We agree with the authors that these questions are pertinent and consistent with published literature, but unfortunately we did not assess these exposures in our study. Instead, we focused on the indoor environment. Our demonstration that administration to mice of airborne dust collected in Amish and Hutterite homes was sufficient to protect from or enhance experimental asthma, respectively, and result in immune profiles consistent with those seen in Amish and Hutterite children supports an important contribution of this environment to the different rates of asthma in these populations.

On the other hand, we have observed that unlike Amish children, young Hutterite children typically do not spend time near farm animals or in the barns, which are much larger and located at much greater distances from their homes than are Amish barns. We hypothesized, therefore, that Hutterite children are not exposed in early life to the asthma-protective factors that have been identified in the European epidemiologic studies of farming (farm animals, hay, and straw)\(^1\)\(^-\)\(^3\) and to which the Amish children are abundantly exposed. We directly tested this hypothesis by examining the effects of barn-dust extracts in a mouse model. Indeed, inhalation of Hutterite barn-dust extract was sufficient to inhibit house-dust mite-induced airway hyperresponsiveness, eosinophilia in the bronchoalveolar lavage (Fig. 1), and the elevation of house-dust mite–specific IgE levels (data not shown), and to induce neutrophilia in the bronchoalveolar lavage, as effectively as inhalation of Amish barn-dust extract. Hutterite barn-dust extract also conferred similar protection in an ovalbumin model (data not shown). Therefore, an environment with robust asthma-protective properties appears to exist within the Hutterite colonies, but Hutterite children are not exposed to this environment in early life.

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Initiation of Renal-Replacement Therapy in the Intensive Care Unit

To the Editor: In their report on the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial, Gaudry et al. (July 14 issue)\(^1\) provide evidence that the early initiation of renal-replacement therapy, as compared with delayed initiation, does not improve clinically relevant outcomes in critically ill patients with acute kidney injury. Their trial at last provides adequate power to draw definitive conclusions.

Here, we present the results of a meta-analysis of all nine randomized trials in which early initiation of renal-replacement therapy was compared with standard practice to treat critically ill patients with acute kidney injury. In the overall population, there was no significant difference in mortality among those receiving early renal-replacement therapy and those receiving delayed therapy, with deaths reported in 327 of 827 patients (39.5%) and in 338 of 899 (37.6%), respectively (P = 0.80) (Fig. 1A). In a subanalysis of five of those trials, there also was no significant between-group difference in the proportion of patients who survived with dependence on renal-replacement therapy, a finding that was reported in 17 of 685 patients (2.5%) receiving early renal-replacement therapy and in 23 of 697 (3.3%) receiving delayed therapy (P = 0.40) (Fig. 1B).

These findings support the conclusions of Gaudry et al. The data also indicate that the cost–benefit ratio probably does not justify the use of
new, expensive biomarkers for the early detection of acute kidney injury in critically ill patients.\(^2\)

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**Figure 1. Meta-Analysis of Nine Trials Comparing the Effects of Early versus Delayed Initiation of Renal-Replacement Therapy.**

Shown are odds ratios for death in nine randomized trials involving critically ill patients with acute kidney injury (Panel A) and odds ratios for survival with dependence on renal-replacement therapy in five of these trials (Panel B). The size of the data points is proportional to the number of patients in the study. In these analyses, the Cochran Q test was used to evaluate the hypothesis of statistical heterogeneity, with statistical significance set at the two-tailed 0.10 level. The extent of statistical consistency was measured by means of the \(\chi^2\) statistic, which was defined as \(100\times(Q−df)/Q\), in which Q denotes Cochran’s heterogeneity statistic and df the degrees of freedom. The Mantel–Haenszel method was used to analyze binary outcomes from individual studies to compute individual and pooled odds ratios and 95% confidence intervals, with a fixed-effects model in case of low statistical inconsistency (\(\chi^2\) statistic, \(≤25\%\)) and a random-effects model in case of moderate or high statistical inconsistency (\(\chi^2\) statistic, \(>25\%\)). All analyses were performed with the use of Review Manager, version 5.2 (Informer Technologies). AKIKI denotes Artificial Kidney Initiation in Kidney Injury, and ELAIN Early versus Late Initiation of Renal-Replacement Therapy in Critically Ill Patients with Acute Kidney Injury. A complete list of references for the cited studies is provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.
TO THE EDITOR: In the AKIKI trial, the investigators found no mortality difference for early versus delayed initiation of renal-replacement therapy for acute kidney injury. However, in the Early versus Late Initiation of Renal-Replacement Therapy in Critically Ill Patients with Acute Kidney Injury (ELAIN) trial, which was reported almost simultaneously with the AKIKI trial results, the investigators found a significant benefit for early initiation of renal-replacement therapy.1

The results of both trials are useful. First, a single-center design, such as that used in the ELAIN trial, tests a consistently applied technique, whereas a multicenter design, such as that used in the AKIKI trial, tests real-life use and may better define a general standard of care. The techniques and timing that are used at center A may not work well at center B. Second, medical patients made up 80% of the population in the AKIKI trial, whereas the patients in the ELAIN trial were nearly all surgical patients. Medical patients with greater complexity of coexisting illnesses may not benefit from the early initiation of renal-replacement therapy. However, the two studies excluded patients with a baseline estimated glomerular filtration rate of less than 30 ml per minute, which limits the applicability of the findings to patients with chronic renal failure who are having an acute episode.

