Augmenting Immune Responses to Varicella Zoster Virus in Older Adults: A Randomized, Controlled Trial of Tai Chi

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OBJECTIVES: To evaluate the effects of a behavioral intervention, Tai Chi, on resting and vaccine-stimulated levels of cell-mediated immunity (CMI) to varicella zoster virus (VZV) and on health functioning in older adults.

DESIGN: A prospective, randomized, controlled trial with allocation to two arms (Tai Chi and health education) for 25 weeks. After 16 weeks of intervention, subjects were vaccinated with VARIVAX, the live attenuated Oka/Merck VZV vaccine licensed to prevent varicella.

SETTING: Two urban U.S. communities between 2001 and 2005.

PARTICIPANTS: A total of 112 healthy older adults aged 59 to 86.

MEASUREMENTS: The primary endpoint was a quantitative measure of VZV-CMI. Secondary outcomes were scores on the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36).

RESULTS: The Tai Chi group showed higher levels of VZV-CMI than the health education group ($P<.05$), with a significant rate of increase ($P<.001$) that was nearly twice that found in the health education group. Tai Chi alone induced an increase in VZV-CMI that was comparable in magnitude with that induced by varicella vaccine, and the two were additive; Tai Chi, together with vaccine, produced a substantially higher level of VZV-CMI than vaccine alone. The Tai Chi group also showed significant improvements in SF-36 scores for physical functioning, bodily pain, vitality, and mental health ($P<.05$).

CONCLUSION: Tai Chi augments resting levels of VZV-specific CMI and boosts VZV-CMI of the varicella vaccine. **J Am Geriatr Soc 55:511–517, 2007.**

Key words: Tai Chi; varicella zoster virus; immunity; shingles; aging

Herpes zoster, or shingles, results from reactivation of latent varicella zoster virus (VZV)[1] and is characterized by a painful vesicular rash.[2] The incidence and severity of herpes zoster increase with age; more than half of all persons in whom herpes zoster develops are aged 60 and older.[3] The pain of herpes zoster and postherpetic neuralgia results in impairments in quality of life comparable with those observed with congestive heart failure, diabetes mellitus type 2, and major depression.[4]

Cell-mediated immunity (CMI) to VZV is thought to be pivotal in determining the risk of herpes zoster.[5–7] The increase in the incidence and severity of herpes zoster observed in older persons correlates with a progressive, age-related decline in circulating VZV-specific memory T-cells, whereas levels of antibody to VZV remain relatively constant.[5–12] In immunocompromised subjects, loss of robust memory T-cell-mediated immunity to VZV also defines susceptibility to herpes zoster.[5] Alternatively, an episode of herpes zoster boosts VZV-specific CMI and effectively "immunizes" an immunocompetent person.[3] Together, these observations suggest that efforts to elicit increases in VZV-specific CMI might provide protection against herpes zoster and postherpetic neuralgia.[6,7] Recently, a large Department of Veterans Affairs cooperative study carried out in adults aged 60 and older demonstrated that administration of a high-potency Oka/Merck VZV vaccine (ZOSTAVAX) reduced the incidence of herpes zoster 51% and the incidence of postherpetic neuralgia by two-thirds;[13] this protection correlated with the magnitude of boosting of VZV-specific CMI. Yet the risk of herpes zoster was not eliminated, despite the efficacy of this high-potency vaccine.[13] Moreover, a number of older adults (e.g., those who are immunosuppressed) will not be eligible to receive this live-attenuated vaccine.

The potential use of a behavioral intervention as an independent means of augmenting virus-specific immunity in older adults, and of complementing vaccine-induced immune responses, has received recent attention.[14–21] However, as previously reported,[22] many such intervention

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studies have suffered from methodological limitations, including small sample size, lack of randomized design, poor standardization of training and implementation, and enrollment of healthy younger participants rather than persons at risk for decreased immune responses.

