Angiotensin-Converting Enzyme Inhibitor Use and Incident Frailty in Women Aged 65 and Older: Prospective Findings from the Women's Health Initiative Observational Study

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OBJECTIVES: To examine the associations between current use, duration, and potency of angiotensin-converting enzyme (ACE) inhibitors and incident frailty in women aged 65 and older who were not frail at baseline.

DESIGN: Data were from the Women's Health Initiative Observational Study (WHI-OS), a prospective study conducted at 40 U.S. clinical centers.

PARTICIPANTS: Women aged 65 to 79 at baseline who were not frail (N = 27,378).

MEASUREMENTS: Current ACE inhibitor use was ascertained through direct inspection of medicine containers at baseline. Components of frailty were self-reported low physical function or impaired walking, exhaustion, low physical activity, and unintended weight. Frailty was ascertained through self-reported and physical measurements data at baseline and 3-year clinic contacts.

RESULTS: By the 3-year follow-up, 3,950 (14.4%) women had developed frailty. Current ACE inhibitor use had no association with incident frailty (multivariate adjusted odds ratio = 0.96, 95% confidence interval = 0.82–1.13). Duration and potency of ACE inhibitor use were also not significantly associated with incident frailty. A similar pattern of results was observed when incident cardiovascular disease events were studied as a separate outcome or when the sample was restricted to subjects with hypertension.

CONCLUSION: Overall, incidence of frailty was similar in current ACE inhibitor users and nonusers. **J Am Geriatr Soc 57:297–303, 2009.**

Key words: ACE inhibitor use; frailty; disability; Women's Health Initiative

In geriatric medicine, the term "frailty" has been used loosely to describe a condition characterized by vulnerability to stressors because of impairment in physiological reserve, leading to risk of adverse health outcomes.[1] The past several years have witnessed progress in moving toward a standard and measurable conceptualization of frailty. Definitions have varied, but frailty phenotypes in recent epidemiological studies have typically included muscle weakness, fatigue, slowness, low physical activity, and unintended weight loss.[2,3] Increasing evidence suggests a relationship between inflammation and risk of disability, frailty, walking speed, and muscle strength.[4–6]

The renin angiotensin system (RAS) is involved in skeletal muscle structure and function and may play a role in the development of physical disability.[7] Angiotensin-converting enzyme (ACE) inhibitors are medications that inhibit the conversion of angiotensin I to angiotensin II, components of the RAS. ACE inhibitor use decreases morbidity and mortality in patients with heart failure. In addition, ACE inhibitor use reduces physical disability in patients with heart failure,[8] most likely because of improvements in cardiovascular function. Even more intriguing are data from epidemiological studies that suggest that ACE inhibitor use is associated with beneficial effects on physical performance and components of the frailty syndrome in people without heart failure. Use of ACE inhibitors in older

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adults with hypertension resulted in positive effects on muscle strength, walking speed, and lower extremity muscle mass.[9,10] A recent randomized controlled trial found that 6 months of treatment with perindopril in older adults who had mobility or functional impairments improved walking capacity at 6 months.[11]

Evidence suggests that ACE inhibitors may have anti-inflammatory effects,[12,13] which may in part be responsible for these beneficial effects. ACE inhibitors were listed as potential targets for prevention of frailty in a recent Research Agenda on Frailty in Older Adults developed by the American Geriatrics Society and the National Institute on Aging.[14] The objective of the current article was to examine whether use of ACE inhibitors at baseline was associated with less incident frailty over 3 years in nonfrail women aged 65 and older in the Women's Health Initiative Observational Study (WHI-OS).

METHODS

Study Sample

This study used data from the WHI-OS, a prospective study of 93,676 women aged 50 to 79 recruited from 1993 to 1998 from 40 clinical centers in the United States. Women were eligible for study inclusion if they were postmenopausal, unlikely to relocate or die within 3 years, and not enrolled in any of the WHI clinical trials. Further details regarding the design, recruitment strategy, and data collection methods have been published.[15] Human subjects review committees at each participating institution reviewed and approved the study.

