Research Protocol

Title	**Caregiver-administered acupressure as long-term intervention to slow the progression of early/mild Alzheimer's disease with blood amyloid and tau biomarkers: a randomized controlled trial**
Protocol No.	CA2025
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Sample Size	188 participants
Study period of Each Subject	12 months
Duration of Entire project	From 01 January 2026 to 31 December 2029

1. Introduction:

Alzheimer's disease (AD) - impacts, symptoms, and diagnosis: AD is the most common type of dementia, accounting for 3/4, that affects millions of people worldwide. About 100,000 elderly aged ≥65 years are suffering from AD in Hong Kong and will increase to 280,000 by 2036 (Wu et al., 2018). These have led to dramatically increasing burdens on families, societies, and public healthcare systems. The symptomatological diagnostic criteria for AD include: (1) the cognitive impairment involves at least two of the following domains: learning and memory, reasoning and task, visuospatial abilities, language functions, changes in personality and behaviour; (2) the symptoms gradually occur over months and years, not suddenly over hours or days; (3) a clear-cut history of worsening of cognition by report or observation; and (4) the initial and most prominent cognitive deficits are evident on history and examination (McKhann et al., 2011).

On the other hand, multiple amyloid (Aβ) and tau products have been validated to predict the risk and the progression of AD. In particular, the plasma Aβ42/40 ratio, p-tau181, and p-tau217 are core biomarkers that are strongly associated with the risk, onset, and progression of AD. An Aβ42/40 ratio of ≥0.170 indicates a lower risk of AD, 0.150-0.169 for intermediate risk, and <0.150 for higher risk. A normal plasma level is 0.49-3.29 pg/ml for p-tau181 and ≤0.15 pg/ml for p-tau217. Plasma p-tau181 and p-tau217 levels increase with age, and higher levels are associated with more severe AD (Mielke & Fowler, 2024; Palmqvist et al., 2024). These biomarkers are thus specifically suitable for the assessment of the outcomes of early and long-term intervention. Additionally, blood glial fibrillary acidic protein (GFAP) and neurofilament light chain protein (NfL) often serve as biomarkers for neuroinflammation associated with the aetiology of AD (Jack et al., 2024).

Acupressure for AD and dementia: Although there are various classes of pharmacological agents available for the treatment of AD, the clinical efficacy is limited and even ineffective (Golde, 2022). This situation has led to the development of non-pharmacological approaches, particularly for early intervention to prevent the progression of AD.

As a convenient therapy, acupressure is increasingly introduced into the management of various cognitive disorders, and demonstrated for particular benefits in improving activities of daily living, agitation, anxiety, depression, and sleep disturbances in older adults living with dementia (Harris et al., 2020; Margenfeld et al., 2019). Acupressure also improved cognitive function and quality of life in older adults living with mild cognitive impairment (Lin et al., 2023; Sun et al., 2021). These studies suggest that acupressure may be an effective preventive approach to AD. However, it is unknown about the efficacy of acupressure as an early and long-term intervention to prevent AD. It is also unknown about the neuropathological mechanisms underlying acupressure in mitigating AD-associated amyloid (Aβ) and tau accumulation. Besides, acupressure also considerably improved functional dependence, mood, and sleep disorders in older adults living with cognitive impairment (Chan et al., 2017; Yeung et al., 2018).

Putative mechanisms of acupressure effects: It is thought that the therapeutic effects of acupressure are achieved mainly via neurophysiological and neurochemical mechanisms (Chen & Zhang, 2025). As a form of mechanical stimulation with particular physical touch, acupressure effectively rebalanced sympathetic and parasympathetic activities of the autonomic nervous system and modulated functions of multiple brain regions (such as the prefrontal cortex and limbic system) via activating tactile receptors and local sensory nerve endings of the skin and muscles. It also broadly regulated various neurotransmitters, particularly stimulating the release of serotonin, dopamine, endorphins, and oxytocin, in turn improving mood, cognitive function, and behavioral responses (Chen & Zhang, 2025; Fricker et al., 2023). Meanwhile, acupressure lowered levels of cortisol, a hormone related to stress

response (Chen & Zhang, 2025). In addition, acupressure activated tactile receptors in the skin and then transmitted relaxation signals to the brain, promoting emotional relaxation and calmness. These effects could explain the robust effects of acupressure in reducing stress-associated disorders and anxiety (Chen & Zhang, 2025). There are thus reasons to believe that acupressure could serve as an effective intervention in preventing and improving cognitive deterioration of older people.