Tai Chi, a traditional Chinese martial art, incorporates aerobic activity, relaxation, and meditation, all of which are reported to boost CMI responses.[14–21] In addition, Tai Chi is a particularly attractive intervention for use in older people, who often have age-related limitations in their ability to tolerate even moderate-intensity exercise.[23] A small controlled pilot study found that Tai Chi Chih (TCC), a westernized, standardized version of Tai Chi, boosted VZV-CMI.[24] However, the small sample size and the use of a wait-list condition that does not control for attention and expectation for benefit constrained conclusions from this study. Moreover, the possible effects of TCC on immune responses to vaccination were not assessed. The paucity of robust studies addressing the effects of this intervention on immunity, and specifically on immunity to VZV in older adults who are at higher risk of herpes zoster, is a significant omission. This clinical trial was conducted to compare the effect of TCC with that of health education (HE) on baseline VZV-specific T-cell immunity in older adults. In addition, it was determined whether TCC might augment the increase in immunity to VZV induced by a licensed live attenuated varicella vaccine (VARIVAX). (The investigational high-potency VZV vaccine evaluated in the Shingles Prevention Study (ZOSTAVAX) was not available for use in this study of TCC.)

METHODS

Design and Population

This randomized, controlled clinical trial allocated older adults to receive TCC or HE (active control intervention) in a 1:1 ratio at study sites in San Diego and Los Angeles between 2001 and 2005. After 16 weeks of TCC or HE, subjects in both groups received a single dose of live attenuated Oka/Merck varicella vaccine, VARIVAX, in accordance with the manufacturer's instructions; they were evaluated 9 weeks later. VARIVAX was licensed in the United States in 1995 for the prevention of varicella in susceptible children and adults. Its widespread use has led to a marked decline in the incidence of varicella and in varicella-related hospitalizations and mortality.[25] Although VARIVAX is intended to immunize susceptible children and adults against varicella, the subjects in this study had experienced varicella earlier in life and were already immune. Institutional review boards at both study sites approved this study.

Older adults were recruited through community newspaper advertisements that stated that the aim of the study was to compare the effects of TCC with that of HE on "health and well-being in healthy older adults." Subjects were offered compensation for participation and completion of the study. A total of 112 community-dwelling participants aged 59 to 86 who responded to advertisements were enrolled and randomly assigned to TCC (n = 59) or HE (n = 53) (Figure 1; San Diego, n = 40; Los Angeles, n = 72). Randomization was performed using a computer-generated schedule independent of treatment personnel. Eligibility criteria included a history of varicella (indicative of prior VZV infection) as confirmed using VZV-CMI responses.[26,27] Major exclusions were evidence of immunocompromise resulting from disease, corticosteroids, or other immunosuppressive or cytotoxic therapy; chronic liver or kidney disease; prior herpes zoster; receipt of immunizations (e.g., hepatitis B vaccine; influenza vaccine) within 1 month before study entry or scheduled over the course of the intervention; any acute intercurrent illness (e.g., thyroid disease, sinusitis, urinary tract infections) that might interfere with interpretation of the study; and presence of a current major psychiatric disorder as determined according to the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnoses.[28] Additional exclusions were an unwillingness to adhere to study protocol or ongoing participation in Tai Chi.

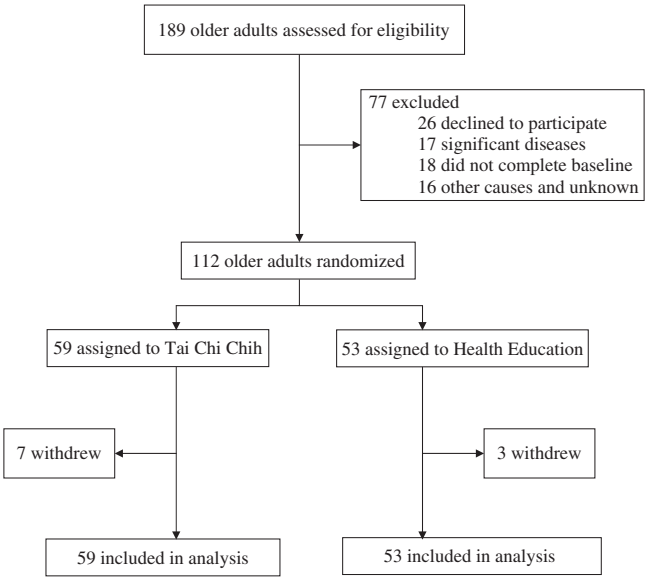

Figure 1. Participant flow and distribution of subjects in study.

