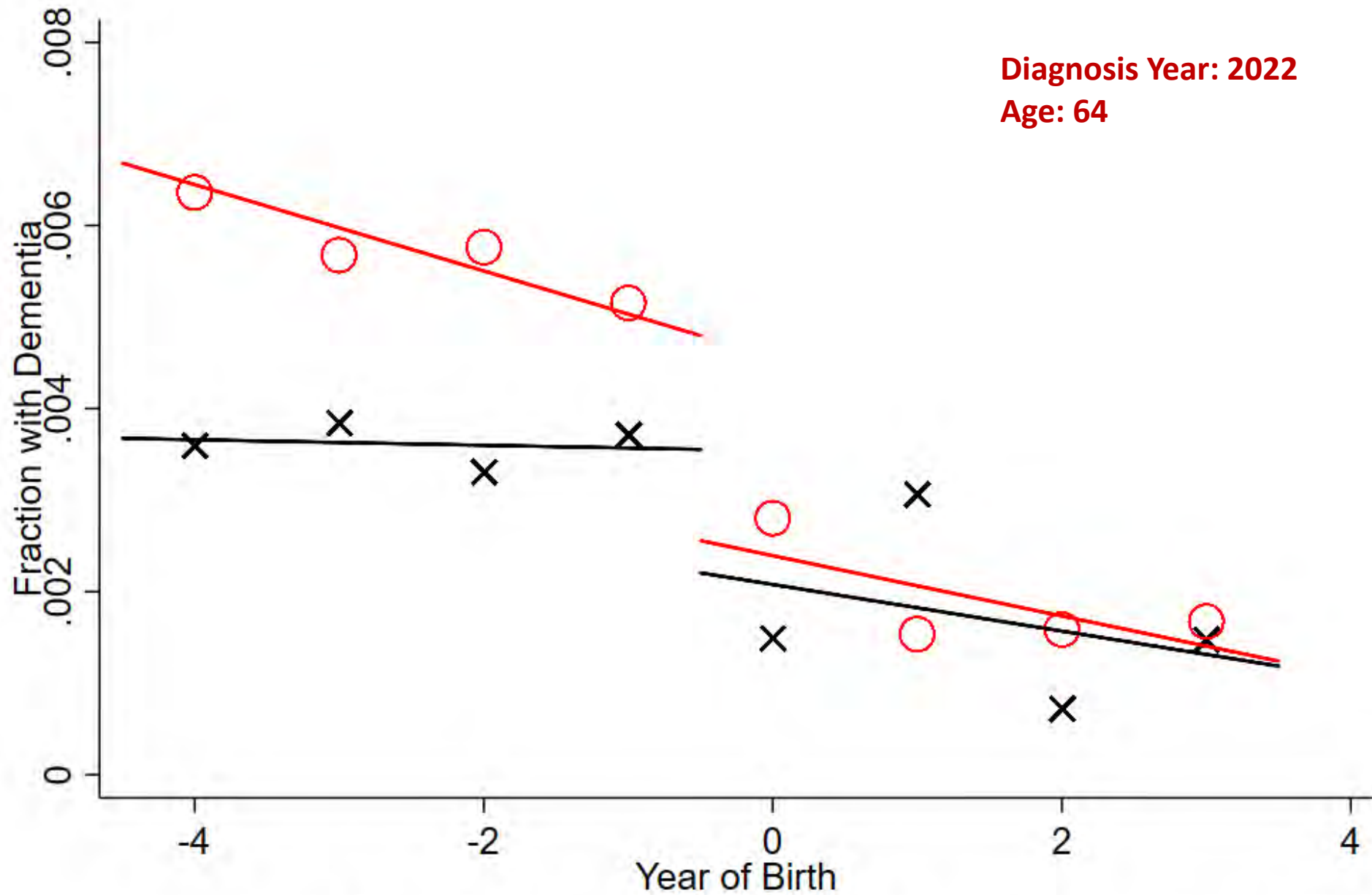


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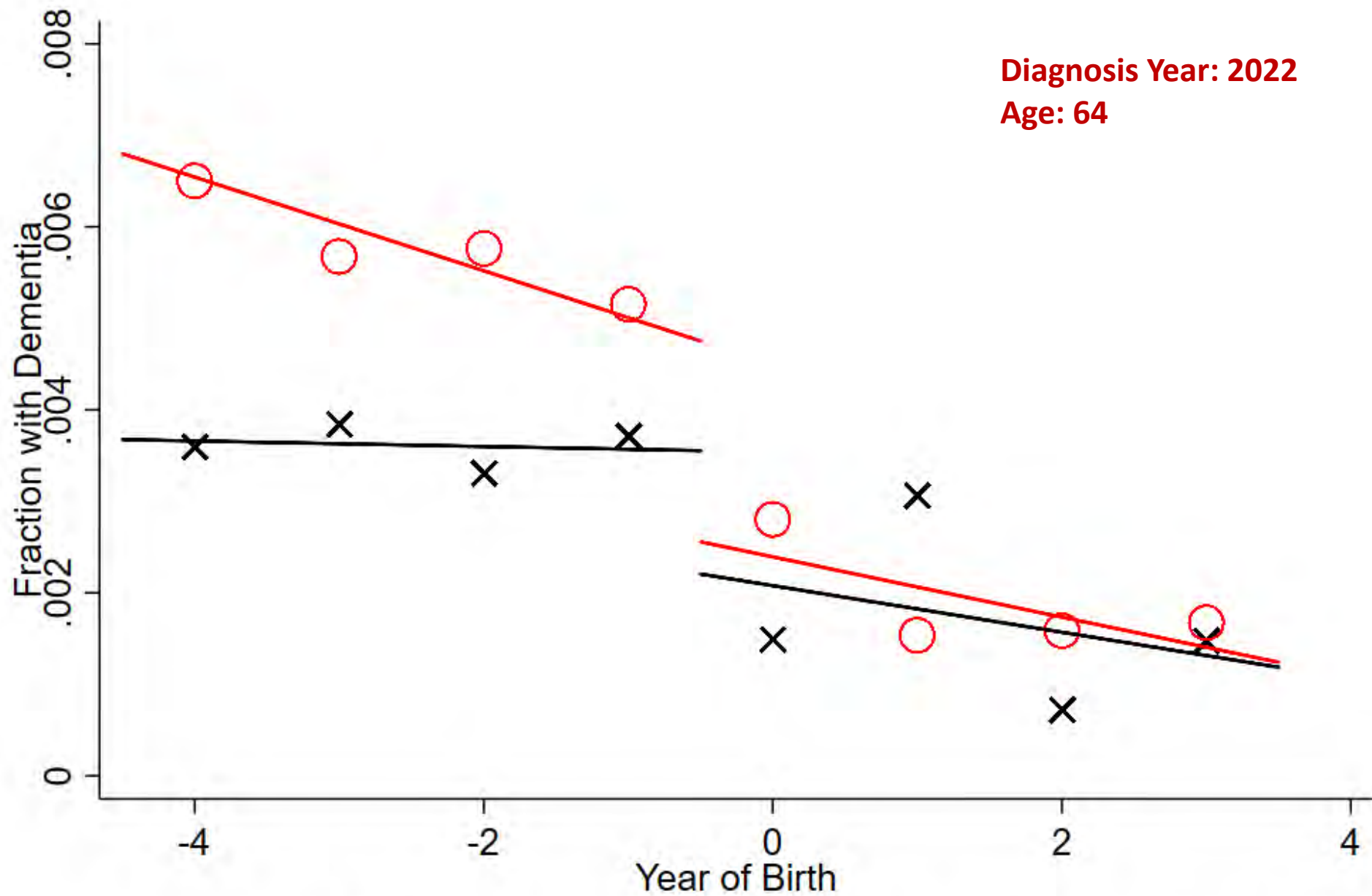
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