This analysis included women aged 65 to 79 who were not frail at baseline (N = 35,902). Women were excluded if they reported at baseline a diagnosis or disease that manifests as frailty (Parkinson's disease, congestive heart failure, stroke, or use of antidepressant medications; n = 2,710) or did not have health insurance (n = 374). Women were also excluded if they died before the 3-year follow-up visit (n = 799) or if information was missing on one of the frailty components (n = 4,641), as described below, leaving a sample of 27,378.

Measurement and Classification of Frailty

The frailty phenotype developed in the WHI cohort was based on criteria previously used[2] and has been found to be strongly associated with future mortality, disability, hospitalization, and hip fracture in older women in the WHI-OS.[3] The components are as follows:

(1) *Muscle weakness or slowness* was measured using the Rand-36 Physical Function Scale (range 0–100). A score in the lowest quartile of this scale was highly associated with measured slow walking speed and low grip strength in the WHI Clinical Trial.[3] To align the scoring with the frailty measure developed by Fried et al.,[2] if a participant met the threshold for frailty on this criterion (e.g., had poor physical function), they received 2 points because this scale measured the muscle strength and walking speed components.

(2) *Exhaustion* was measured using the Rand-36 Vitality Scale (range 0–100) using four items pertaining to the previous 4 weeks: "Did you feel worn out? tired? or full of pep? Did you have a lot of energy?"

(3) *Low physical activity* was classified using a questionnaire that assessed the frequency and duration of four speeds of walking and activities in the prior week.[16,17] Kilocalories of energy expended in 1 week on leisure time activity was calculated (metabolic equivalent score = kcal/wk × kg).[18]

(4) *Shrinking*, or unintentional weight loss, was defined as *unintentional* weight loss of more than 5% of body weight in the previous 2 years, based on measured weight at the baseline and 3-year clinic visits in combination with a self-reported item on whether recent weight loss was intentional at the 3-year follow-up.

A frailty component was classified as present if the participant had a score in the lowest quartile of the distribution for that component or had unintentional weight loss. Participants were classified as frail ($\geq$3 points), prefrail (1 or 2 points), or not frail (0 points).[2,3]

ACE Inhibitor Exposure

WHI participants were asked to bring all current medications taken regularly to their first screening interview. Clinic interviewers entered each medication name and strength directly from the containers into a database that assigned drug codes using Medi-Span software (First DataBank, Inc., San Bruno, CA). Women reported duration of use for each current medication. A woman was categorized as a user or nonuser of an ACE inhibitor based on the medication inventory at screening. Participants could be taking other antihypertensives. Duration of use was categorized as less than 2 years, 2 to 5 years, or 5 or more years. Information on tablet strength, but not prescribed dose, was available.

To examine dose effect, strength of the tablet was used as a proxy to define an equivalent "dose" for the ACE inhibitors. One unit of equivalent dose was based on lisinopril 10 mg (enalapril 10 mg, benazapril 10 mg, quinapril 10 mg, ramipril 2.5 mg, fosinopril 10 mg, trandolapril 2 mg, captopril 50 mg). Low equivalent dose was defined as less than 1 standardized unit, medium equivalent dose as 1 standardized unit, and high equivalent dose as greater than 1 standardized unit.

Other Covariates

Data on demographic (race or ethnicity, age, family income, education, living arrangement), health behavior characteristics, and medical history were obtained according to self-report at baseline. Alcohol consumption was estimated from a food-frequency questionnaire. Smoking was classified as current, past, or never. Level of physical activity (above the range indicating frailty) was measured in kcal of energy expenditure. Body mass index (BMI) was defined using measured height and weight at baseline as weight (kg) divided by height (m^2). Current use of calcium channel blockers, beta-blockers, diuretics, and statins was ascertained at baseline. Information was collected on duration of previous use of postmenopausal hormone therapy (HRT), which was defined as current, past, or never use of any estrogen with or without progestin.

Medical conditions at baseline included self-reported physician diagnosis of arthritis, treated diabetes mellitus (oral medication or insulin), hypertension (taking hypertensive medication or blood pressure >140/90 mmHg), and cancer. Participants were considered to have a history of coronary heart disease (CHD) if they self-reported a physician diagnosis of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft or percutaneous transluminal coronary angioplasty procedures (CABG/PTCA). Incident cardiovascular outcomes included clinical MI, definite and possible CHD death, angina pectoris, CABG/PTCA, carotid artery disease, heart failure, and stroke. These events were ascertained initially according to annual self-report and confirmed through medical records that local clinic physicians and then a panel of central adjudicators reviewed and adjudicated.[19] Depressive symptoms were assessed using a six-item short form[20] of the Center for Epidemiologic Studies Depression Scale.