Intervention

Subjects received 16 weeks of TCC or HE administered to groups of seven to 10 persons. TCC sessions lasted 40 minutes and were given three times per week for a total 120 minutes of weekly instruction. HE was also allocated a 120-minute period of instruction per week, an identical amount of instructor time as given to TCC. The rationale communicated to subjects was that TCC is a health management intervention that incorporates meditation and repetitive physical activity to promote well-being in aging, whereas HE aims to promote healthy behaviors and well-being by providing knowledge about health management. For TCC, objectives and learning activities related to the specific set of 20 exercises employed were identified according to a therapist manual,[29] with verification of skills attainment and weekly supervision by master's level TCC instructors. The HE intervention involved 16 didactic presentations on a series of health-related themes provided by a physician or licensed clinical psychologists with group discussion, as previously described.[30] Treatment credibility and expectation were assessed for change after the second treatment session using a 5-point Likert scale.[31]

Assessment and Outcome Measures

The primary outcome variable was a quantitative measure of VZV-CMI, which was assessed on five occasions: at baseline (before randomization) and at Weeks 8, 12, 16 (at the conclusion of the sessions and before vaccination), and 25 (approximately 9 weeks after completion of the intervention and vaccination). At baseline, a number of factors that have been associated with variations in susceptibility to herpes zoster were also assessed, including age, sex, socioeconomic status, marital status and social contacts, health functioning, and severity of depressive symptoms.[3,32] The Medical Outcomes Study 36-item Short Form survey (SF-36) was used to evaluate general health status,[33] and the Beck Depression Inventory was used to assess severity of depressive symptoms;[34] both measures were administered at baseline and 8, 12, 16, and 25 weeks. Participants were also monitored for exposure to varicella zoster, the occurrence of herpes zoster or pain symptoms, use of other treatments, and daily TCC practice time. Finally, given that TCC incorporates a component of physical activity, average weekly metabolic equivalents were determined over the course of the trial.[35]

Assay of Immunity to VZV-CMI

VZV-CMI was assessed by measuring the frequency of peripheral blood mononuclear cells (PBMCs) and specifically CD4+CD45RO+T-cells or memory T-cells that proliferate in response to VZV antigen (VZV responder cell frequency (VZV-RCF)).[27,36–39] Using previously described methods,[24,27,36,37] a technician blinded to the subjects' group allocation conducted VZV-RCF assays within 2 hours of sample acquisition, with VZV-RCF expressed as the mean number of VZV-specific proliferating cells per 10^5 PBMCs. The coefficients of variation for interassay replicates obtained over a 3- to 5-month interval were less than 12%. All assay values were reviewed for validity (e.g., distribution of positive wells, magnitude of the response in control wells) before unblinding, and 5.5% of assay results were rejected as invalid and were processed as missing data. Given the assay range, VZV-RCF values were constrained to 0.5 and 64 VZV responder cells per 10^5 PBMC.

Vaccination

At the end of the intervention, subjects received one subcutaneous injection of 0.5 mL of the live-attenuated Oka/Merck varicella vaccine, VARIVAX, with an estimated minimum potency of 1,350 plaque-forming units. VARIVAX contains less than 7% of the amount of VZV in the investigational zoster vaccine, ZOSTAVAX, that was shown to reduce the incidence of herpes zoster and postherpetic neuralgia in older adults.[13]

Statistical Analysis

Comparison of treatment groups at entry was performed using unpaired *t* tests for continuous data and chi-square for discrete data. The general effects of the intervention over time were assessed using a group (TCC vs HE) by time (baseline, Week 8, Week 12, Week 16, and Week 25) repeated-measures analyses of variance and covariance for log-transformed VZV-RCF values and other repeated measures (e.g., SF-36 subscales) covarying for baseline values. Secondary analyses of VZV-RCF values included a covariate if there was a significant difference in a background variable between the two treatment groups and the background variable was significantly related to the VZV-RCF values. For time effects from baseline to Week 25, linear growth curve estimates were generated to evaluate growth curve slopes in the two groups. Greater improvements in VZV-RCF and other variables over time were hypothesized for the TCC group. For missing data, multiple imputation procedures (SAS PROC MI) were used with analyses performed with SAS PROC MI-ANALYZE, which generates corrected standard errors and confidence intervals and tests parameters such as mean differences and growth slope values. All analyses used an intention-to-treat approach.

RESULTS

Characteristics of the Study Subjects

The mean age in both groups was 70, and there were no significant pretreatment differences with respect to sex, ethnicity, marital status, educational level, annual income, number of social contacts, severity of depressive symptoms, SF-36 scores, or weekly physical activity (Table 1). Although participants in the HE group had higher baseline scores on SF-36 role physical ($P<.05$) and bodily pain ($P=.09$), neither score correlated with any of the VZV-RCF assessments.

