

Genetic perspective on the relationship between female reproductive traits, exercise, and bone health outcomes: Evidence from a national database

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We studied over 51,000 East Asian women to understand how reproductive timing affects bone health. Later menopause was found to protect against osteoporosis, while exercise independently strengthened bones. These findings highlight the combined role of genetics and lifestyle, offering new directions for personalized osteoporosis prevention strategies.

Background:

Female reproductive traits influence bone health, including bone mineral density (BMD) and fracture risks, through estrogen exposure. However, these causal relationships remain unclear due to confounding. Understanding these relationships is crucial for osteoporosis prevention strategies.

Objective:

To investigate causal relationships between age at menarche (AAM), age at natural menopause (ANM), and bone health outcomes, and examine gene-exercise interactions using Mendelian randomization.

Methods:

We analyzed 51,049 East Asian women from Taiwan Biobank, randomly split into discovery (n=25,500) and validation (n=25,549) subsets. Instrumental variables included 15 single-nucleotide polymorphisms (SNPs) for AAM and 36 SNPs for ANM. Outcomes were BMD Z-scores, T-scores, and osteoporosis. We performed univariable and multivariable Mendelian randomization (MR), followed by gene-exercise interaction analysis using the ordinary least squares (OLS) regression method. Mean participant age was 51.1 years, with average AAM of 13.3 years and ANM of 59.8 years.

Results:

Genetically determined late ANM was associated with BMD Z scores ($\beta = 0.045$, 95% confidence interval [0.021, 0.069]), BMD T scores ($\beta = 0.046$, 95% confidence interval [0.020, 0.072]), and reduced osteoporosis ($\beta = -0.106$, 95% confidence interval [-0.154, -0.058]) in multivariable MR analysis. AAM showed no consistent causal effects due to pleiotropy. In OLS regression, regular exercise habits ($P < 0.001$) were independently significantly associated with increased BMD T scores and BMD Z scores, as well as PRS_{ANM} ($P < 0.01$). Although no overall gene-exercise interaction was observed, specific gene-exercise interactions were identified: PRS_{AAM} interacted with martial arts and golf, while PRS_{ANM} interacted with dance and golf (all $P < 0.05$).

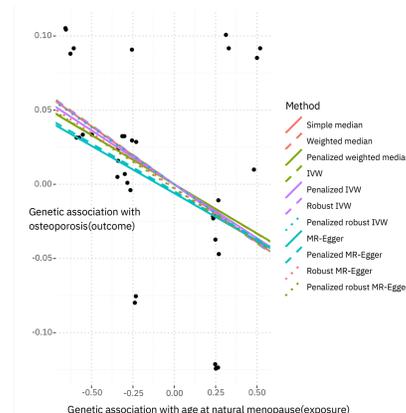


Fig1. Scatter plot of age of natural menopause on osteoporosis

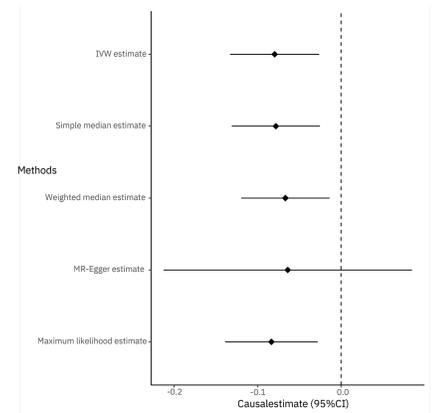


Fig2. Forest plot of age of natural menopause on osteoporosis

	β	S.E.	P-value		β	S.E.	P-value
Walking				Martial arts			
PRSAAM x Exercise (METs/week)	-0.02274	0.023197	0.327	PRSAAM x Exercise (METs/week)	0.049504	0.022624	0.0287
PRSANM x Exercise (METs/week)	-0.0146	0.014335	0.308	PRSANM x Exercise (METs/week)	0.008186	0.014042	0.56
Lower limb exercise (logging, power walking, rope jumping)				Yoga			
PRSAAM x Exercise (METs/week)	0.026119	0.018081	0.149	PRSAAM x Exercise (METs/week)	0.007886	0.05911	0.894
PRSANM x Exercise (METs/week)	0.003234	0.010592	0.76	PRSANM x Exercise (METs/week)	0.04962	0.031249	0.112
Swimming				Bicycle			
PRSAAM x Exercise (METs/week)	0.005545	0.065792	0.933	PRSAAM x Exercise (METs/week)	0.059388	0.033292	0.0745
PRSANM x Exercise (METs/week)	-0.06875	0.039028	0.0782	PRSANM x Exercise (METs/week)	0.010279	0.021351	0.63
Gymnastics				Racquet sports			
PRSAAM x Exercise (METs/week)	0.048613	0.035296	0.168	PRSAAM x Exercise (METs/week)	0.012667	0.029074	0.663
PRSANM x Exercise (METs/week)	0.010022	0.024399	0.681	PRSANM x Exercise (METs/week)	-0.01628	0.029559	0.582
Weightlifting				Golf			
PRSAAM x Exercise (METs/week)	0.004739	0.066959	0.944	PRSAAM x Exercise (METs/week)	-1.1777	0.303286	0.000103
PRSANM x Exercise (METs/week)	0.013137	0.049841	0.792	PRSANM x Exercise (METs/week)	0.724769	0.307142	0.0183
Dance (aerobic ballroom, or hula hoop)				Other sports (soccer, croquet and basketball)			
PRSAAM x Exercise (METs/week)	0.021023	0.021564	0.33	PRSAAM x Exercise (METs/week)	0.339992	0.461021	0.461
PRSANM x Exercise (METs/week)	0.026138	0.012192	0.032	PRSANM x Exercise (METs/week)	0.039334	0.321975	0.903

Table 1. Interaction effects between exercise types and polygenic risk scores for age at menarche and age at menopause on osteoporosis.

Conclusion:

Late ANM provides casual protection against osteoporosis in East Asian women, while the effects of AAM remain uncertain. Exercise benefits bone health with activity-specific genetic interactions. These findings support personalized osteoporosis prevention strategies incorporating both genetic risk assessment and targeted exercise recommendations, particularly for women with early menopause predisposition.