nationality, and underlying conditions associated with severe Covid-19. We provide several robustness checks in our article. In summary, there is robust evidence, both from our study and the Turkish study,[1] that this inactivated SARS-CoV-2 vaccine is highly effective against severe Covid-19 and related hospitalization and death.

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1. Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 2021;398:213-22.
2. Cifras oficiales: COVID-19. 2021 (https://www.gob.cl/coronavirus/cifrasoficiales/).
3. Blyth CR. On Simpson's paradox and the sure-thing principle. J Am Stat Assoc 1972;67:364-6.

DOI: 10.1056/NEJMc2112423

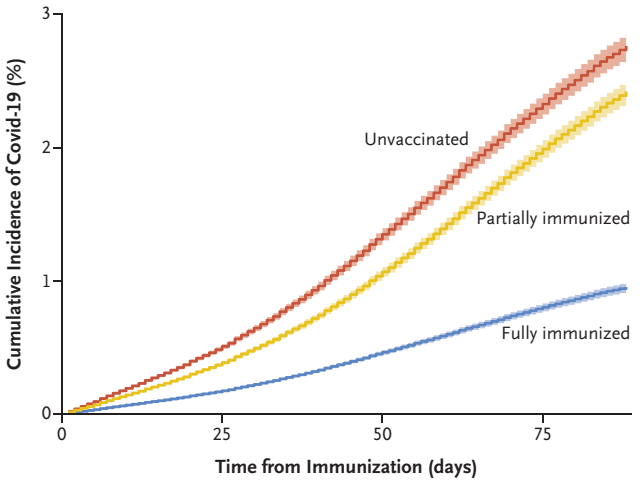


**Figure 1. Estimated Cumulative Incidence Curves for Symptomatic Covid-19 among Unvaccinated, Partially Immunized, and Fully Immunized Participants.**
Shown is a comparison of the cumulative incidence curves among unvaccinated, partially immunized (assessed ≥14 days after receipt of the first dose of the CoronaVac vaccine), and fully immunized participants (assessed ≥14 days after receipt of the second dose) in Chile from February 2 to May 1, 2021. The curves show the model estimates, with 95% pointwise confidence intervals (shaded areas), as evaluated in Chilean men, 60 to 69 years of age, who had a monthly income of $850 to $920 (in U.S. dollars), had one or more coexisting conditions, and resided in the Metropolitan Region, where the capital, Santiago, is located.

# Physical Rehabilitation in Patients with Heart Failure

**TO THE EDITOR:** In the Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial, Kitzman and colleagues (July 15 issue)[1] report the efficacy of an early, customized physical rehabilitation program in a cohort of frail patients hospitalized with heart failure. The trial emphasized the importance of nonpharmaceutical treatments in such patients, an approach that is often neglected in clinical routine.

However, some aspects of the study need to be considered when interpreting the results. First, only a minority of screened patients were able to participate in the rehabilitation program and underwent randomization. This factor along with a continuous decline in adherence raise doubts about the transferability of these measures to real-world practice. Second, unlike previous studies conducted in this context,[2] the REHAB-HF trial was not powered for hard clinical end points. Therefore, the results do not permit a conclusion regarding the clinical benefits and risks of the intervention. Since the causes of heart failure and the accompanying risks of cardiovascular events are highly heterogeneous in such patients,[3,4] clinical end points and safety issues have to be addressed in large, sufficiently powered trials.

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1. Kitzman DW, Whellan DJ, Duncan P, et al. Physical rehabilitation for older patients hospitalized for heart failure. N Engl J Med 2021;385:203-16.

2. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439-50.
3. Khan MS, Li L, Yasmin F, et al. Assessment of heterogeneity in heart failure-related meta-analyses. Circ Heart Fail 2020;13(11):e007070.
4. Iorio A, Pozzi A, Senni M. Addressing the heterogeneity of heart failure in future randomized trials. Curr Heart Fail Rep 2017;14:197-202.

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**TO THE EDITOR:** Kitzman et al. report promising results from an intervention involving early physical rehabilitation in older adults hospitalized with acute heart failure. The authors observed significantly increased scores on the Short Physical Performance Battery (SPPB) in the intervention group as compared with the control group.

Among the patients, who were assessed for frailty status according to the modified Fried criteria,[1] both frailty and "prefrailty" were highly prevalent, occurring in 97% of the participants. However, no mention was made of the possible presence of sarcopenia, the age-related loss of muscle mass and function. Although closely related, frailty and sarcopenia are not identical. Sarcopenia can be viewed as a biologic substrate of physical frailty.[2] Moreover, the concept of frailty involves more than physical frailty alone.

The patients' scores on the chair rise test imply low muscle strength, which is considered to be the primary determinant of sarcopenia, according to recent diagnostic criteria,[3] an observation that encourages further evaluation of muscle mass and quality and of physical performance. Moreover, recent research has shown that SPPB scores of 8 or less may be diagnostic of severe sarcopenia.[4] Accordingly, a sarcopenia workup would be welcomed in this study, since the demonstrated effects of physical rehabilitation could be the result of treating the underlying sarcopenia.

