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RESEARCH

Association between heart failure in asymptomatic stages and skeletal muscle function assessed by ultrasonography in community-dwelling older adults

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Abstract

Background Symptomatic heart failure (HF) negatively affects the quantity and quality of skeletal muscles. However, the association between asymptomatic HF and skeletal muscle function remains unclear. We aimed to use ultrasonography to elucidate the association between asymptomatic HF and skeletal muscle function in community-dwelling older adults.

Methods This cross-sectional study comprised community-dwelling older adults aged ≥ 60 years who could perform activities of daily living independently and had never had symptomatic HF ($n = 52$, 76.3 ± 6.1 years). The participants were classified into three groups namely, non-HF ($n = 26$), stage A ($n = 19$), and stage B ($n = 7$) according to the HF stage criteria of the American Heart Association /American College of Cardiology /Heart Failure Society of America guideline. Skeletal muscle quantity and quality were assessed using ultrasonography (thickness and echo intensity) of the rectus femoris (RF) and vastus intermedius (VI) muscles. The group effects on muscle thickness and echo intensity in each group were assessed using a multivariate analysis.

Results Both muscles consistently demonstrated significant group effects on the thickness and echo intensity. Thicknesses of the RF ($p = 0.020$) and VI ($p = 0.035$) were lower in the stage B group than that in the non-HF group. The echo intensities in the RF ($p = 0.006$) and VI ($p = 0.009$) were higher in the stage B group than that in the non-HF group.

Conclusion Asymptomatic HF negatively associated with the characteristics of skeletal muscle function, as assessed by ultrasonography in community-dwelling older adults. The stage B HF contributes to reduced skeletal muscle function as well as symptomatic HF.

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Keywords Asymptomatic, Heart failure, Skeletal muscle, Ultrasonography, Echo intensity, Community-dwelling older adults

Background

With the aging population, the number of patients with heart failure (HF) has been steadily increasing worldwide [1–3]. Moreover, the average age of HF onset has been increasing [3, 4]. Approximately 35 – 45% of older adults with HF often report a loss of skeletal muscle mass and strength, also termed as sarcopenia [5, 6]. Furthermore, sarcopenia [5, 7] and skeletal muscle quantity [8, 9] and quality [10] are the independent prognostic factors for patients with HF. Accordingly, clinicians should detect the loss of skeletal muscle function at an earlier stage and suppress or prevent its progression.

By contrast, the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guideline for the management of HF defines four stages (A to D) that emphasize the development and progression of the disease [11]. The early asymptomatic stages are considered "at-risk for HF" (stage A) and "pre-HF" (stage B). Subsequently, the patients progresses to "symptomatic HF" (stage C) and "advanced HF" (stage D), without reversal. Previous reports have not clarified the characteristics of skeletal muscles at each stage of HF. Particularly, the changes in the mass and quality of skeletal muscle in community-dwelling older adults with stage A and B asymptomatic HF are unclear. Inflammation and metabolic abnormalities are important intervening factors in the mechanism underlying skeletal muscle dysfunction in patients with HF [12, 13]; thus, dysfunction may occur even in community-dwelling older adults with asymptomatic HF.

In clinical and community settings, skeletal muscle function is assessed widely using ultrasonography, which is safe, inexpensive, and time-efficient [9, 14–18]. Yamada et al. demonstrated the potential muscle quality and quantity indicators for diagnosing sarcopenia using ultrasonography; the muscle thickness and echo intensity are useful indicators of the muscle mass and function, respectively [18].

Therefore, we aimed to elucidate the characteristics of skeletal muscles assessed using ultrasonography in community-dwelling older adults with stages A and B HF.

Methods

Study design and participants

This cross-sectional survey was conducted among community-dwelling older adults aged≥60 years. The participants were recruited through advertisements in local newspapers and through public recruitment in Oamishirasato City, Japan. The inclusion criteria were as follows: (i) able to communicate in Japanese and (ii) displayed sufficient cognitive and motor functions to complete a self-administered questionnaire. The participants who did not agree to participate or those with a history of acute HF were excluded from the study. This study was conducted in accordance with the guidelines of the Declaration of Helsinki. The research protocol was reviewed and approved by the Ethics Committee of Edogawa Hospital (approval number: 2020-34).