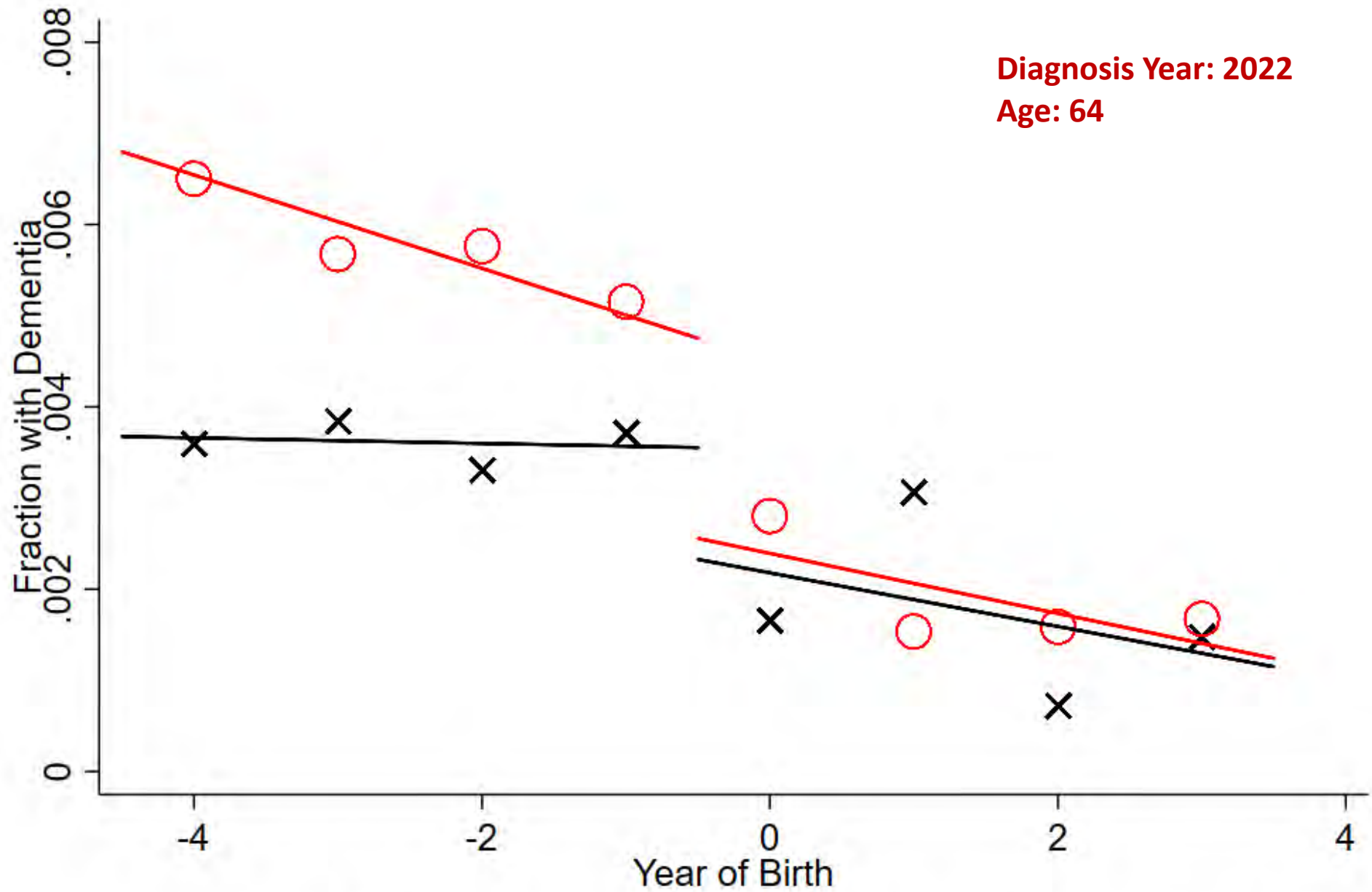


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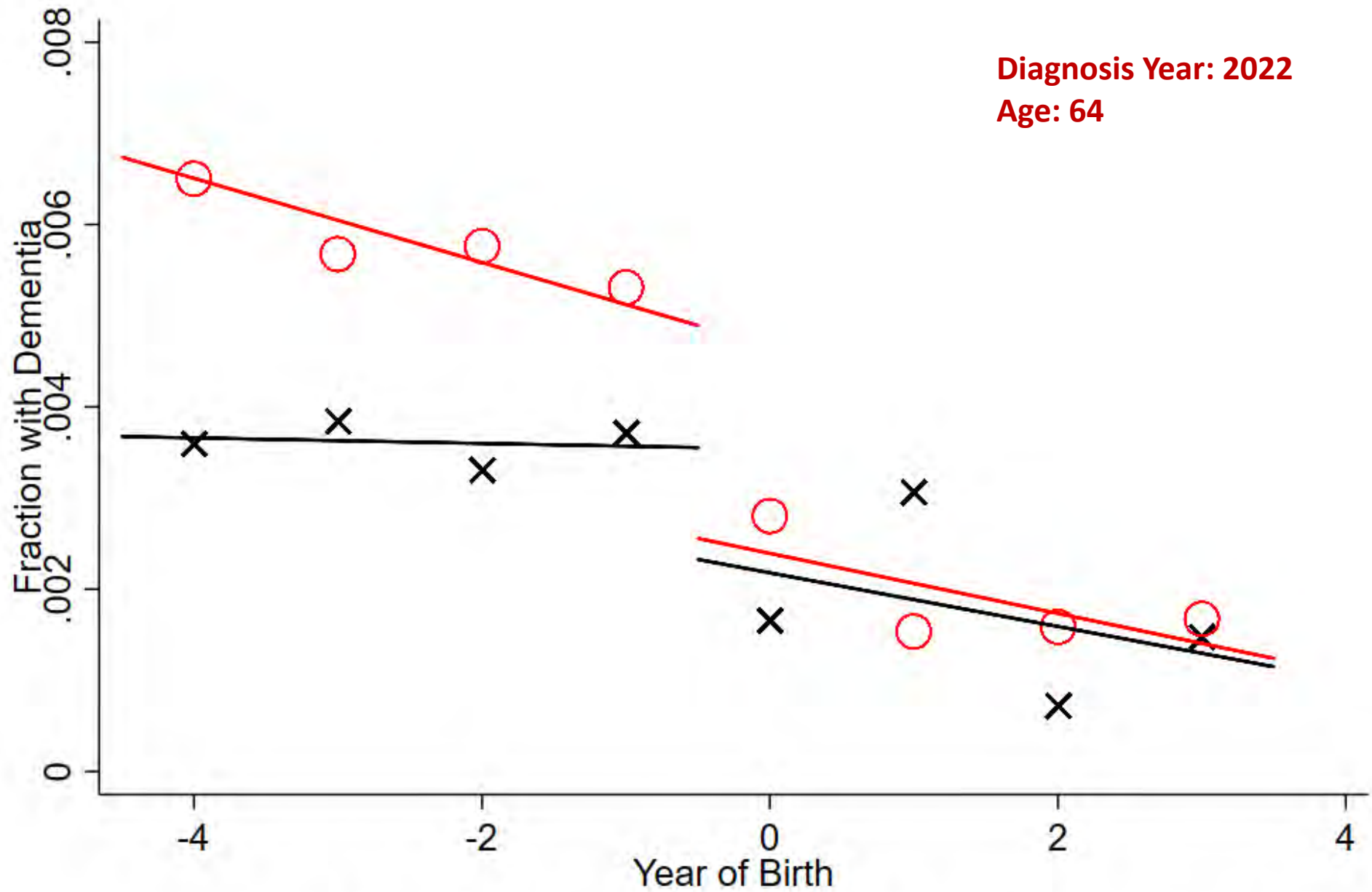


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