Our related studies: We have published three randomized controlled trials of acupressure for insomnia disorder and stress-related symptoms (Cheung et al., 2020; Tiwari et al., 2016; Yeung et al., 2018). Moreover, we have developed caregiver-administered acupressure called 'Comfy Acupressure for the Elderly (CAE)' (https://www.youtube.com/watch?v=pAqNIZPKmnM), and confirmed that CAE effectively improved the quality of life and sleep quality of frail older adults, and reduced their pain intensity and frequency (Chan et al., 2017).

Between October 2020 and August 2024, we further completed a randomized controlled trial of evaluating the effectiveness of CAE in community-dwelling older people living with various types of dementia. A total of 118 who were aged above 65 years participated in the study. All subjects had a clinical diagnosis of dementia with mild to moderate severity (Reisberg et al., 1982). They were randomized to receive routine care alone as a control (n = 59) and plus CAE (n = 59) for 12 weeks. CAE was conducted for 3 sessions a week by caregivers at nursing homes. The primary outcome was baseline-to-endpoint changes in the Montreal Cognitive Assessment, Hong Kong version (HK-MoCA) score. The secondary outcomes included the Forward and Reverse Digit Span test for cognitive function. Baseline characteristics are summarized in Table 1. The discontinuation rate was 10.2% (12/118). The CAE group had significantly greater improvement than the routine care control group from baseline to 12 weeks on HK-MoCA score (mean difference [MD] = 1.62, 95% confidence interval [CI] = 0.37, 2.88, P = 0.012), Forward Digit Span (MD = 1.58, 95% CI = 0.34, 2.81, P = 0.013), and Reverse Digit Span (MD = 0.70, 95% CI = 0.04, 1.36, P = 0.038) (Figure 1A). Subgroup analysis revealed that CAE had significantly greater improvement on HK-MoCA in subjects with mild cognitive impairment and mild dementia, but not on moderate dementia (Figure 1B). The mean difference between CAE and the routine care control was 1.67 ± 3.63 (standard deviation [SD]), which will be used for sample size calculation (see below). These results proved the effectiveness of CAE in reducing cognitive deterioration of older adults, particularly with early/mild dementia, necessitating further conducting a long-term intervention study in preventing the progression of early/mild AD.

2. Aims and Hypotheses to be Tested:

The hypotheses are that: (1) the 12-month CAE early long-term intervention could produce greater effects in slowing the progression of AD by improving cognitive deterioration, blood amyloid and tau pathological products, functional dependency, and comorbid symptoms in older adults living with early/mild AD compared to least acupressure control (LAC); (2) the CAE intervention is cost-effective compared with LAC. An assessor-blinded, randomized, controlled trial will be designed to: (1) compare the effectiveness of CAE and LAC 12-month interventions in improving cognition, functional dependency, comorbid symptoms, blood amyloid and tau biomarkers in older adults living with early/mild AD; (2) to examine whether the 12-month CAE intervention is cost-effective compared with LAC by conducting a nested economic evaluation using health-related quality of life measured by the 5-level EQ-5D version (EQ-5D-5L) to derive quality-adjusted life years (QALYs).

Table 1. Baseline characteristics [a]

Characteristic	Routine care (n=59)	CAE (n=59)	*P* value [b]
Age (years)	85.3 ± 7.2	84.8 ± 8.7	0.756
Gender (female), n (%)	41 (69.5)	35 (59.3)	0.249
Dementia type, n (%)			0.577
Mild cognitive impairment (pre-AD)	22 (37.3)	27 (45.8)	
Alzheimer's disease (AD)	24 (40.7)	17 (28.8)	
Other types	13 (22.0)	15 (25.4)	
Baseline HK-MoCA	8.8 ± 5.9	10.9 ± 7.3	0.092
Baseline digital span (forward)	8.6 ± 3.9	9.1 ± 3.9	0.522
Baseline digital span (reverse)	1.7 ± 2.4	2.0 ± 2.3	0.554

a. **CAE,** Comfy Acupressure for the Elderly; **HK-MoCA,** Montreal Cognitive Assessment, Hong Kong version.

b. Continuous variables (mean ± SD) were analyzed with Student t-test and categorical variables were analyzed with Chi-square (χ^2) test.