Measurement of muscle thickness and echo intensity

An ultrasound device (Miruco; NIPPON SIGMAX Co., Ltd., Tokyo, Japan) with a 10-MHz linear probe ultrasonic diagnostic system was used to collect ultrasound images of the thigh muscle. Muscle thickness and echo intensity were evaluated as described by Yamada et al. [18]. The participants were placed supine in a completely relaxed position, and a trained examiner placed the probe midway between the anterior superior iliac spine and the proximal end of the patella. An ultrasonographer scanned the subcutaneous adipose tissue, rectus femoris (RF), vastus intermedius (VI), and femur at this site. The ultrasound images recorded in the two trials were averaged as the representative images for analysis. These images were stored on an ultrasound device as a Joint Photographic Expert Group (JPEG) file. The thigh muscle thickness and echo intensity were assessed using a JPEG file. The echo intensity was calculated by 8-bit gray-scale analysis using Adobe Photoshop Elements (Adobe Systems, Inc., San Jose, CA, USA). The regions of interest (ROI) included maximum skeletal muscle without any bone or surrounding fascia. The mean echo intensity of the ROI is expressed as a value ranging from 0 (black) to 255 (white). The echo intensity of the quadriceps femoris was calculated as the mean echo intensity of the rectus femoris and the vastus intermedius. Muscle thickness was measured using an electronic scale on a JPEG file viewer in Adobe Photoshop Elements. We defined thickness of the rectus femoris muscle as the distance between the subcutaneous fascia and the deep aponeurosis. Similarly, we defined muscle thickness of the vastus intermedius as the distance between the aponeurosis and the bone-muscle interface. The quadriceps femoris muscle thickness was obtained as the sum of the rectus femoris and vastus intermedius thicknesses. These analyses were performed by a single investigator trained in the surgical technique for an ultrasound image analysis.

HF stages and other parameters

We investigated the HF stages and other parameters, such as the age, sex, height, weight, body mass index

(BMI), comorbidities, and physical frailty. The participants were interviewed using a questionnaire (Table S1) regarding the presence of underlying medical conditions and were classified into three groups, non-HF, stage A, and stage B according to the HF stage criteria of the AHA/ACC/HFSA guidelines [11]: the non-HF comprises individuals without any of the risk factors for HF in the current medical conditions.; the stage A comprises individuals at risk for HF but without current or previous symptoms / signs of HF and without structural / functional heart disease; the stage B comprises individuals with structural heart disease but without overt signs or symptoms of HF. Physical frailty was assessed using the revised Japanese version of the Cardiovascular Health Study criteria, which defines a score of 0 as robust, 1 to 2 as physical pre-frailty, and ≥3 as frailty [19]. In addition, we assessed the following secondary indices of skeletal muscle function: skeletal muscle mass index (SMI) using a bioelectrical impedance data acquisition system (InBody S10; Inbody Japan Inc., Tokyo, Japan) [18] and knee extension strength using a hand-held dynamometer (μ-Tas MT-1; ANIMA, Tokyo, Japan) [18].

Statistical analysis

Data are expressed as mean±standard deviation (SD) for normally distributed variables and as median with interquartile range for non-normally distributed data. Categorical data are expressed as numbers and percentages. We performed a one-way analysis of variance, followed by the Tukey's post-hoc test and chi-square test to compare characteristics among the three groups.

Regarding the main analysis, we used an analysis of covariance (ANCOVA) adjusted for the generalized propensity score [20] to assess the group effects on the muscle thickness and echo intensity in each muscle. The generalized propensity score was calculated using the age, sex, and BMI. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P<0.05$ all analysis.