Statistical Analysis

Baseline characteristics were compared for women according to baseline ACE inhibitor use using chi-square tests for heterogeneity for categorical variables and *t*-tests for continuous variables. Multinomial logistic regression models were used to examine associations between ACE inhibitor use (current use, duration, equivalent dose) and incident frailty, adjusting for important confounding factors. The models adjusted for independent predictors of incident frailty identified in a previous report[3] and variables significantly associated with exposure in the bivariate analyses: age, income, education, ethnicity, whether a participant lived alone, BMI, smoking, alcohol, physical activity, HRT use, self-reported health, treated diabetes mellitus, depressive symptoms, arthritis, history of cancer, history of CHD (MI, angina pectoris, CABG/PTCA), systolic blood pressure, diastolic blood pressure, number of antihypertensive medications, and statin use. Interactions between current ACE inhibitor use and age, BMI, diabetes mellitus, smoking, baseline frailty score, and statin use were explored by testing the significance of cross-product terms. At the design stage, it was estimated that this analysis had 80% power to detect odds ratios (ORs) in the range of 0.80 to 0.85.

ACE inhibitor use is more common in people with hypertension, diabetes mellitus, and history of CHD, which place users at an inherently higher risk of future cardiovascular disease (CVD) events than nonusers. Because incident CVD events could lead to frailty, a protective effect of ACE inhibitor use with frailty could be masked, and the OR would appear to be biased toward the null. Additional analyses were conducted to reduce confounding by indication. Multinomial logistic models were constructed to examine ACE inhibitor use in relation to non-CVD frailty by separating out women who experienced an intervening CVD event. In these analyses, frailty and incident CVD were modeled as separate outcomes. In addition, additional analyses were conducted restricting the sample to subjects with hypertension and to those with hypertension taking less than two antihypertensive medications. The latter restriction was applied to select a more-homogenous group of participants with hypertension (e.g., similar risk for CVD events).

RESULTS

At baseline, 8.0% of women (n = 2,192) were current users of ACE inhibitors, and 66.9% of these were current users for 2 or more years (n = 1,467). For women who had strength information (n = 2,173), 2.3%, 3.3%, and 2.3% were using a low, medium, and high equivalent dose, respectively.

ACE inhibitor use at baseline was associated with lower income, lower education, minority race or ethnicity, living alone, higher BMI, lower alcohol consumption, use of multiple antihypertensives, statin use, lower self-rated health status, higher levels of comorbidity, and prevalence of several health conditions (e.g., treated diabetes mellitus, hypertension, arthritis, history of CHD, Table 1). The average diastolic (76.6 ± 10.3 vs 73.8 ± 9.2, $P < .001$) and systolic blood pressures (138.5 ± 18.9 vs 130.0 ± 17.7, $P < .001$) were higher in participants using ACE inhibitors than in nonusers.

By the 3-year follow-up contact, 3,950 women had developed frailty (14.4%). Current ACE inhibitor use had no association with incident frailty (OR = 0.96, 95% confidence interval (CI) = 0.82–1.13, Table 2). Duration and equivalent dose of ACE inhibitor use were not significantly associated with incident frailty either. There were no significant interactions between current ACE inhibitor use and age, BMI, diabetes mellitus, smoking, baseline frailty score, and statin use. A similar pattern of results was observed when incident frailty was studied in the absence of intervening CVD events (data not shown).

When restricting the sample to subjects with hypertension, the association between ACE inhibitor use and frailty was similar to that in the analysis of the entire sample (OR = 0.96, 95% CI = 0.81–1.13). When restricting the sample to subjects with hypertension using less then two antihypertensive medications, there was a moderate association between equivalent dose of ACE inhibitor and lower risk of frailty (Table 3). ORs were lower for women who used a low dose (OR = 0.76, 95% CI = 0.53–1.11) and medium dose (OR = 0.71, 95% CI = 0.52–0.98) but not a high dose (OR = 1.15, 95% CI = 0.78–1.71; $P = .04$).