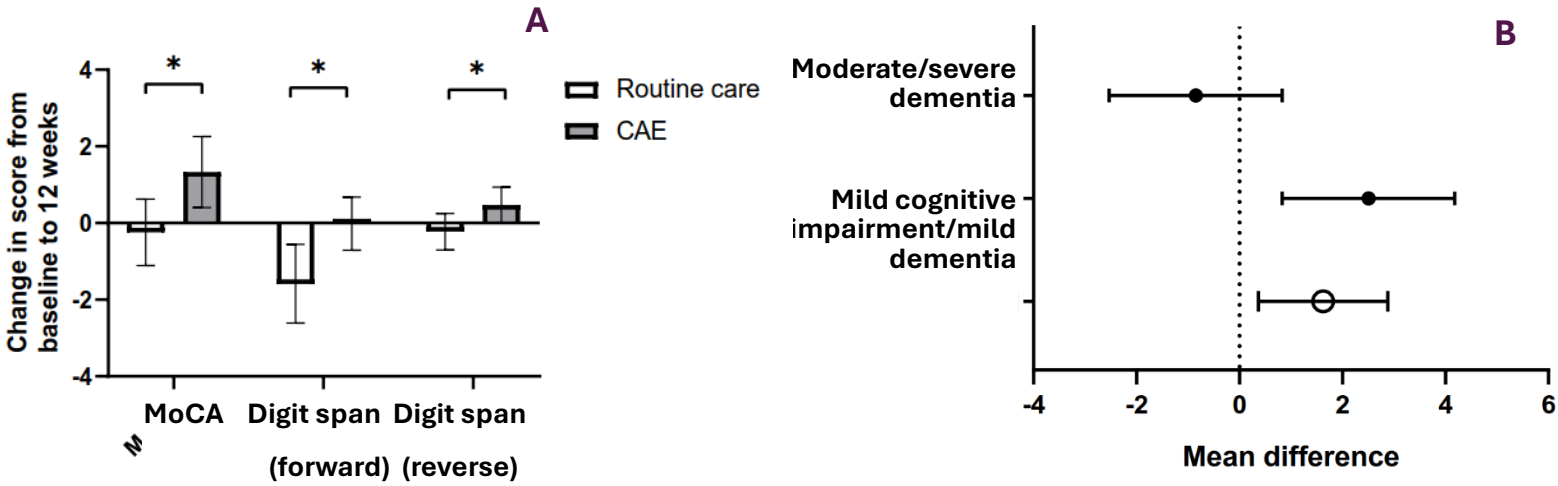


Figure 1. A. Elderly with dementia received routine care alone (n = 59) and plus CAE (n = 59) for 12 weeks. Cognitive performance was examined using MoCA, forward and reverse digit span test. Data are expressed mean ± mean ± standard error of the mean (SEM). * indicates P < 0.05. **B.** Subgroup analysis was conducted on MoCA in subjects with Mild Cognitive Impairment and Mild Dementia, and Moderate Dementia. **CAE,** Comfy Acupressure for the Elderly; **MoCA,** Montreal Cognitive Assessment.