Neither study reported details regarding the status of extracellular fluids. Both fluid overload and volume depletion increase mortality.2 This aspect should be addressed in future trials of renal-replacement therapy in critically ill patients.

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THE AUTHORS REPLY: The meta-analysis by Pasin et al. confirms the absence of difference with respect to mortality according to the timing of renal-replacement therapy among critically ill patients. The inability of neutrophil gelatinase-associated lipocalin values to discriminate between patients who should receive renal-replacement therapy and those who should not further attests to the current limited utility of biomarkers.3,2

We agree with Canaud and Cohen regarding the differences between the AKIKI and ELAIN trials.1 One of the most important differences is that the early-initiation group in the ELAIN trial consisted of patients with mild acute kidney injury (Kidney Disease: Improving Global Outcomes grade 2 [KDIGO 2]), and the delayed-initiation group consisted of those with more severe injury (KDIGO 3). Thus, the so-called delayed-initiation group in the ELAIN trial actually corresponds to the early-initiation group in the AKIKI trial.

Moreover, the delay in the initiation of renal-replacement therapy between strategies was under 24 hours in the ELAIN trial but more than 50 hours in the AKIKI trial. It is unclear why such a small delay in the timing of this therapy may have resulted in considerable decreases in both the duration of renal-replacement therapy and hospital stay (in favor of early initiation) in the ELAIN trial. Furthermore, the Kaplan–Meier analysis regarding mortality in the ELAIN trial shows that this small delay did not affect mortality at day 30 or day 60 but only at day 90, probably because more patients died between day 60 and day 90 in the delayed-initiation group than in the early-initiation group. The fragility index (a measure of the number of events on which statistical significance depends) may be very low and should be reported in studies involving critically ill patients.3 In the ELAIN trial, three fewer deaths in the early-initiation group would have resulted in a nonsignificant between-group difference in mortality (P=0.06 by Fisher’s exact test).

Finally, in contrast to the conduct of the AKIKI trial, decisions to withhold or withdraw treatments were not mentioned in the ELAIN trial. Such information may be very important in an open-label study involving critically ill patients with high death rates. Positive single-center studies are often contradicted by multicenter ones.4 We agree that we did not include patients with acute kidney injury and severe preexisting renal failure. In our experience, however, such patients are rare. We are in the process of analyzing our data with respect to fluid status.
TO THE EDITOR: Simsek Kiper et al. (June 30 issue) link Pyle’s disease to a deficiency of secreted frizzled-related protein 4 (sFRP4), a soluble Wnt inhibitor, and demonstrate its specific effects on cortical bone (which is unusually thin in persons with Pyle’s disease) versus trabecular bone (which is increased in persons with Pyle’s disease). In sFRP4-deficient mice, the inhibition of cortical bone formation, which determines bone strength at large, was shown to be mediated through bone morphogenetic protein (BMP)-dependent induction of sclerostin, a key Wnt inhibitor in bone. Given the small amount of trabecular bone in the mouse femur, are bone marrow–derived osteoblasts that are obtained from the femur indeed representative of trabecular bone? Second, did the authors assay levels of dickkopf 1 (Dkk1)? Dkk1 also inhibits Wnt and — like sclerostin — is a downstream target of BMP signaling. Therefore, Dkk1, in addition to sclerostin, may contribute to the suppression of bone formation. Moreover, blocking sclerostin increases the expression of Dkk1 in bone, which partially limits the bone-forming effects of sclerostin inhibition. Thus, Wnt signaling has multiple redundant safeguards to fine-tune bone formation. Therapeutically, this complexity may require the use of bispecific antibodies against more than one Wnt inhibitor to fully restore Wnt signaling, bone formation, and ultimately bone strength.

No potential conflict of interest relevant to this letter was reported.

2. Kamiya N, Kobayashi T, Mochida Y, et al. Wnt inhibitors Dkk1 and Sost are downstream targets of BMP signaling through the type IA receptor (BMPRIA) in osteoblasts. J Bone Miner Res 2010;25:200-10.

THE AUTHORS REPLY: We isolated bone marrow–derived osteoblasts from the femora and tibiae of mice that were 10 weeks old, an age at which both the femur and the tibia contain trabecular bone. It is well established that enhancement of canonical Wnt signaling is associated with increases in bone mass. Our studies clearly show that sFRP4 deficiency has a marked anabolic effect on trabecular bone in humans and mice. Given that trabecular bone resides in the marrow and that the properties of sFRP4-deficient bone marrow–derived osteoblasts (e.g., the Wnt canonical pathway — but not the noncanonical pathway — is activated in these cells) are consistent with the changes observed in trabecular bone (increased bone mass), we concluded that these cells better reflect the cellular activities in the trabecular bone compartment than do calvarial cortical osteoblasts. With regard to the second point, sFRP4 deficiency was associated with increased Dkk1 expression in both bone marrow–derived and calvarial osteoblasts (Fig. 1). This is not surprising: Dkk1 is a well-known canonical...