DISCUSSION

In this prospective study of more than 25,000 women aged 65 and older, current use of ACE inhibitors was not significantly related to the development of frailty at 3 years of follow-up. Risk of frailty was not related to duration or equivalent dose of ACE inhibitor exposure. Results were similar when the sample was restricted to subjects with hypertension or when frailty outcomes in the absence of intervening CVD events were examined, although when restricting the sample to subjects with hypertension taking less than two antihypertensive medications, a lower risk for frailty was found in subjects using low and medium equivalent doses.

To the authors' knowledge, this is the first large prospective study to examine ACE inhibitor use in relation to incident frailty. Other studies that have reported beneficial effects of ACE inhibitor use in older adults beyond the known benefits in heart failure have examined related outcomes such as walking speed, muscle mass, or weight loss. In an observational study of 641 disabled older women

Table 1. Baseline Characteristics According to Baseline Angiotensin-Converting Enzyme Inhibitor Use (N = 27,378)

Characteristic	User	Nonuser	*P*-Value
	n (%)		
Age			.07
65–69	1,076 (49.1)	12,876 (51.1)	
70–79	1,116 (50.9)	12,310 (48.9)	
Family income, $			<.001
<20,000	408 (20.3)	3,821 (16.5)	
20,000–34,999	578 (28.7)	6,701 (28.9)	
35,000–49,999	442 (21.9)	5,096 (21.9)	
50,000–74,999	348 (17.3)	4,234 (18.2)	
≥75,000	238 (11.8)	3,371 (14.5)	
Education			<.001
High school or less	488 (22.4)	5,238 (20.9)	
School after high school	861 (39.6)	9,216 (36.8)	
College degree or higher	826 (38.0)	10,615 (42.3)	
Ethnicity			.003
White	1,920 (87.6)	22,407 (89.0)	
Black	131 (6.0)	1,064 (4.2)	
Hispanic	43 (2.0)	485 (1.9)	
American Indian	7 (0.3)	53 (0.2)	
Asian or Pacific Islander	69 (3.1)	824 (3.3)	
Unknown	22 (1.0)	353 (1.4)	
Living alone at baseline	731 (33.7)	7,924 (31.7)	.05
Body mass index			<.001
Underweight	17 (0.8)	363 (1.5)	
Normal	749 (34.4)	11,405 (45.7)	
Overweight	827 (38.0)	8,925 (35.8)	
Obese	584 (26.8)	4,262 (17.1)	
Smoking			.73
Never smoked	1,170 (54.2)	13,487 (54.3)	
Past smoker	909 (42.1)	10,348 (41.7)	
Current smoker	79 (3.7)	990 (4.0)	
Alcohol intake, drinks/wk			<.001
0	691 (31.8)	6,712 (26.8)	
<1	647 (29.7)	7,682 (30.7)	
1–14	730 (33.6)	9,446 (37.7)	
>14	107 (4.9)	1,197 (4.8)	
Hormone therapy use			.96
Never used	1,019 (46.5)	11,644 (46.3)	
Past use	366 (16.7)	4,257 (16.9)	
Current use	806 (36.8)	9,258 (36.8)	
Calcium channel blocker use	337 (15.4)	2,509 (10.0)	<.001
Beta-blocker use	270 (12.3)	2,312 (9.2)	<.001
Diuretic use	604 (27.6)	2,713 (10.8)	<.001
Other antihypertensive use	59 (2.7)	567 (2.3)	.19
Number of antihypertensive medications			<.001
0	0 (0.0)	18,856 (74.9)	
1	1,156 (52.7)	4,612 (18.3)	
2	803 (36.6)	1,509 (6.0)	
≥3	233 (10.6)	209 (0.8)	
Statin use	372 (17.0)	2,324 (9.2)	<.001
Self-reported health			<.001
Excellent	154 (7.1)	4,918 (19.7)	
Very good	886 (40.8)	11,902 (47.6)	
Good	974 (44.9)	7,330 (29.3)	
Fair or poor	156 (7.2)	855 (3.4)	
Activity of daily living disability	22 (1.0)	255 (1.0)	.97
Treated diabetes mellitus	188 (8.6)	581 (2.3)	<.001
Hypertension	2,122 (98.0)	10,867 (43.7)	<.001
Depressive symptoms			
0	621 (28.9)	7,391 (29.8)	.54
1–2	869 (40.4)	9,907 (40.0)	
3–4	419 (19.5)	4,900 (19.8)	
≥5	243 (11.3)	2,587 (10.4)	
History of arthritis	1,198 (55.1)	12,874 (51.5)	.001
History of cancer	315 (14.5)	3,602 (14.4)	.96
History of coronary heart disease	249 (11.6)	1,720 (7.0)	<.001
Any comorbid condition	1,630 (74.4)	12,524 (49.7)	<.001

