

## Regression To The Mean In Osteoarthritis Trials

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**Disclosures:** None

**INTRODUCTION:** Improvement in pain reported in clinical trials for osteoarthritis (OA) is strongly depending on the regression-to-the-mean (RTM) phenomenon. RTM has been estimated to explain about 1 NRS point (0-10 scale) of the absolute improvement since baseline (1). However, the potential effects of RTM on the typical secondary patient-relevant outcomes in trials for knee OA are unknown.

**METHODS:** We included participants of Osteoarthritis Initiative public dataset who fulfilled inclusion criteria typically required for enrolment in a clinical trial (2). These included: age 40-79 years, symptomatic knee OA, Kellgren-Lawrence grade 2-3, use of pain medication more than half the days of a month in past 12 months, numerical rating scale (NRS) pain of 4 to 9 in the target knee. We studied observed changes in the mean levels of WOMAC physical function (higher score =worse function) and KOOS QOL (higher=score better QOL) with respect to conditioning on current knee pain. Each person could be included multiple times. Ethical approval for use of all subject information was provided by the OAI.

**RESULTS SECTION:** We identified 459 subjects who fulfilled inclusion criteria on at least one annual follow-up between year 1 and year 8. The mean level of WOMAC knee function and KOOS QOL at each follow-up time point was similar, about 17, and about 51 respectively. However, at the time of fulfilling the inclusion criteria (theoretical inclusion in a trial), the mean level of physical function in the same subjects was 23.4 and 43, respectively. The mean improvement in WOMAC physical function between the theoretical point of inclusion in a trial, and 1 and 2 years later, respectively, was 2.5 (95% CI 1.7 to 3.2) and 3.1 (95% CI 2.3 to 3.8). The corresponding improvement in KOOS QOL was 2.7 (95% CI ,1.7 to 3.7) and 4.2 (95% CI, 3.1 to 5.3), respectively.

**DISCUSSION:** RTM is a known phenomenon, but investigators often tend to oversee its importance when interpreting effectiveness of treatments, in particular in trials not using placebo as a comparator. As for limitations, our estimates are based on data from one North American observational cohort, and we cannot exclude that any potential treatments or interventions under the study period may have influenced our estimates. Further, in the present study we only had access to data from on annual follow-ups. Hence, the size of RTM in shorter time frame, e.g., 6 weeks, 3 months, or 6 months, remains to be established. However, due to often rapidly fluctuating symptoms in OA, we believe the phenomenon in OA trials is present to a similar extent also with shorter follow-up times.

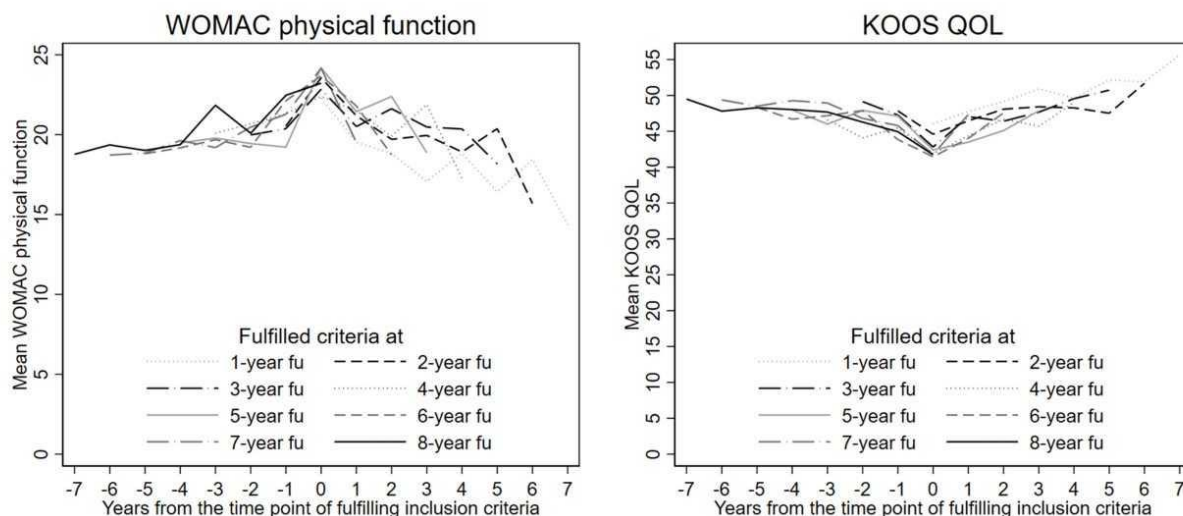
**SIGNIFICANCE/CLINICAL RELEVANCE:** RTM in a typical knee OA trial is likely not only to explain improvement in pain, but also albeit to a lesser extent, improvement in knee function and QOL. RTM is a phenomenon that often misleads the investigators' to overinterpret effectiveness as RTM neither represents improvement from the intervention nor placebo response from the intervention and its context.

### REFERENCES:

- 1) Englund, M., & Turkiewicz, A. (2023). Pain in clinical trials for knee osteoarthritis: estimation of regression to the mean. *The Lancet Rheumatology*. [https://doi.org/10.1016/S2665-9913\(23\)00090-5](https://doi.org/10.1016/S2665-9913(23)00090-5)
- 2) Hochberg MC Guermazi A Guehring H et al. Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial. *JAMA*. 2019; 322: 1360-1370

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### IMAGES AND TABLES:



**Figure.** Mean levels of physical knee function and knee-related quality of life (QOL) among 547 persons fulfilling criteria for inclusion in a hypothetical knee osteoarthritis trial, illustrating the occurrence of regression to the mean when conditioning on knee pain at inclusion. Time 0 means the moment when fulfilling the criteria. Each line represents a cohort of subjects fulfilling criteria at one follow-up occasion (between year 1 and year 8 post baseline).