Plan of Investigation:

Study design (outline)

This is an assessor-blinded, randomized controlled trial. A total of 188 older adults aged 60-85 years with early/mild Alzheimer's disease (AD) will be recruited from care and attention homes for the elderly and elderly activity centres. They will be randomly assigned to receive least acupressure control (LAC, n = 94) and Comfy Acupressure for the Elderly (CAE, n = 94), administered by caregivers (i.e., trained research assistants), for 3 sessions a week for 12 months. The primary outcome is the change in the Montreal Cognitive Assessment, Hong Kong version (HK-MoCA) score from baseline. The secondary outcomes include functional independence, psychological well-being, sleep quality, and health-related quality of life. The outcomes will be assessed at baseline and once bimonthly thereafter, totalling 7 sessions. A linear mixed-effect model will be applied to compare the primary and secondary outcomes. Three blood samples will be collected at baseline, 6 months, and 12 months, respectively, and the baseline blood sample will be immediately measured for the measurement of plasma Aβ42, Aβ40, p-tau181, and p-tau217, blood glial fibrillary acidic protein (GFAP) and neurofilament light chain protein (NfL). Two-way repeated measures analysis of variance (ANOVA) will be used to detect significant differences in blood biomarkers between the two groups. Linear regression will be conducted to examine inter-correlations between clinical outcomes and biomarker levels. Health and social care resource use will additionally be recorded at baseline, 6 months, and 12 months for the economic evaluation to examine the cost-effectiveness of the CAE intervention compared with LAC.

Subjects (with justification on the sample size)

Inclusion criteria: To ensure diagnostic accuracy, both clinical and biomarker inclusion criteria are included based on the recently published Revised Criteria for Diagnosis and Staging of AD (Jack et al., 2024). Eligible subjects must meet all the following three criteria: (a) are aged 60-85 years; (b) have at least one of the following abnormal plasma amyloid and tau levels: Aβ42/Aβ40 ratio ≤ 0.17, p-tau217 > 0.15 pg/ml, or/and p-tau181 > 3.3 pg/ml. These blood biomarkers have been well validated in the pathological diagnosis of AD (Jack et al., 2024; Mielke & Fowler, 2024; Palmqvist et al., 2024; Wang et al., 2025); and (c) have mild neurocognitive disorder with the HK-MoCA in classifying mild neurocognitive disorder, in which mild neurocognitive disorder is defined as those whose HK-MoCA score falls between the 16th and 2nd percentile of his/her peers adjusted for age and education. This cutoff screening tool is specifically developed and validated in Chinese older adults (Yeung et al., 2014, 2020).

Exclusion criteria: Subjects will be excluded if they: (a) show moderate-to-severe dementia, as evidenced by a HK-MoCA score falling below the 2nd percentile of his/her peers adjusted for age and education (Yeung et al., 2020); (b) cannot proficiently communicate due to language function impairment; (c) have severe skin lesions on acupressure areas; (d) had a surgery on the head or neck; or (e) have a medical condition that is a contraindication for acupressure.

Estimation of sample size: Clinical and biomarker parameters are used and compared in the estimation of sample size. The greater number will be applied in the study.

Clinical parameter: In our aforesaid trial, CAE treatment for 12 weeks produced a 1.67 ± 3.63 (SD) score greater improvement than the routine care control on HK-MoCA in subjects with mild cognitive impairment and mild dementia. We conservatively assume that the CAE 12-

month intervention could yield at least 1.67 ± 3.63 (SD) greater improvement on HK-MoCA than LAC. The following formula is then used to calculate the sample size,

$$n = \frac{2}{(M/SD)^2} \times C_{p,power}$$

where n is the number of subjects required in each arm; M is the mean difference that is equal to 1.67. SD is standard deviation, which is 3.63. $C_{p,power}$ is equal to 7.9 when the two-tailed level of α and power (1-β) are set at 0.05 and 80%, respectively. It requires 75 subjects per group.