(*Continued*)

without heart failure, continuous users of ACE inhibitors over the 3-year observation period had a slower decline in muscle strength and walking speed than users of other antihypertensive medications.[9] In a cross-sectional analysis of data from the Health, Aging and Body Composition study, use of ACE inhibitors was associated with larger lower extremity muscle mass than use of other antihypertensive agents.[10] Data from the Cardiovascular Health Study suggest that, in older individuals with hypertension, use of an ACE inhibitor was associated with less annual weight loss,[21] but these investigators did not find an association between ACE inhibitor use and upper extremity muscle strength as measured according to grip strength. A recent randomized controlled trial in older adults with mobility or functional impairments without heart failure found that individuals receiving perindopril for 6 months were able to walk on average 30 m farther in 6 minutes than those taking placebo. Improvements were not found in secondary outcome measures that are more akin to the components of the frailty measure, such as timed up-and-go or repeated chair stands, although the study was not powered for these secondary outcomes.[11] The authors commented that improvements in walking may have been in part due to improved cardiovascular function rather than muscle strength. Furthermore, a cross-sectional analysis found no association between ACE inhibitor use and walking speed or grip strength.[22] Taken together, these studies suggest that ACE inhibitor use is not consistently associated with any particular component of the frailty construct or the composite phenotype.

Confounding by indication is a source of bias that could obscure or mask completely any protective association between ACE inhibitor use and development of frailty. The present study employed several strategies to address confounding by indication, including multivariate adjustment, multinomial logistic regression, interaction testing, and restriction to address the problem that ACE inhibitors

Table 2. Adjusted* Odds Ratios (ORs) Relating Angiotensin-Converting Enzyme (ACE) Inhibitor Use to Risk of Frailty at 3-Year Follow-Up: Women's Health Initiative Observational Study (N = 27,378)

	Not Frail	Prefrail		Frail		
ACE Inhibitor Use	**n**	**n**	**OR (95% CI)**	**n**	**OR (95% CI)**	***P*-Value†**
Current ACE inhibitor use						
Nonuser	14,155	7,527	1.00	3,504	1.00	.88
User	1,030	716	1.00 (0.88–1.14)	446	0.96 (0.82–1.13)	
Years of ACE inhibitor use						
Nonuser	14,155	7,527	1.00	3,504	1.00	.59
<2	321	262	1.16 (0.95–1.42)	142	0.96 (0.75–1.24)	
2–5	337	215	0.91 (0.74–1.12)	146	0.96 (0.74–1.24)	
>5	372	239	0.95 (0.78–1.16)	158	0.97 (0.76–1.24)	
Potency of ACE inhibitor use‡						
Nonuser	14,155	7,527	1.00	3,504	1.00	.73
Low	300	221	1.09 (0.88–1.35)	112	0.88 (0.67–1.16)	
Medium	429	287	0.95 (0.78–1.14)	187	0.95 (0.75–1.19)	
High	292	203	1.00 (0.80–1.25)	142	1.08 (0.83–1.41)	

* ORs derived from multivariate multiple logistic regression analysis adjusting for age, income, education, ethnicity, body mass index, smoking, alcohol, physical activity, hormone replacement therapy use, whether a participant lived alone, self-reported health, diabetes mellitus, depressive symptoms, arthritis, history of cancer, history of coronary heart disease, systolic blood pressure (tertiles and linear), diastolic blood pressure (tertiles and linear), number of antihypertensive medications, and statin use.

† *P*-value from the aforementioned regression model, where significance corresponds to the overall effect of ACE inhibitor exposure variable and frailty.

‡ Nineteen were missing information on strength of tablets.