Adherence to Intervention

Of 112 subjects allocated to the intervention, 102 (91%) completed the intervention and were followed to 25 weeks (to the end of the postvaccination period) (Figure 1). Of the seven withdrawals in TCC, six withdrew because of difficulties with time commitments or transportation, and one did not like the class. Of the three withdrawals in HE, two withdrew because of difficulties with the time commitment and one because of health problems. Attendance at treatment sessions was high; TCC participants attended a mean ± standard deviation of 83 ± 20%, and HE subjects attended 80 ± 20% of all sessions.

The two interventions were perceived as equally credible, with subjects in the TCC and HE groups reporting a similar level of confidence, respectively, that "TCC (or health education) would be successful in improving health in older adults" (4.1 ± 0.2 vs 4.2 ± 0.3). In addition, participants in the TCC and HE were equally "confident in recommending TCC (or HE) to a friend" (4.3 ± 0.3 vs 4.1 ± 0.2).

Over the course of the intervention period, TCC participants showed a significant increase in the number of minutes of at-home TCC practice per week, from 111 ± 61 minutes at Week 8 to 213 ± 146 minutes at Week 16 ($P<.001$). In addition, TCC participants maintained this level of practice after completion of the intervention sessions (during the postvaccination period) and reported a mean of 149 ± 122 minutes per week of TCC practice at Week 25. Despite these increases in TCC practice, overall physical activity, as measured according to metabolic equivalents expended per week, did not change over the course of the trial in either group ($P=.64$; Table 2), which suggests that participants in the TCC group substituted TCC for other aerobic activity.

Table 1. Baseline Characteristics of the Study Participants

Characteristic	Tai Chi Chih (n = 59)	Health Education* (n = 53)
Demographic		
Age, mean ± SD	69.6 ± 6.2	70.2 ± 7.5
Sex, n (%)		
Male	18 (30.5)	23 (43.4)
Female	41(69.5)	30 (56.6)
Ethnicity, n (%)		
White	48 (81.4)	43 (81.1)
Non-white	11 (18.6)	10 (18.9)
Marital status, n (%)		
Married	28 (47.5)	30 (56.6)
Not married	31 (52.5)	23 (43.4)
Education, years, mean ± SD	16.7 ± 2.4	15.8 ± 2.5
Annual income, $1,000, mean ± SD	64.0 ± 73.6	66.8 ± 60.2
Psychosocial, mean ± SD		
Social support		
Number of contacts	3.1 ± 1.7	2.9 ± 1.6
Satisfaction	5.7 ± 0.5	5.7 ± 0.5
Beck Depression Inventory score†	4.9 ± 4.3	4.6 ± 4.4
Health functioning (SF-36 scores), mean ± SD‡		
Physical functioning	81.9 ± 18.1	80.0 ± 19.0
Role physical	70.3 ± 34.2	84.4 ± 23.6
Bodily pain	71.5 ± 18.7	77.6 ± 18.8
General health	80.3 ± 15.4	81.0 ± 13.3
Vitality	66.9 ± 16.3	68.1 ± 17.2
Social functioning	91.2 ± 15.4	93.2 ± 12.6
Role emotion	82.8 ± 27.4	87.7 ± 22.2
Mental health	83.1 ± 13.3	81.1 ± 13.8
Physical activity		
Metabolic equivalents per week, mean ± SD§	255.4 ± 26.3	254.9 ± 27.0

* Group comparisons are not significantly different, with all $P > 0.2$ except for Medical Outcomes Study 36-item Short Form (SF-36) role physical ($P < .05$) and bodily pain ($P = .09$).
† Higher scores indicate greater depressive symptoms.
‡ Lower scores indicate greater impairments.
§ Metabolic equivalents calculated according to methods previously published.[35]
SD = standard deviation.

Intervention Effects: VZV-Specific CMI and Responses to Vaccination

The primary outcome of interest was VZV-CMI as measured according to VZV-RCF. Figure 2 displays the mean VZV-RCF level at study entry (baseline), across the intervention (Weeks 8, 12, and 16), and postvaccination (Week 25). The treatment groups did not differ significantly in entry (baseline) levels of VZV-RCF. The ANCOVA covarying for baseline levels showed that mean levels of VZV-RCF were significantly greater in the TCC group than in the HE group at 8, 12, 16, and 25 weeks after initiation of the intervention (95% confidence interval (CI) = 0.01–0.18; $P < .05$). In addition, there was an overall increase in VZV-RCF over the entire 25 weeks of evaluation (from baseline to week 25) for both groups (95% CI = 0.003–0.01; $P < .001$). Adjustment for nesting of group cohorts for each intervention did not alter the results. Neither the number of sessions attended nor the weekly minutes of TCC practice was related to the magnitude of the increase in VZV-RCF. None of the demographic variables were correlated with increases in VZV-RCF. No subject reported exposure to varicella zoster during the trial.