Results

Participant characteristics

Table 1 presents the characteristics of the participants. Fifty-two participants were divided into the non-HF ($n=26$), stage A ($n=19$), and stage B ($n=7$) groups. Their mean age was 76.3±6.1 years, without significant differences among the groups. The complication rate of diabetes mellitus was approximately 15% for both stages A and B. The complication rates of dyslipidemia ($p=0.023$), hypertension ($p<0.001$), and orthopedic disease ($p=0.047$) differed among the groups, both of which tended to be higher in stage A group than in other

Table 1 Characteristics

	Overall	Non-HF	Stage A	Stage B	*P* value
	***n*=52**	***n*=26**	***n*=19**	***n*=7**	
Age (years)	76.3 ± 6.1	74.6 ± 5.3	77.6 ± 7.0	78.7 ± 5.8	0.140
Sex (male, %)	11.5	11.5	5.3	28.6	0.256
Height (cm)	152.2 ± 7.2	152.6 ± 7.3	150.5 ± 6.2	155.1 ± 9.3	0.324
Weight (kg)	53.6 ± 8.4	52.3 ± 7.9	54.0 ± 7.8	57.7 ± 11.4	0.316
BMI	23.1 ± 3.0	22.4 ± 2.9	23.8 ± 3.3	23.8 ± 2.3	0.256
Comorbidities (%)					
Orthopedic disease	19.2	7.7	36.8	14.3	0.047
Diabetes	7.7	0	15.8	14.3	0.114
Dyslipidemia	11.5	0	26.3	14.3	0.023
Hypertension	36.5	0	84.2	42.9	< 0.001
Stroke	3.8	3.8	5.3	0	0.826
Osteoporosis	3.8	0	5.3	14.3	0.201
Cancer	5.8	0	10.5	14.3	0.190
Frailty status* (%)					
Robust	48.1	65.4	42.1	0	0.039
Pre-frailty	46.2	30.8	52.6	85.7	
Frailty	5.8	3.8	5.3	14.3	
Revised J-CHS criteria components					
Shrinking	3 (5.8)	2 (7.7)	1 (5.3)	0 (0)	0.736
Weakness	7 (13.5)	2 (7.7)	4 (21.1)	1 (14.3)	0.430
Exhaustion	12 (23.1)	4 (15.4)	4 (21.1)	4 (57.1)	0.064
Slowness	6 (11.5)	9 (33.3)	2 (10.5)	2 (28.6)	0.303
Low activity	16 (30.8)	8 (31.3)	7 (36.8)	4 (57.1)	0.120

* Evaluated by the revised J-CHS criteria

BMI, body mass index; J-CHS, Japanese version of the Cardiovascular Health Study groups. The frailty status differed among the groups ($p=0.039$). Few participants in all groups demonstrated frailty; however, the proportion of participants with pre-frailty increased with the HF stage, with >85% in the stage B group.

Differences in each skeletal muscle indicator by the HF stage

Table 2 summarizes the differences in each skeletal muscle indicator according to the HF stage. Significant differences were observed between the HF stages for all indicators. The RF thickness was thinner in the stage B group than that in the non-HF group ($p=0.016$). The thickness in the stage B group was thinner than that in the stage A group ($p=0.043$). The VI thickness ($p=0.017$) and SMI ($p=0.003$) were significantly thinner in group B than that in the non-HF group. Both the RF ($p=0.001$) and VI ($p=0.004$) echo intensities were higher in the stage B group than those in the non-HF group. RF ($p=0.033$) and VI ($p=0.014$) echo intensities in the stage B group were higher than those in the stage A group (Fig. 1). In addition, the knee extension strength was significantly lower in the stage A ($p=0.025$) and B ($p=0.002$) groups than that in the non-HF group.

Association between the HF stage and muscle thickness or echo intensity

Table 3 summarizes the ANCOVA results, which verified the relationship between the HF stage and the RF and VI muscle thicknesses. For both RF ($p=0.02$) and VI ($p=0.035$) muscles, the stage B group demonstrated lower muscle thickness values than the non-HF group. Table 4 summarizes the results that verify the relationship between the HF stage and the RF and VI echo intensities. For both RF ($p=0.006$) and VI ($p=0.009$) muscles, the stage B group demonstrated higher echo intensity values than the non-HF group. As a secondary analysis, participants were classified into active group and non-active groups based on the presence or absence of low activity, a subcomponent of the revised J-CHS criteria, in order to determine the effect of participant activity on each skeletal muscle index. The participants were classified into active group and non-active group, respectively. The values of each skeletal muscle index were then compared between the groups. The Results showed that only knee extension strength was significantly higher in the active group compared to the non-active group ($p=0.011$), and there was no difference in the muscle thickness and echo intensity (Table S2).