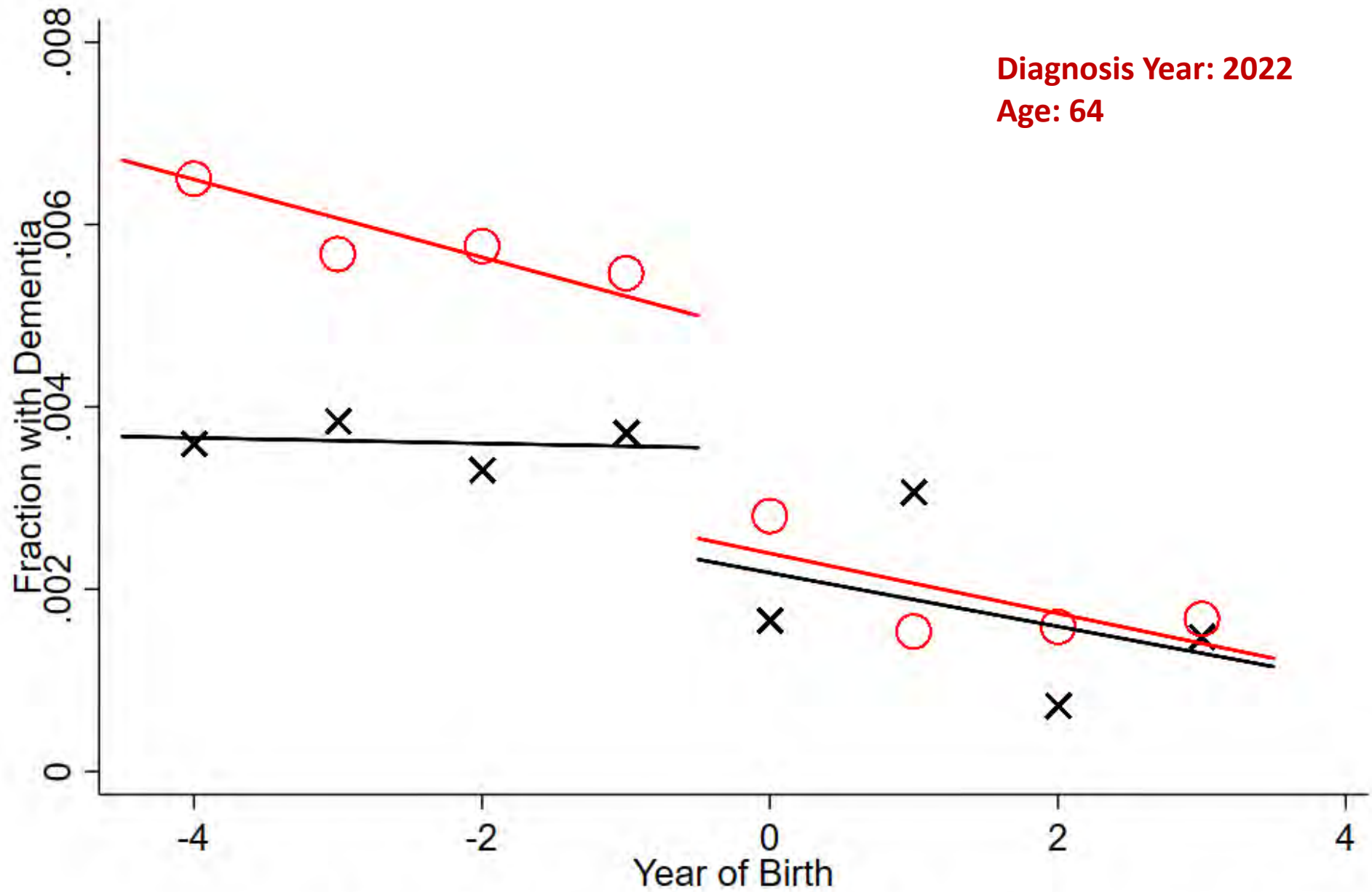


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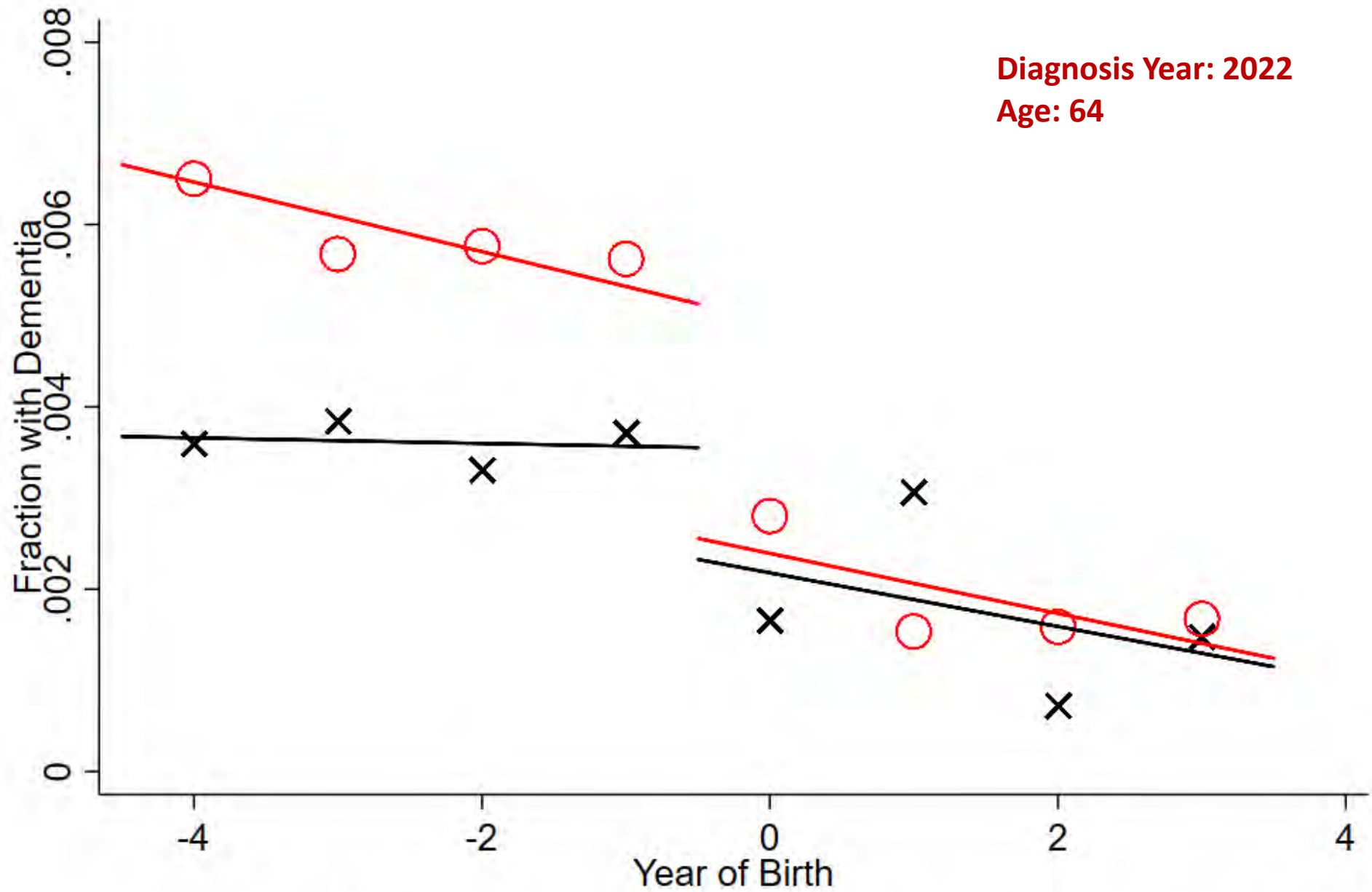


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