Biomarker parameter: To ensure that the power yielded from the sample size obtained in the aforesaid clinical parameter is sufficient to detect the Aβ/tau-associated mechanisms, we separately calculate and compare it with the sample size using the biomarker parameter. Due to the absence of studies on the effects of acupressure/manual therapy on AD-related biomarkers, we refer to data obtained from a placebo-controlled trial of aducanumab, an approved monoclonal antibody on plasma p-tau181 in patients with early AD (Toda et al., 2024). For a conservative estimate, we use the results of low doses (3 or 6 mg/kg). The low dose of aducanumab once every 4 weeks for 76 weeks reduced the plasma p-tau181 level by an average of 1.02 pg/ml (SD, 0.54 pg/ml) versus placebo. At the most conservative point, we assume that one-year acupressure produced only 1/4 of the effects of the low-dose aducanumab on plasma p-tau181. M (mean difference) = 0.26 pg/ml and SD = 0.54 pg/ml are then obtained and applied to the above formula, with a two-tailed level of α = 0.05 and power (1-β) = 80%. 69 subjects per group are needed, confirming that the sample size required to detect the Aβ/tau mechanisms is less than that needed to detect the clinical difference. The greater number of 75 subjects per group is hence applied for the further estimation.

With a sample of 75 participants per group after accounting for anticipated dropout, α = 0.05 (two-tailed) and 80% power are adequately powered to detect a minimum between-group difference of 0.25 pg/ml in plasma p-tau181 levels (SD = 0.54 pg/ml), equivalent to approximately 25% of the effect size observed with low-dose aducanumab in the reference trial (Toda et al., 2024). This effect size corresponds to Cohen's d ≈ 0.46, indicating a medium effect, suggesting the current sample size provides sufficient sensitivity for exploratory detection of biologically meaningful changes in AD-related plasma biomarkers. Furthermore, using Fisher's r-to-z transformation with two-tailed α = 0.05 and 80% statistical power, a sample size of 75 participants per group (150 total) is sufficient to detect a minimum correlation of r ≈ 0.23 between changes in blood biomarkers and changes in cognitive outcomes. This detection threshold is lower than the range of effect sizes reported in the existing literature for associations between biomarkers and cognitive function. Specifically, it was found that longitudinal changes in plasma p-tau181 were associated with cognitive decline (cognitively impaired: r = 0.34, P < .001) (Moscoso et al., 2021), and plasma levels of GFAP, p-tau181, and NfL were negatively correlated with MoCA/MMSE scores (r = 0.266 - 0.325, p ⩽ 0.001) (Liang et al., 2025). Therefore, the current sample size is sufficient to examine the inter-correlation between blood biomarkers and changes in cognitive outcomes. As no studies have yet investigated the effects of acupressure or manual therapy on AD-related biomarkers, this biomarker analysis will also serve as an exploratory investigation.

Economic evaluation**:** The economic evaluation is a secondary, exploratory component of the trial; the sample size is determined by the primary clinical outcome and is not separately powered to detect differences in cost-effectiveness.

Discontinuation rate: Although no data are available for estimation of the discontinuation rate of long-term (one-year) acupressure intervention, we assume a discontinuation rate of 20% in the proposed study based on the following elaboration. Our preliminary pilot study showed

only a 10.2% (12/118) dropout rate for caregiver-administered acupressure for 12 weeks in elderly with moderate and severe dementia. One 6-month self-administered acupressure study on cognitive functions in older adults with mild cognitive impairment reported a 16% dropout rate (Sun et al., 2021). Our three previous studies showed even lower dropout rates (7.0-9.7%) in self-administered acupressure for the treatment of stress disorders, insomnia, and chemotherapy-induced peripheral neuropathy for 8-16 weeks (Cheung et al., 2020, 2025; Yeung et al, 2022). According to our experience in previous studies, compared to self-administered acupressure, caregiver-administered performed acupressure (such as CAE) was more acceptable and comfortable. Moreover, the CAE will be conducted in care centres rather than at home. This will largely increase adherence. Therefore, a 20% dropout rate over one year is realistic. A total of 188 subjects (n = 94 each group) are then recruited in the consideration of this dropout rate.

Sample size for stratified randomization: The 188 participants proposed for recruitment are distributed across 8 strata defined by 2 age groups (60–74 years; 75–85 years) × 2 care setting types (care and attention homes for the elderly and elderly activity centres) × 2 HK-MoCA score percentile groups (16th–9th; <9th–2nd), yielding approximately 23–24 participants per stratum, substantially exceeding the minimum of 4 required to complete at least one block per stratum (block size = 4). Stratified randomization improves statistical efficiency by ensuring balance across key prognostic factors (design effect $\leqslant 1$), such that the standard two-group formula already yields a conservative estimate and no upward adjustment is warranted. Although a downward adjustment is theoretically permissible, it seems not to be adopted in practice, as the required reduction depends on the correlation between stratification factors and the primary outcome, a parameter that cannot be reliably estimated prior to trial initiation, and any overestimation would risk insufficient statistical power. Therefore, 94 subjects per group (188 in total) remain valid and appropriate for the proposed stratified randomization design.