Discussion

Our primary findings were as follows: (1) Asymptomatic HF negatively associated with the characteristics of skeletal muscle function, as assessed by ultrasonography in community-dwelling older adults; (2) the stage B group demonstrated significantly lower values of muscle thickness and higher values of echo intensity than that in the non-HF group.

Skeletal muscle quantity and quality affect the prognosis and physical function of the patients with HF [7, 21]. In addition, the patients with asymptomatic HF report reduced quantity and quality of skeletal muscle, compared with healthy individuals. The assessment of skeletal muscle function in patients with symptomatic HF is an important part of the pathophysiological evaluation [12, 13]. However, no studies have examined the mechanism by which the stage A or B HF and asymptomatic HF affect the skeletal muscle function. This study provides novel evidence that stage B HF significantly reduces the skeletal muscle thickness and increases echo intensity. Our results necessitate paying attention to the risk of skeletal muscle dysfunction from asymptomatic HF, i.e., stage B HF.

It was difficult to determine the detailed mechanisms underlying these results; however, the following possibilities are based on previous studies. Potential risk factors for HF from the asymptomatic stage may induce skeletal muscle dysfunction. Furthermore, potential risk factors

Table 2 Difference of each skeletal muscle indicator in older adults according to heart failure stage

	Overall	**Non-HF**	**Stage A**	**Stage B**	***P* value***
	***n*=52**	***n*=26**	***n*=19**	***n*=7**	
Quantity					
RF thickness, cm	1.63 ± 0.34	1.70 ± 0.31	1.65 ± 0.33	1.31 ± 0.33†¶	0.020
VI thickness, cm	1.33 ± 0.37	1.46 ± 0.42	1.26 ± 0.24	1.04 ± 0.27†	0.013
SMI, kg/m^2	6.01 ± 0.82	6.28 ± 0.75	5.95 ± 0.72	5.17 ± 0.78‡	0.004
Quality					
RF echo intensity	101.5 ± 17.1	95.6 ± 13.6	102.7 ± 15.4	120.2 ± 21.0‡¶	0.002
VI echo intensity	54.7 ± 20.5	50.2 ± 13.5	52.6 ± 16.1	77.1 ± 37.0‡¶	0.006
Knee extension strength, Nm/kg	0.44 ± 0.16	0.51 ± 0.14	0.40 ± 0.14†	0.29 ± 0.15‡	0.001

*A result of one-way analysis of variance

†, $p<0.05$ vs. Non-HF; ‡, $p<0.01$ vs. Non-HF; ¶, $p<0.05$ vs. Stage A for post hoc test

HF, heart failure; RF, rectus femoris muscle; SMI, skeletal muscle mass index; VI, vastus intermedius muscle