CI = confidence interval.

are disproportionately prescribed to older women with a greater risk of CVD events. In fact, when restricting the sample to subjects with hypertension using monotherapy or no medication for hypertension, the most homogenous group in terms of CVD risk, less risk was found for those using ACE inhibitors for 2 years or more and for those using low or medium equivalent doses, with only the latter reaching statistical significance. These results should be interpreted with caution and require replication in other cohorts or randomized trials, because the analysis according to dose

Table 3. Adjusted* Odds Ratios (ORs) Relating Angiotensin-Converting Enzyme (ACE) Inhibitor Use to Risk of Frailty in Participants with Hypertension Taking Less than Two Antihypertensive Medications: Women's Health Initiative Observational Study (N = 10,330)

	Not Frail	Prefrail		Frail		
ACE Inhibitor Use	**N**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**	***P*-Value†**
Current ACE inhibitor use						
Nonuser	4,783	2,917	1.00	1,515	1.00	.25
User	559	360	0.97 (0.82–1.16)	196	0.83 (0.66–1.04)	
Years of ACE inhibitor use						
Nonuser	4,783	2,917	1.00	1,515	1.00	.26
<2	174	137	1.14 (0.87–1.50)	73	0.97 (0.69–1.38)	
2–5	184	101	0.77 (0.57–1.03)	59	0.76 (0.53–1.10)	
≥5	201	122	1.01 (0.77–1.33)	64	0.76 (0.53–1.09)	
Potency of ACE inhibitor use						
Nonuser	4,783	2,917	1.00	1,515	1.00	.04
Low	175	135	1.18 (0.90–1.55)	55	0.76 (0.53–1.11)	
Medium	249	136	0.76 (0.58–0.98)	87	0.71 (0.52–0.98)	
High	132	87	1.11 (0.80–1.53)	53	1.15 (0.78–1.71)	

* ORs derived from multivariate multinomial logistic regression analysis adjusting for age, income, education, ethnicity, body mass index, smoking, alcohol, physical activity, hormone replacement therapy use, whether a participant lived alone, self-reported health, diabetes mellitus, depressive symptoms, arthritis, history of cancer, history of coronary heart disease, systolic blood pressure (tertiles and linear), diastolic blood pressure (tertiles and linear), number of antihypertensive medications, and statin use.

† *P*-value from the aforementioned regression model, where significance corresponds to the overall effect of ACE inhibitor exposure variable and frailty.

CI = confidence interval.

was exploratory and because of the use of tablet strength as a proxy for dose.

ACE inhibitors may preserve skeletal muscle function through direct and indirect effects on skeletal muscle, involving inflammatory and metabolic pathways.[7] ACE inhibitors may decrease inflammation by inhibiting interleukin-6 and tumor necrosis factor alpha production,[12,13] factors that have been associated with lower muscle mass and strength.[23] Treatment with ACE inhibitors improves metabolic efficiency by increasing insulin sensitivity and glucose uptake by skeletal muscle[24,25] and may delay or prevent muscle loss by modulation of the insulin-like growth factor (IGF) system,[26,27] but data are conflicting regarding whether the IGF system contributes to declining muscle strength and functional disability in older adults.[28–30]

Strengths of this study include its prospective design, objective assessment of ACE inhibitor use, inclusion of more than 2,000 current ACE inhibitor users, consideration of a large number of covariates related to the development of frailty, and the ability to separate out adjudicated, intervening CVD events, although a few limitations should be noted. Information was available only on prescription strength and not actual dose of ACE inhibitor medication, and medication adherence was unknown. The timing of initiation and discontinuation of ACE inhibitor use in relation to the onset of frailty during follow-up was not measured. Lack of physical performance measurements is another weakness. Finally, despite the measures taken to control for confounding, such as stratification and adjustment, all observational studies of pharmacological exposures are subject to issues related to confounding by indication.

CONCLUSION

In conclusion, this large prospective study of generally healthy older women showed no association between current ACE inhibitor use and the development of frailty over 3 years of follow-up. A lower risk of frailty was noted in women taking less than two antihypertensive agents using low and medium doses, but clinicians should not assume that older adults treated with ACE inhibitors have a lower risk of developing frailty. Whether ACE inhibitor use has a beneficial effect on physical performance and other components of frailty warrants further study, especially in sufficiently powered randomized controlled trials.

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