Methods

Screening and recruitment: The screening and recruitment will be conducted in local care and attention homes for the elderly and elderly activity centres, but not in day care centres or nursing homes. The reason is that our preliminary study has found that the severity of dementia of majority of elderly in the two former care centres is generally mild. Most elderly in day care centres and nursing homes suffered moderate and severe dementia. As care procedures may be different between care and attention homes for the elderly and elderly activity centres, care setting type will serve as a stratum included in stratified randomization (see **Stratified randomization** and **Data processing and analysis** sections below).

For biomarker screening, potential subjects are required to give written consent for blood collection, and the following points will be included in the informed consent: (1) one 5-ml blood sample will be collected to measure plasma Aβ42, Aβ40, p-tau217, and p-tau181 (procedure as described in Blood sample collection and biomarker analysis section below); (2) the values will serve as the baseline data if they meet the eligibility and consent for the participation of the study within one month of post-screening sample collection; (3) for those who give the informed consent beyond one month after the screening sample collection, an additional blood sample will be collected for baseline assessment.

Caregivers, general physicians, and social workers of care centres will help identify potential eligible subjects and refer to research assistants of the research team who will be in charge of the screening to confirm the eligibility of the subjects.

Stratified randomization, central allocation, and blindness: To minimize the imbalance of participant groups, stratified randomization (1:1) will be conducted with age, care centre, and baseline HK-MoCA score. Random codes will be produced in advance using simple, complete, non-sequential random codes with a block of 4. The detailed explanation is seen in **Estimation of sample size** section.

Following the completion of stratification, random codes will be provided to participants via central allocation, i.e., site investigators who are responsible for confirming subjects' eligibility will call the coordinator to obtain a random code to allocate LAC or CAE group. Treatment conditions will be blind to clinical assessors and data analysts.

Intervention:

Routine care: All participants of the LAC and CAE groups will continue their current routine care and medications as usual. The routine care may include physiotherapy and intellectual activities. The concomitant medications and routine care will serve as covariates included in the outcome analysis.

CAE and LAC intervention will be conducted in care centres 3 times per week for 12 consecutive months by investigators, trained research assistants and student research assistants. All sessions of intervention for a participant will be done, in most cases, by the same intervener throughout 12 months of the study so as to eliminate deviations from different interveners. The detailed information about the location of acupoints, traditional Chinese Medicine (TCM)-based therapeutic effects, and acupressure procedures of CAE and LAC are attached in Table 2.

CAE: CAE protocol is initially developed on the basis of TCM theory and practice, with an aim to improve the quality of life and prevent aging and age-related conditions in older adults. CAE consists of 12 steps, which need about 15 minutes to complete and concentrate on the acupoints on the face, head, neck, shoulder, and hand. All chosen acupoints are conveniently operated by performers after proper training. The CAE video demonstration is accessible at https://www.youtube.com/watch?v=pAqNIZPKmnM.

LAC: In order to control "placebo" effects of CAE and increase study adherence of participants of the control group, least acupressure control (LAC) is applied to the control group based on the following two principles: (1) the acupoints chosen are unrelated or less related to the treated syndromes according to TCM theory; and (2) the number of acupoints used, intensity, and duration of acupressure are kept to the least level at which the therapeutic effects produced are minimal, but participants are aware of receiving active acupressure. The similar regimen, minimum acupuncture stimulation (MAS), has been well validated in our two previous studies (Zhang et al., 2020a,b). The following three acupoints in which locations are matched with CAE acupoints in the head, neck/shoulder, and hand are used for LAC: Tongtian (BL7), Jianzhen (SI9), and Shousanli (LI10). The completion of one LAC session needs about 3 to 4 minutes.

