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High blood pressure and osteoarthritis: friends or foes? Comment on the article by Funck-Brentano et al

To the Editor:

A vascular etiology of osteoarthritis (OA) has been proposed for decades (1,2). I read with interest the recent article by Funck-Brentano and colleagues, regarding a novel causal relationship between low blood pressure and OA (3), which provided new insight into the vascular origin of OA pathologies. I appreciate the authors' dedicated efforts in big data analytics to elucidate the puzzle of OA, a multifactorial, prevalent, debilitating, disability-associated chronic condition. However, there are a few issues concerning the data comprehensiveness, accuracy, and representativeness that are worth mentioning.

First, it is noteworthy that diastolic blood pressure (BP) was not included in this analysis, for unknown reasons. In fact, diastolic BP as well as systolic BP has been reported to be associated with symptomatic knee OA in the Framingham Osteoarthritis Study (4). Unlike other components of metabolic syndrome, this association remained statistically significant after adjustment for body mass index (BMI). In addition, pulse pressure, the difference between systolic BP and diastolic BP, has been associated with incident radiographic knee OA based on data from the Osteoarthritis Initiative (5). Therefore, it is worthwhile to explore the relationship between diastolic BP and a hospital diagnosis of OA, although radiographic OA versus symptomatic OA was not distinguished by Funck-Brentano and colleagues (3).

Second, many environmental and behavioral factors such as climate, temperature, time of day, eating, drinking, and physical activity will affect the BP reading accuracy. The average of 2 systolic BP measures in a single visit might not be representative or adequate in indicating either low or high BP. Information on the repeated systolic BP measurements during the follow-up visits, which are available in the UK Biobank database, would be desirable. Moreover, the level of physical activity is a known confounding factor that affects both the systolic BP reading and the risk of OA. However, the authors mentioned that the impact of physical activity could not be analyzed in their study due to the lack of genome-wide association study data (3).

Third, systolic BP (rather than a hospital diagnosis of hypertension or the use of antihypertensive medication) was included as an exposure parameter in this Mendelian randomization (MR) analysis. The use of antihypertensive medication, especially taking more than 3 antihypertensive medications, has been reported to confer decreased odds of developing incident OA (5). Funck-Brentano and colleagues only excluded (but did not investigate) those who received antihypertensive medication for the sensitivity analysis in this MR study. Hypertension is a frequently encountered vascular comorbidity in patients with primary OA (6). It has been associated with the risk of radiographic knee OA, although this association diminished after adjustment for BMI (4). However, as Funck-Brentano et al have pointed out, that study might have been underpowered to detect hypertension as a BMI-independent risk factor for OA, given the relatively smaller population of 991 participants (4). Regretfully, the current MR analysis on systolic BP and the risk of OA using a much larger data set of 384,838 subjects (3) did not fill this research gap. As mentioned above, systolic BP readings from a single visit could not indicate the BP status (e.g., hypertension).

The question of whether low or high BP is good or bad in OA remains unanswered. In my opinion, it seems too early to conclude a causal relationship between low BP and the risk of OA, which could have been just a numeric association. I am very interested in Funck-Brentano and colleagues' responses to the above concerns.

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Reply

To the Editor:

We thank Dr. Wen for his interest in our study. Besides causal associations of high BMI and high bone mineral density with increased risk of OA, we observed evidence of a causal association between low systolic BP and increased risk of OA. The interpretation of a possible inverse causal relationship between systolic BP and OA is indeed challenging. Our responses to the questions raised by Dr. Wen regarding this possible causal association are presented below.

First, regarding the reproducibility of the measures of systolic BP in the UK Biobank, our primary analysis was performed using a 2-sample MR approach. We used instrument variables and summary data from a previously published genome-wide association study (GWAS) on BP (1). Therefore, for this main analysis, we did not use the measured values for systolic BP in the UK Biobank, but we rather used the genetic determinants of systolic BP found in other cohorts. However, when using 1-sample MR analyses (i.e., using genetic determinants of systolic BP in the UK Biobank), we observed similar results as with the 2-sample MR analyses. Finally, when excluding patients receiving antihypertensive medications, the results were unchanged (see Supplementary Tables 14 and 15 of our article).

Second, regarding diastolic BP, we acknowledge that we did not perform MR analyses for this specific trait, which is a limitation that was decided a priori to reduce multiple testing. Measurement of diastolic BP is less accurate than systolic BP, especially in individuals >50 years of age, and diastolic BP is a poorer predictor of cardiovascular events (2). In the International Consortium for Blood Pressure GWAS, genetic variants for diastolic BP and systolic BP are similar, but with stronger beta values for systolic BP (1). Hence, we focused only on systolic BP in our analyses.

We believe that previously reported observational associations between elevated BP or hypertension and OA have been biased by other confounders, including BMI. We propose that decreasing systolic BP may in fact be deleterious for the joint, in contrast to its beneficial effects for many other organs. However, further studies are needed to confirm this hypothesis.

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Genetic disorders should be considered prior to diagnosing interstitial pneumonia with autoimmune features: comment on the review by Wilfong et al

To the Editor:

We read with great interest the recent review by Wilfong and colleagues on interstitial pneumonia with autoimmune features (IPAF) (1). We agree that the creation of a disease classification for patients with interstitial lung disease (ILD) who have components of autoimmunity, but not a specific rheumatologic diagnosis, necessitates ongoing conversation between rheumatologists and pulmonologists on the challenges of diagnosis and management.

The IPAF classification criteria (2) require exclusion of patients with alternative etiologies. In this era of genetic advancement, a growing collection of monogenic diseases can present with ILD and multisystem immune dysregulation. For example, clinical features of a patient with STAT3 gain-of-function syndrome (3) or CTL-A4 haploinsufficiency (4) could very well fit the criteria for IPAF (2). The mention of such disorders was missing from the otherwise comprehensive review by Wilfong et al. Admittedly, patients with these disorders typically present with early-onset disease and sufficient extrapulmonary manifestations that further investigation would likely be performed for a unifying diagnosis.

However, due to the possibility of advanced age at symptom onset and the probability of predominant lung involvement,