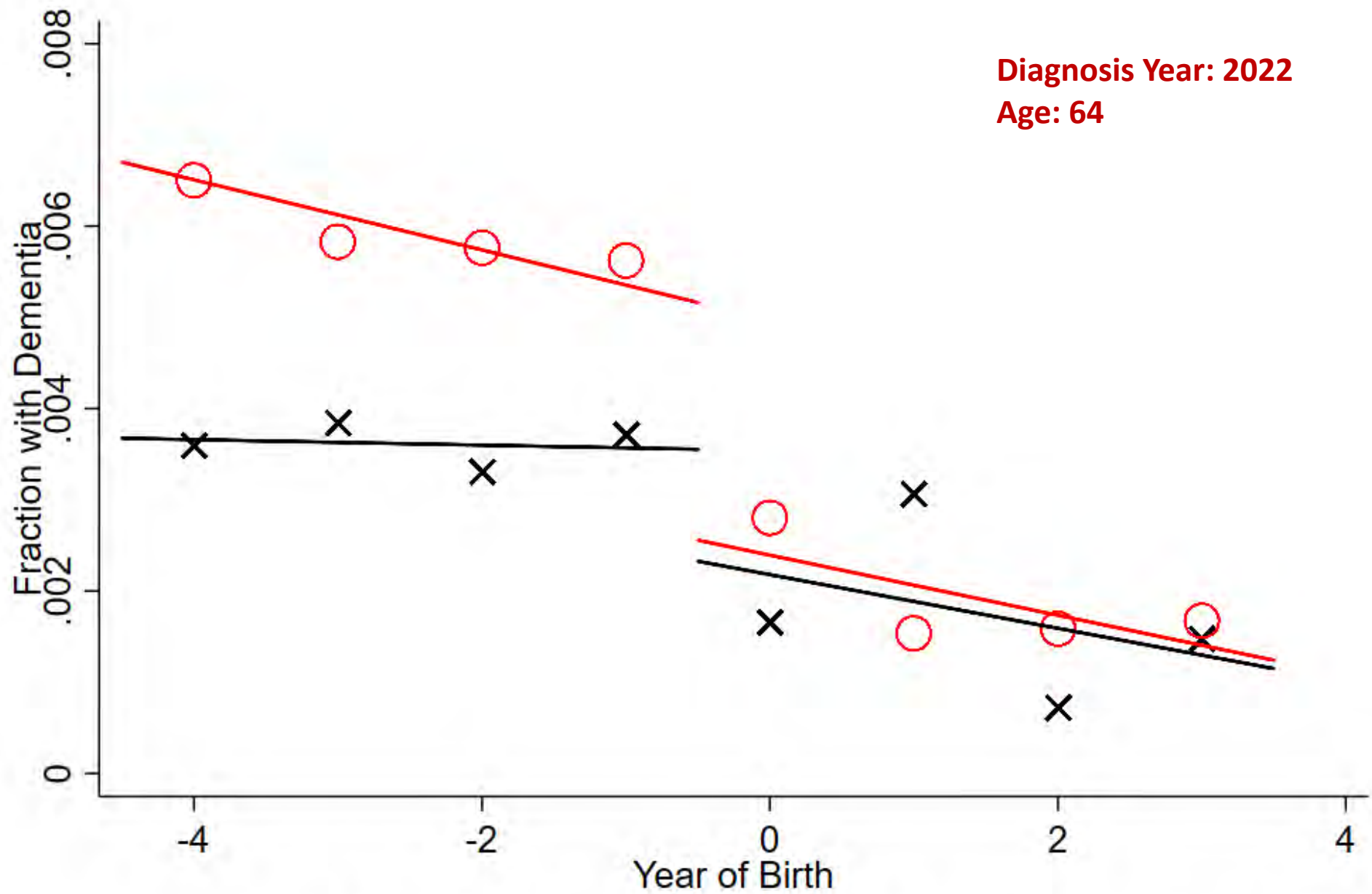
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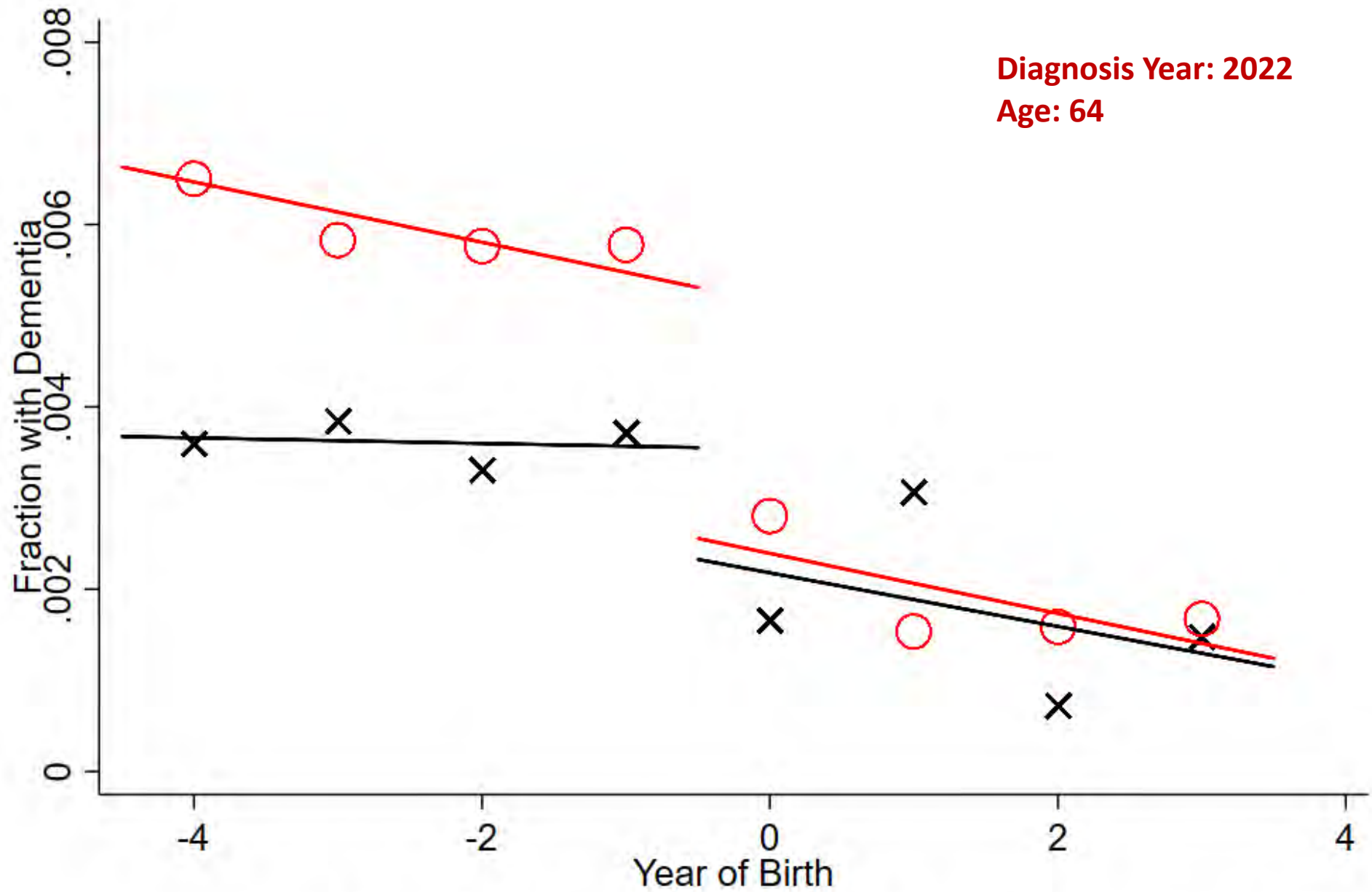
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