Termination criteria and post-termination management: To ensure participants' safety, those who cannot tolerate acupressure or are hospitalized due to the aggravation of their condition will discontinue the study and be given individual clinical treatment.

Table 2. Acupressure procedures

A. Procedures and traditional Chinese Medicine (TCM) theory of "Comfy Acupressure for the Elderly (CAE)"

Step	Location of Operating acupoints/regions operated	Procedure	TCM-based therapeutic effects
Step 1: Opening Tianmen	From the center of the eyebrow to the forehead	Apply massage oil to the center of the subject's forehead, then use the pad of the index and middle fingers of both hands, or the middle finger alone, to synchronously push straight upward from the midpoint between the subject's eyebrows (EX-HN3, Yintang) to the hairline (GV24, Shenting). Repeat 15 times.	"Opening Tianmen" has the effects of opening the orifices and rejuvenating the mind. It is often used to treat insomnia, headaches, eye pain, depression, and anxiety, etc.
Step 2: Pushing Kangong	From the inside to the outside of the eyebrows	Apply massage oil to the subject's eyebrow, then use the pad of the index and middle fingers of both hands, or the middle finger alone, to synchronously push from the medial end of both eyebrows (BL2, Cuanzhu) to the depression on the supraorbital margin, at the lateral end of the eyebrows (SJ23, Sizhukong). Repeat 15 times.	"Pushing Kangong" can refresh the brain and improve eyesight. It is often combined with "Opening Tianmen" to improve mentality and mood.
Step 3: Pressing and Kneading Taiyang	Acupoint EX-HN5 (Taiyang)	Using the pad of the middle finger of both hands, press and knead the acupoint EX-HN5 (Taiyang), in synchronized circular motion. Knead deeply to move the subcutaneous layer of the skin, instead of just rubbing the surface. Repeat 15 times.	Taiyang is an extra meridian acupoint that can refresh the brain and improve eyesight. It is used to treat headaches, vision problems, forgetfulness, agitation, and sleeplessness.

Step 4: Kneading Face	7 facial acupoints: GB14, (Yangbai), EX-HN5 (Taiyang), SI18 (Quanliao), LI20 (Yingxiang), ST6 (Jiache), ST4 (Dicang) and CV24 (Chengjiang)	Using the pads of the index, middle, and ring fingers of both hands, or the middle finger alone, to synchronously massage the subject's face in circular motion, following the sequence below: forehead, temporal area, orbital area, zygomatic area, cheek area, nasal area, lower jaw. Focus on the following acupoints: GB14, (Yangbai), EX-HN5 (Taiyang), SI18 (Quanliao), LI20 (Yingxiang), ST6 (Jiache), ST4 (Dicang), and CV24 (Chengjiang) by repeating the circular kneading action on each acupoint. Repeat the action 3 times.	Facial acupoints are Yang meridian acupoints, massaging the face from top to bottom can promote the circulation of *qi* and blood of the head, enhancing the brain functions.
Step 5: Grasping Wu Jing	The head area that Du meridian, Bladder meridian, and Gallbladder meridian circulate	Place a thin towel on the subject's head, then place one hand on top of the towel, with the pad of the middle finger on the Du meridian, index and ring fingers on the Bladder meridian, and thumb and little finger on the Gallbladder meridian. Move and synchronize all 5 fingers to lift and press on the treatment area. Move the hand up and down the meridians and sideways to cover the subject's entire head. Repeat for 3 minutes, spending 1 minute on the top, 1 minute on the sides, and 1 minute on the back of the skull.	"Grasping Wu Jing" can relax the head, promoting the flow of *qi* and blood circulation of the head, and has good effects in improving memory declines, headaches, dizziness, insomnia, etc.
Step 6: Pressing and Kneading Fengchi	Acupoint GB20 (Fengchi)	Place a thin towel on the subject's head, then use both thumbs or the thumb and index/middle finger of one hand to synchronously press and knead the acupoint GB20	Fengchi is a key acupoint for protecting against external pathogens, clearing the head, refreshing the mind, and calming agitation and anxiety.