Growth curve analyses revealed that the rate of increase in VZV-RCF in the TCC group was nearly twice that of the HE group; the rate of increase in VZV-RCF in the TCC group was significant (0.009 log VZV-RCF per week; 95% CI = 0.004–0.01; $P < .001$), whereas that in the HE group was not (0.0046 log VZV-RCF per week; 95% CI = 0.001–0.01; $P = .11$). Subjects in the TCC group achieved an average level of VZV-RCF postvaccination that was comparable with the mean level of VZV-RCF previously reported in studies of healthy adults 30 years their junior (indicated by the dashed line in Figure 2).[40]

Figure 3 presents the mean percentage increase in VZV-RCF from baseline to Week 16 (to the end of the intervention) and from baseline to Week 25 (to 9 weeks postvaccination) in the two groups. By Week 16, the TCC group showed a statistically significant 24% increase in VZV-RCF (95% CI = 0.06–0.43; $P < .01$), whereas the 13% increase in VZV-RCF observed in the HE group was not significant (95% CI = 0.02–0.29). After intervention plus vaccination (from baseline to week 25), the TCC group showed an overall increase in VZV-RCF of 38% (95% CI = 0.18–0.58; $P < .001$), whereas the HE group showed an increase from baseline of 28% (95% CI = 0.07–0.50; $P < .01$). The 24% increase in VZV-RCF produced by the TCC alone was similar to the 28% increase in VZV-RCF produced by HE and vaccination together (Figure 3). In addition, the 38% increase in VZV-RCF produced by TCC plus vaccination was significantly greater than the 14% increase produced by vaccination alone in the TCC group (95% CI = 0.49–0.04; $P < .03$).

Intervention Effects: Secondary Outcomes

For severity of depressive symptoms, an overall time effect (95% CI = 0.09–0.04; $P < .001$) was found, with significant improvements in the TCC ($P < .05$) and HE groups ($P < .05$) (Table 2). For measures of health functioning, overall time effects were found for SF-36 measures of physical functioning (95% CI = 0.03–0.20; $P < .01$), bodily pain (95% CI = 0.08–0.37; $P < .01$), vitality (95% CI = 0.09–0.31; $P < .001$), and mental health (95% CI = 0.02–0.19; $P < .01$). Growth curve analyses showed significant improvements in SF-36 scores from baseline to Week 25 for physical functioning ($P < .05$), bodily pain ($P < .05$), vitality ($P < .05$), and mental health ($P < .05$) in the TCC group but not in the HE group (Table 2). For role emotional, a significant worsening was found from baseline to Week 25 in the HE group but not in the TCC group, which may reflect a mismatch between expectations and improvement at the end of the treatment.

Safety and Concurrent Treatments

None of the subjects developed herpes zoster, and no subjects reported new symptoms of pain during the course of the trial, which together suggest that the intervention does

Table 2. Change in Secondary Outcomes from Baseline to Week 25

Secondary Outcomes	Tai Chi Chih (n = 59)	Health Education (n = 53)
	Mean (95% Confidence Interval)	
Psychosocial		
Beck Depression Scale score	−1.68 (−2.42 to −0.94)*	−1.33 (−2.28 to −0.38)*
Health functioning (Medical Outcomes Study 36-item Short Form score)		
Physical functioning	3.36 (0.98–5.74)*	2.17 (−1.12–5.46)
Role physical	5.67 (−1.83–13.17)	−0.91 (−8.61–6.79)
Bodily pain	6.68 (2.56–10.81)*	3.79 (−1.53–9.11)
General health	0.62 (−1.94–3.19)	0.22 (−3.41–3.84)
Vitality	5.82 (2.49–9.16)*	3.71 (−0.03–7.44)
Social functioning	1.82 (−1.44–5.07)	−0.54 (−3.83–2.76)
Role emotional	0.01 (−6.49–6.51)	−7.64 (−15.13 to −0.14)*
Mental health	3.22 (0.70–5.75)*	1.89 (−1.17–4.95)
Physical activity		
Metabolic equivalents per week	1.95 (−5.85–9.75)	1.17 (−6.46–8.80)

* Slope significantly different from 0 ($P < .05$).

not induce VZV reactivation. No participant reported use of other behavioral or complementary medicine practices at any assessment.

