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Genetic predisposition to later puberty causes lower bone density in children and adults

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People whose genetic makeup triggers a later-than-average start to puberty have lower bone mineral density, especially in their lower spine. Because adolescence is a critical period for accruing bone, this effect may increase a person's risk of osteoporosis and bone fractures later in life.

"If an individual is genetically programmed for later puberty, we found that he or she tends to have lower bone mineral density during childhood as well as in adulthood," said geneticist Struan F. A. Grant, PhD, one of three scientists from Children's Hospital of Philadelphia (CHOP) who co-led a study published Oct. 25, 2017 in the *Journal of Bone and Mineral Research*.

Scientists already knew that later puberty was linked to lower bone mineral density, and that both are risk factors for osteoporosis. This study was the first to analyze the associations between genetic determinants of puberty timing and measurements of bone mineral density.

The researchers drew on data from the Bone Mineral Density in Childhood Study (BMDCS), funded by the NIH. That study included sophisticated bone and growth measurements during annual visits for up to seven years in over 2,000 healthy children, adolescents and young adults during 2002 to 2010. Babette S. Zemel, PhD, another co-study leader, was the principal investigator of the BMDCS at CHOP, where she directs the Nutrition and Growth Laboratory.

In the current research, the study team used a relatively new tool called a "genetic risk score" (GRS), which enables collective study of a group of genetic variants in one go. "We generated a genetic risk score in the BMDCS study based on hundreds of genetic variants associated with later puberty in children, and looked for associations with bone mineral density measurements," said first author Diana Cousminer, PhD, a CHOP geneticist with expertise in the genetics of puberty. The researchers performed these analyses separately in boys and girls, and also in publicly available corresponding genetic data on bone mineral density in adults.

For both boys and girls, the GRS for later puberty associated with lower bone mineral density in both a longitudinal cohort of 933 individuals who each had up to seven assessments, and in a cross-sectional cohort of 486 individuals. The results varied according to the part of the skeleton where bone mineral density was measured, with lowest density in the lower back and hip bones.

In a separate analysis called "Mendelian Randomization," the study team found that later puberty caused lower bone mineral density in both adult men and adult women. They also detected a strong causal effect in adolescent girls, while finding no causal relationship for adolescent boys. Cousminer said the number of boys in their analysis may not have been large enough to show a significant effect.

The current research builds on several previous studies of bone health performed by CHOP scientists, using BMDCS data. Earlier this year, they showed that gains in bone mineral continue even after teenagers attain their adult height, reinforcing the importance of late adolescence for building bone strength. A 2016 study found that children and adolescents with higher levels of physical activity had higher bone density, even when they had genetic variants that predisposed them to weaker bones. That research, co-led by Zemel and Grant, strengthened

the evidence that high-impact, weight-bearing physical activity improves bone health in children and adolescents.

Other researchers have previously shown an epidemiological link between later puberty and the risk of bone fracture and osteoporosis late in life. The current study did not include data from elderly people, and so could not directly perform a genetic analysis of osteoporosis risk. Cousminer added that the CHOP team's future studies will address this question by using data from older research subjects.

"Now that we are aware of the risks to lifelong bone health if someone is genetically predisposed to later puberty, we can work on strategies such as promoting weight-bearing physical activity, to optimize bone density during skeletal development," said Zemel.

More information: Diana L Cousminer et al, Genetically Determined Later Puberty Impacts Lowered Bone Mineral Density in Childhood and Adulthood, *Journal of Bone and Mineral Research* (2017). DOI: 10.1002/jbmr.3320

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