**PRESS RELEASE**

***Genetics helps to unravel key components of fracture risk***

A large international collaboration has tracked down 15 variations in the genome that are related to the risk of suffering osteoporotic fractures, a major healthcare problem affecting worldwide more than 9 million individuals every year. The collaboration went a step further and used genomic information on other risk factors to examine their causal role on developing fractures; finding that only bone mineral density and muscle strength are directly involved in fracture susceptibility. Genetic predisposition to other clinical risk factors like vitamin D levels and calcium intake, historically considered to be crucial mediators of fracture, were not found to be directly predisposing fracture. These findings postulate that interventions aimed at increasing bone and muscle strength are more likely to be successful in preventing fractures than widespread supplementation of vitamin D or other risk factors not mediating the disease process.

The international collaboration was conformed by a team of researchers bringing together researchers from Europe, Canada, USA, Asia and Australia, to form the largest effort to date investigating the genetics of osteoporosis and fracture risk. The study co-lead by researchers from Erasmus University Medical Center in Rotterdam, The Netherlands and McGill University in Montreal, Canada, comprised 185,057 cases and 377,201 controls part of the Genetic Factors of Osteoporosis (GEFOS) Consortium, the UKBiobank Study and the 23andMe® biotech company.

This, the first genome-wide association study (GWAS) for fracture risk has provided important insight on the biologic mechanisms leading to fracture. “Notably, all identified genomic positions (known as loci) are also associated with variation in bone mineral density (BMD), a measurement used to determine bone strength and diagnose osteoporosis,” says Katerina Trajanoska, Erasmus MC researcher and first author of the publication published in *the British Medical Journal*. “This is in line with our additional analysis (i.e., Mendelian randomization, a statistical method using genetic information to determine causal relations between risk factors and disease outcomes), showing that BMD is the most important determinant of fracture risk and that prevention strategies aiming to increase or maintain BMD levels are the most likely to be successful” adds Trajanoska.

“Some of the identified genetic variants are related to genes part of pathways currently targeted by recently developed osteoporosis medication, while other novel ones hold potential to become drug targets in the near future”, states Fernando Rivadeneira, Genetic Epidemiologist from Erasmus MC and leading author of the publication. “Yet, one of the most important insights from our work for patients at risk of osteoporosis, is

obtaining additional evidence from the genetic studies that “widespread” vitamin D supplementation is unlikely to be effective for the prevention of fracture” adds Rivadeneira.

Vitamin D supplementation is widely prescribed as they make part of the clinical guidelines for osteoporosis management and fracture prevention. However, recent meta-analyses of randomized controlled clinical trials failed to confirm any benefit of vitamin D and calcium supplementation in patients without pronounced deficiency of these factors. Thus, these findings and those derived from our study highlight the need to re-assess its wide-spread use in clinical practice. “Patients using osteoporosis medication should not discontinue their supplements before consulting with their treating physicians. Procuring a healthy lifestyle with a balanced diet and remaining physically remain the main pillars of a sustainable bone health” advices Rivadeneira to the general public.

Link to the paper: https://www.bmj.com/content/362/bmj.k3225