DISCUSSION

This randomized, controlled trial showed that TCC increased resting levels of VZV-specific CMI to a degree comparable with levels induced by varicella vaccine (VARIVAX) in the HE group. Furthermore, the combination of TCC and varicella vaccine boosted VZV-RCF nearly 40%, to levels of VZV-specific CMI comparable with those previously observed in adults who were 30 years younger (an age at which the incidence and severity of herpes zoster are substantially lower than they are in persons aged 60 and older).[3,32,40] Level of VZV-specific CMI plays a pivotal role in determining the risk and severity of herpes zoster, although the authors know of no data showing that increases in VZV-specific CMI of this magnitude in older adults are sufficient to provide protection from herpes zoster.

The finding that TCC significantly increased resting levels of VZV-RCF may have broad implications. VZV-RCF measures primarily VZV-specific memory T-cells (CD4+ CD45RO+ T-cells),[27] and the capacity of TCC to increase the number of circulating VZV-specific memory T-cells may generalize to memory T-cells specific for antigens of other pathogens that cause severe disease in older adults, such as influenza viruses and *Streptococcus pneumoniae*.

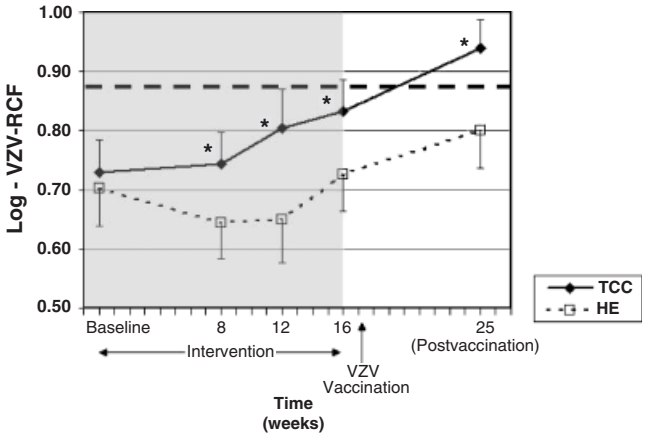

Figure 2. Effects of Tai Chi Chih (TCC) versus health education (HE) on varicella zoster virus (VZV)-specific immunity measured using VZV responder cell frequency (RCF) (mean ± standard error of the mean). The TCC group had significantly higher levels of VZV-RCF than the HE group (*$P < .05$). The horizontal dotted line refers to the mean value of VZV-RCF previously reported in 30- to 40-year-old adults.[40] The shaded area indicates the duration of the intervention from baseline to Week 16.

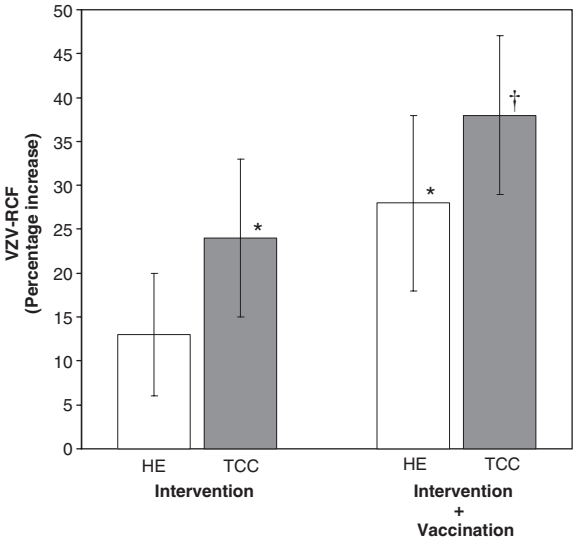

Figure 3. Percentage increase of varicella zoster virus responder cell frequency (VZV-RCF) (mean ± standard error of the mean) during the intervention (from baseline to Week 16) and during the intervention plus vaccination (from baseline to Week 25) in the Tai Chi Chih (TCC) versus health education (HE) groups. $P <$ *.01; †.001.

