requires their doses of lithium to be reduced to maintain plasma levels within the therapeutic range.”

2. “This is an important consideration, especially because even mild to moderate CKD (glomerular filtration rate, 45 to 59 mL/min/1.73 m²) is associated with mineral and bone disorder.”

3. “Thus, patients taking lithium who did not develop CKD may have been taking higher doses but have similar, if not lower, blood levels of lithium than those taking much smaller doses. The article’s result that patients receiving high defined daily dose of lithium had relatively lower risks of fracture may therefore reflect their lack of CKD rather than protective benefits of lithium itself.”

While this mechanism proposed by Houle et al is hypothetically possible, we believe that it is quite unlikely, as the basic premises for it are probably false for the following reasons. First, the authors’ claim that “most patients receiving lithium therapy long term develop some level of chronic kidney disease” (without providing a reference to support this statement) is, at the very least, an overstatement. In fact, with modern serum-lithium and serum-creatinine–monitored lithium treatment, CKD is far from that common. Second, in a study published in JAMA Psychiatry in 2015, based on data from the sources also used for our recent study, Kessing et al reported that bipolar disorder itself is associated with CKD independent of drug treatment. Furthermore, not only the number of lithium prescriptions but also the number of anticonvulsant prescriptions were positively associated with development of CKD. Taken together, this suggests that the association between lithium treatment and CKD may in fact not be a result of lithium per se but rather a result of confounding by indication or bias. Third and finally, the positive association between the number of redeemed lithium prescriptions (proportional to defined daily dose) and the risk of CKD reported by Kessing et al directly counters this concluding statement from Houle et al regarding our study: “The finding in this article that patients receiving high defined daily dose of lithium had relatively lower risks of fracture may therefore reflect their lack of CKD rather than protective benefits of lithium itself.” For these reasons, we believe that the mechanism proposed by Houle et al can only play a negligible role (if any) in the cumulative dose-response–like association between lithium and reduced risk of osteoporosis observed in our study.

Ole Köhler-Forsberg, MD, PhD, DMSc
Christopher Rohde, MD
Søren Dinesen Østergaard, MD, PhD

Author Affiliations: Psychosis Research Unit, Aarhus University Hospital – Psychiatry, Aarhus, Denmark (Köhler-Forsberg); Department of Clinical Medicine, Aarhus University, Aarhus, Denmark (Köhler-Forsberg, Rohde, Østergaard); Department of Affective Disorders, Aarhus University Hospital – Psychiatry, Aarhus, Denmark (Köhler-Forsberg, Rohde, Østergaard).

Corresponding Author: Søren Dinesen Østergaard, MD, PhD, Department of Affective Disorders, Aarhus University Hospital – Psychiatry, Palle Juul-Jensens Boulevard 175, 8200 Aarhus N, Denmark (scoeoess@rm.dk).

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CORRECTION

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