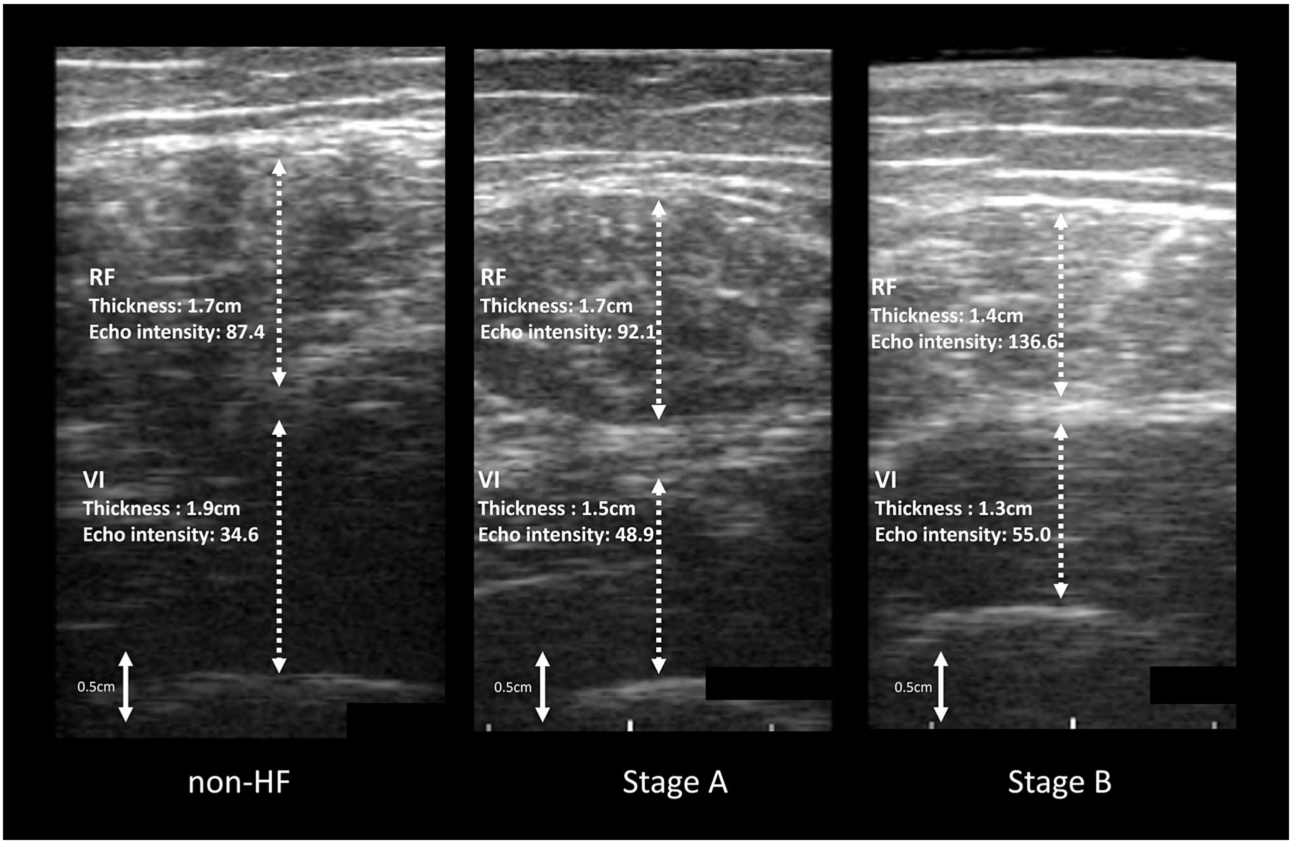

Fig. 1 Representative ultrasonographic images for the thigh muscle in each group. HF, heart failure; RF, rectus femoris muscle; VI, vastus intermedius muscle

Table 3 Association between heart failure stage and muscle thickness

HF stage	RF thickness				VI thickness			
	Std. β	B	(95% CI)	*P* value *	Std. β	B	(95% CI)	*P* value *
Non-HF	ref.				ref.			
Stage A	–0.02	–0.02	(–0.23 – 0.20)	0.882	–0.24	–0.18	(–0.41 – 0.04)	0.111
Stage B	–0.36	–0.36	(–0.65 - – 0.06)	0.02	–0.32	–0.34	(–0.66 - – 0.03)	0.035

*A result of ANCOVA adjusted for generalized propensity score calculated using age, sex and BMI

Abbreviation: HF, heart failure; RF, rectus femoris muscle; VI, vastus intermedius muscle

Table 4 Association between heart failure stage and echo intensity

HF stage	RF echo intensity				VI echo intensity			
	Std. β	B	(95% CI)	*P* value *	Std. β	B	(95% CI)	*P* value *
Non-HF	ref.							
Stage A	0.17	6.11	(−3.26–15.48)	0.196	0.05	2.3	(−9.78–14.38)	0.703
Stage B	0.38	18.91	(5.80–32.02)	0.006	0.38	22.74	(5.85–39.64)	0.009