Furthermore, for infectious diseases for which no vaccine is yet available (e.g., human immunodeficiency virus, avian influenza), the capacity of a behavioral intervention such as TCC to increase resting levels of memory T-cells may offer unique benefits. It must be recognized, however, that VZV-specific memory T-cells were enumerated in PBMC, and the observed increases could reflect redistribution, rather than increases in total pool size. VZV antibody levels do not correlate with herpes zoster risk.[5–9]

Older adults often respond poorly to immunizations. The data reported here show that TCC and varicella vaccine had an additive effect, resulting in a substantially higher level of VZV-RCF than vaccine alone. TCC might improve the efficacy of other vaccines (e.g., influenza) in older adults, which would have further public health implications. However, it is not known whether administration of TCC before or after vaccination might augment primary, as well as anamnestic, immune responses.

Behavioral treatments such as TCC may modulate memory T-cell function via decreases of sympathetic outflow. Aging is associated with increases in circulating levels of catecholamines[41] that are known to inhibit memory T-cell function as well as CMI responses to antigenic challenge.[42] TCC decreases sympathetic activity,[43] and TCC training over 12 months is reported to improve aerobic fitness, as measured according to an increase in maximum oxygen uptake and decreases in blood pressure.[44] Tai Chi is unique in bringing together exercise, relaxation, and meditation as one behavioral intervention, and it is not known whether these individual components induce similarly robust increases in VZV-CMI. No relationship was found between weekly minutes of TCC practice and magnitude of the increase in VZV-RCF, possibly because a threshold of practice was achieved in which all TCC participants maintained weekly practice throughout the trial.

Health functioning across multiple domains improved in older adults after TCC. These findings are consistent with prior observations[24] and are particularly striking, because baseline scores at study entry were already above the population norms for older adults. Inclusion of a structured control group is of particular methodological importance; it permitted the conclusion that the observed effects of TCC on health functioning were independent of the effects of coming together as a group; ratings for treatment credibility indicate similar expectation for improvement and response to instruction in the two groups. No correlations were found between measures of health functioning and increments in VZV-specific CMI.

TCC, which contributed to high levels of treatment attendance, adherence, and maintenance that persisted even after formal administration of TCC had ended, is highly accessible to older adults. Nevertheless, this study has several limitations. Participants were in good health relative to their age-matched peers, and there were potential treatment-related "ceilings" on various outcomes, including VZV-RCF and health functioning. For example, vaccination was administered at the end of the intervention period, at a time when subjects were fully proficient in TCC and increases in resting levels of VZV-CMI were present. A "ceiling," as defined according to average levels of VZV-RCF in middle-aged adults, may have blunted the ability of vaccination to achieve further increases. Future trials should consider vaccination after TCC proficiency and practice is achieved but before substantial increases in resting levels of VZV-CMI have occurred. Second, it is not known whether TCC would be associated with similar improvements in VZV-specific CMI or health functioning in older adults with significant medical morbidity. Third, sampling of older adults with higher social status and income may have influenced the high levels of treatment adherence. In addition, it is not known whether these results would generalize to older adults with lower social status and education, although neither income nor educational level correlated with increases in VZV-RCF. Fourth, this study was only 6 months in duration, and an extended follow-up period was not carried out to determine whether the practice of TCC was maintained or whether its effects on VZV-specific CMI and health functioning were durable. Fifth, the nonblinding of subjects may have been a source of bias. Finally, whether TCC decreased the incidence of shingles was not assessed. Given the low annual incidence of herpes zoster (approximately 10–12 cases per 1,000 persons per year in this age group),[13] this would require evaluation of a large number of subjects. The Shingles Prevention Study enrolled 38,546 older adults to test the efficacy of an investigational zoster vaccine (ZOSTAVAX) on the frequency and severity of herpes zoster[13] and found that levels of VZV-CMI were significantly lower in subjects who developed herpes zoster than in those who did not. The study reported here demonstrated significant positive effects of TCC on VZV-specific CMI; thus, the clinical implications of the present study persist despite its limitations.

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Author Contributions: Drs. Irwin and Oxman were responsible for the study's concept and design. Dr. Olmstead was responsible for data management and statistical analysis. The report was drafted by Drs. Irwin, Olmstead, and Oxman and approved by all authors.

Sponsor's Role: No funding source had any direct role in the study design; in the collection, analysis, or interpretation of the data; in the writing of the manuscript; or in the decision to submit the report for publication. The correspondent had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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