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1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-M156.
2. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet 2019;393:2636-46.
3. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
4. Phu S, Kirk B, Bani Hassan E, et al. The diagnostic value of the Short Physical Performance Battery for sarcopenia. BMC Geriatr 2020;20:242.

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**THE AUTHORS REPLY:** The trial inclusion criteria were purposefully broad and the exclusion criteria purposefully narrow in order to enhance generalizability. Among the patients who appeared to have preliminary eligibility on electronic screening, 349 of 410, or 85%, consented to participate in the trial and underwent randomization. These numbers support the generalizability of the findings and the potential uptake of the intervention. The misperception of a lower rate of inclusion is understandable, because in contrast with most trials, we included in our CONSORT diagram any patient whose record was "touched" in any way, including by means of automated electronic screening algorithms. For example, 7261 patients were ineligible because heart failure was not the reason for the index hospitalization.

Adherence to the intervention was excellent. Excluding deaths and medical appointments or events, adherence during the 3-month intervention was 78%. Furthermore, at 6-month follow-up, 83% of participants reported regular exercise, suggesting behavioral change, a requisite for long-term adherence. These adherence rates in frail patients with acute heart failure are higher than those in previous trials involving exercise interventions in patients with chronic heart failure (HF-ACTION trial, approximately 40%)[1] and those with acute heart failure (EJECTION-HF trial, approximately 43%).[2] This supports the efficacy of our comprehensive adherence strategy.

We agree with the comments from Dupont and colleagues. We have shown that older patients with heart failure, particularly those with heart failure with preserved ejection fraction, have multiple skeletal muscle abnormalities, including sarcopenia, which contribute to their severe physical dysfunction, and that the improvements in function following exercise inter-

ventions are primarily due to improved skeletal muscle function.[3]

We agree with Brunner regarding heterogeneity of the patients with heart failure in our trial. Notably, patients with preserved ejection fraction and those with reduced ejection fraction were included in the trial. We recently reported that among these two phenotypes, the participants with heart failure with preserved ejection fraction had significantly worse physical dysfunction and frailty at baseline and appeared to receive much greater benefit from the intervention, including benefit in terms of improved physical functioning and quality of life and lower rates of frailty, rehospitalization, and death.[4]

Although the outcomes in our trial are clinically meaningful, we agree that a larger trial, adequately powered for clinical events and safety, will be needed to effect change in clinical practice and reimbursement. Ideally, such a trial would focus on patients with heart failure with preserved ejection fraction, given their worse baseline status, greater response to the intervention, and limited treatment options as compared with those with heart failure with reduced ejection fraction.

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1. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439-50.
2. Mudge AM, Denaro CP, Scott AC, et al. Addition of supervised exercise training to a post-hospital disease management program for patients recently hospitalized with acute heart failure: the EJECTION-HF randomized phase 4 trial. JACC Heart Fail 2018;6:143-52.
3. Kitzman DW, Haykowsky MJ, Tomczak CR. Making the case for skeletal muscle myopathy and its contribution to exercise intolerance in heart failure with preserved ejection fraction. Circ Heart Fail 2017;10(7):e004281.
4. Mentz RJ, Whellan DJ, Reeves GR, et al. Rehabilitation intervention in older patients with acute heart failure with preserved versus reduced ejection fraction. JACC Heart Fail 2021 June 29 (Epub ahead of print).

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## Targeted Temperature Management after Cardiac Arrest

**TO THE EDITOR:** After the first trial involving targeted temperature management (TTM),[1] the guidelines called for a temperature between 32°C and 36°C in comatose patients following out-of-hospital cardiac arrest.[2] The authors of the TTM2 trial[3] are to be congratulated in determining that there was no significant difference in outcomes whether hypothermia or normothermia (with fever avoidance) was targeted. We wonder, however, about the generalizability of the TTM2 cohort in which 75% of patients had shockable rhythms, 90% had cardiac arrests, and 80% received bystander-initiated cardiopulmonary resuscitation (CPR). Outcomes following cardiac arrest are known to be superior in persons with shockable rhythms[4]; bystander-initiated CPR is associated with an increase in survival that is three times as high as that without it.[5] Unfortunately, recent European data indicate that only 20% of persons in cardiac arrest have a shockable rhythm, that 58% of such persons receive bystander-initiated CPR (with rates as low as 13% in some locations), and that the rate of survival to hospital discharge is only 8%.[4] Indeed, we wonder whether any intervention strongly affected the outcome in the setting of the TTM2 trial, which benefited from excellent local responses that may be unobtainable in most communities.

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1. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197-206.
2. Nolan JP, Sandroni C, Böttiger BW, et al. European Resusci-