*A result of ANCOVA adjusted for generalized propensity score calculated using age, sex and BMI

Abbreviation: HF, heart failure; RF, rectus femoris muscle; VI, vastus intermedius muscle

for HF, abnormal glucose metabolism, hypertension, and dyslipidemia induce elevated oxidative stress and inflammatory responses, suggesting that they may influence the skeletal muscle mass loss and increase ectopic fat [22]. In addition, these intervening factors are part of a pathway that reduces skeletal muscle function in patients with symptomatic HF [12, 13]. However, reduced skeletal muscle function leads to increased insulin resistance and decreased fatty acid metabolism and physical activity [23, 24]. Thus, the role of reduced skeletal muscle function in the development of each disease cannot be ruled out. Therefore, researchers should examine the relationship between HF stage progression and changes in the skeletal muscle function through longitudinal studies.

The strength of this study lies in the use of ultrasonography, a feasible method for assessing skeletal muscles in a wide range of clinical settings. It facilitated determining the association between asymptomatic HF and skeletal muscle properties. Echo intensity, used to assess the skeletal muscle quality, is correlated strongly with the percentages of intramuscular adipose and connective tissues assessed using muscle biopsy [25] and magnetic resonance imaging (MRI) [15]. Intermuscular fat mediates mitochondrial dysfunction within the skeletal muscles by promoting insulin resistance [26]. Furthermore, Nakano et al. mentioned that higher echo intensity in the skeletal muscle is associated with lower peak exercise oxygen uptake in patients with HF [21]. Thus, an echo intensity assessment may facilitate evaluating the skeletal muscle function, which is an important determinant of physical function. Particularly, it is difficult to assess the risk of skeletal muscle dysfunction in community-dwelling individuals with asymptomatic HF using methods, such as muscle biopsy and MRI owing to limitations in the testing environment, cost, and time. Furthermore, skeletal muscle assessment using ultrasonography may be a feasible alternative.

The present study has some limitations. First, we performed a small cross-sectional study; thus, the study population may not reflect the characteristics of the general population of Japanese community-dwelling older adults. Second, the skeletal muscle function was assessed at only one time point; therefore, the status of the skeletal muscle before the development of asymptomatic HF was unknown. This warrants a long-term longitudinal study to clarify the causal association between asymptomatic HF and skeletal muscle dysfunction and to examine the relationship between HF stage progression and changes in skeletal muscle function. Third, in the present study, the HF stage classification was performed based on information on medical conditions obtained through a questionnaire, and was not supported by supplementary assessment such as echocardiography or blood biochemistry data. Therefore, it is possible that such information was influenced by biases such as participants' memory and comprehension, and it cannot be denied that false positives and false negatives in the HF stage classification occurred. Finally, because the echo intensity attenuates with depth, the evaluated skeletal muscles were limited to the superficial muscles of the thighs. Therefore, it is unclear whether these muscles have characteristics similar to those of others.

Conclusion

The asymptomatic HF negatively associated with the characteristics of skeletal muscle function, as assessed by ultrasonography in community-dwelling older adults. The stage B HF contributes to reduced skeletal muscle function as well as symptomatic HF. To clarify these causal relationships, researchers should investigate the relationship between HF progression and changes in skeletal muscle function, longitudinally.

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
ANCOVA	Analysis of covariance
BMI	Body mass index
HF	Heart failure
HFSA	Heart Failure Society of America
JPEG	Joint Photographic Expert Group
MRI	Magnetic resonance imaging
RF	Rectus femoris
ROI	Regions of interest
SD	Standard deviation
SMI	Skeletal muscle mass index
VI	Vastus intermedius

Supplementary Information

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Supplementary Material 1

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Author contributions

TS and AI contributed to the conception or design of the work. TS, YK, TK, MS, IK, YA, DS, WS, NI and AI contributed to the acquisition, analysis, or interpretation of data for the work. TS drafted the manuscript. YK, TK, MS, IK, YA, DS, WS, NI and AI critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The research protocol was reviewed and approved by the Ethics Committee of Edogawa Hospital (approval number: 2020-34). Written informed consent was obtained from all subjects. This study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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