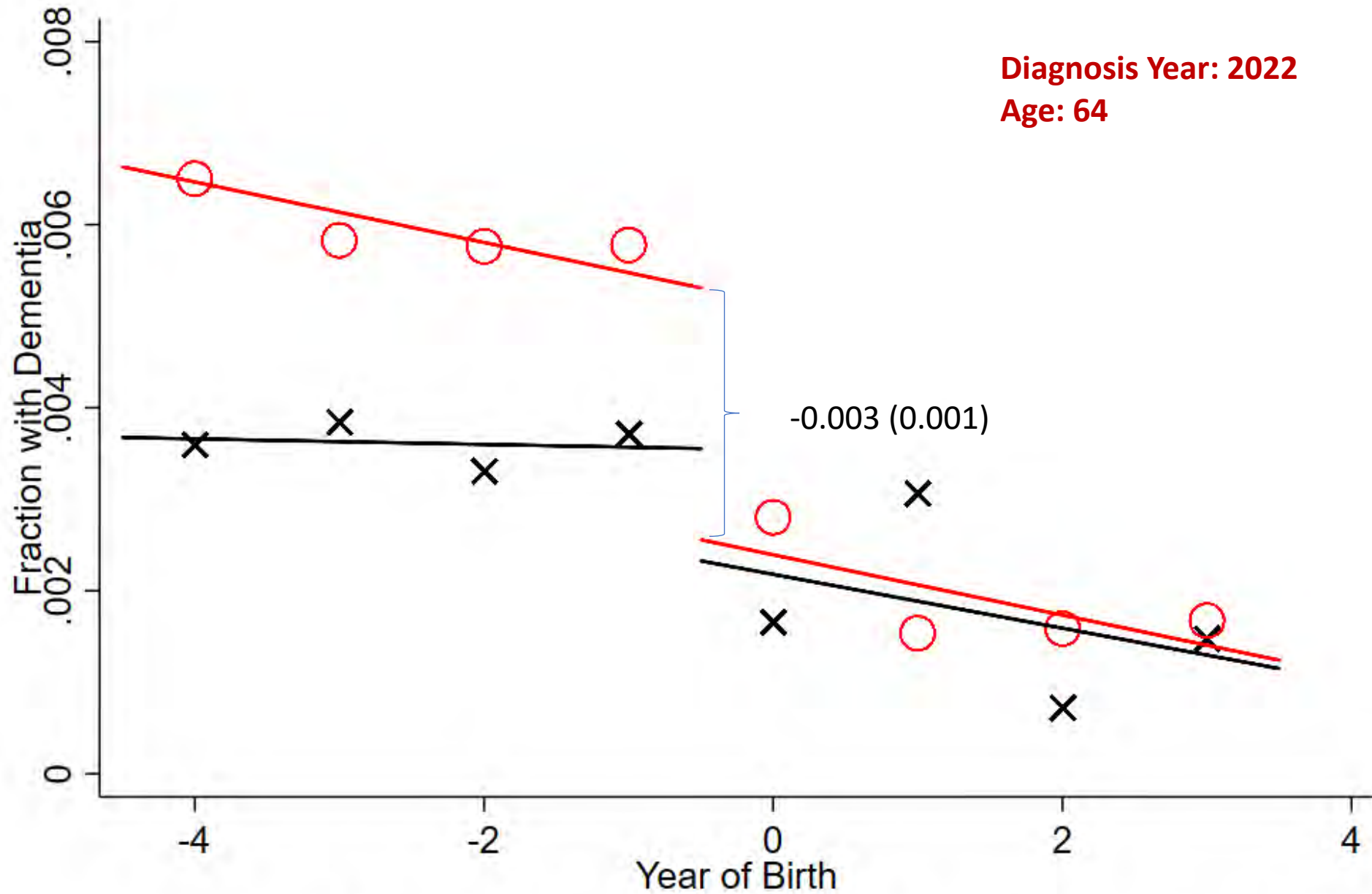
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Conclusions

- Extra secondary education driven by the 1972 ROSLA significantly reduced rates of dementia diagnosis 50 years later
- Education also delayed onset; ROSLA effects grow as sample ages
- Using genetics, it is possible to identify those at much greater risk of dementia; these markers are relatively unconfounded by parental economic and health background
- Those with high and low genetic risk for AD were similarly affected by the ROSLA in terms of education, but those at high risk saw their AD prevalence decrease twice as much.
- As a result, the gap in ADRD prevalence between those with high and low genetic risk practically disappeared among cohorts affected by the reform