		(Fengchi) on both sides of the neck. Repeat 5 times.	
Step 7: Pressing and kneading the neck	Neck	Place a thin towel on the subject's neck area and use the thumb and index/middle finger of one hand to lift and massage both sides of the neck. Ensure that the action is rhythmic and synchronized. Repeat for 3 minutes, spending 1 minute on the upper, 1 minute on middle, and 1 minute on the lower part of the neck.	The Du channel, Ren channel, and many Yang meridians travel throughout the neck. Massaging the neck promotes the circulation of *qi* and blood into the head, improving the nutritional supply of the brain.
Step 8: Pressing and Kneading Jianjing	Acupoint GB21 (Jianjing)	Place a thin towel on the subject's shoulder, then use both hands to massage the shoulder muscle with mellow force. Ensure that the action is rhythmic and synchronized. Repeat for 3 minutes.	Pressing Jianjing promotes muscle strength, alleviates shoulder stiffness and soreness, and improves insomnia and restlessness.
Step 9: Pressing and Kneading Tianzong	Acupoint SI11 (Tianzong)	Use the thumbs or middle fingers of both hands to synchronously massage the acupoint SI11 (Tianzong) on both sides of the back. Repeated 5 times.	Pressing Tianzong relieves pain of the shoulders and upper limbs and enhances joint functions, and improves the mind.
Step 10: Pushing Qiaogong	Anterior cervical sternocleidomastoid muscle	Apply massage oil to the subject's sternocleidomastoid muscles in the front neck area, then use the pads of the index and middle fingers, or the middle finger alone, move swiftly downwards from the back of the ear, along the sternocleidomastoid muscle. The movement should be light and cause no discomfort to the subject. Repeat 50 times on each side.	Qiaogong can calm the liver and extinguish wind, pacify the heart, and soothe the mind.
Step 11: Grasping Jianjing	Acupoint GB21 (Jianjing)	Place a thin towel on the subject's shoulder, then use the thumbs and index/middle fingers of both hands to lift and grasp the shoulder muscle of both shoulders with	"Grasping Jianjing" has similar therapeutic effects to pressing Jianjing.

		appropriate force. Repeat 5 times.	
Step 12: Grasping Hegu	Acupoint LI4 (Hegu)	Use the thumb and index/middle fingers of one hand to lift and grasp the acupoint LI4 (Hegu) of both hands of the subject with appropriate force. Repeat 5 times.	"Grasping Hegu" can dispel wind, release the exterior, relieve pain, and strengthen immunity. It is often used for stroke sequelae, psychogenic tension, and pain.

B. Procedures and traditional Chinese Medicine (TCM) theory of "Least Acupressure Control (LAC)"

Step	Operating location	Procedure	TCM-based therapeutic effects
Step 1: Pressing and Kneading Tongtian	Acupoint BL7 (Tongtian)	Use the thumbs or middle fingers of both hands to massage the acupoint BL7 (Tongtian) on the head in synchronized circular motion. Knead softly to move the subcutaneous layer of the skin, instead of just rubbing the surface. Repeat for 1 minute.	Tongtian is often used to relieve nasal discomfort and treat upper orifice diseases.
Step 2: Pressing and Kneading Jianzhen	Acupoint SI9 (Jianzhen)	Use the thumbs to synchronously and softly massage the acupoint SI9 (Jianzhen) on both sides of the back. Repeat for 1 minute.	Pressing Jianzhen can relieve shoulder and neck pain, and improve limited upper limb movement.
Step 3: Pressing and Kneading Shousanli	Acupoint Ll10 (Shousanli)	Use the thumbs to softly massage the acupoint Ll10 (Shousanli) of both hands of the subject in synchronized circular motion. Repeat for 1 minute.	Pressing Shousanli can relax muscles and tendons, relieve swelling and pain. It is often used to treat elbow and arm pain, numbness, and weakness.

Assurance of study adherence: In addition to LAC that is applied to increase study adherence of participants of the control group, assistants who perform LAC and CAE will keep close communication with participants via social media (WhatsApp and WeChat) and send reminders for appointments of acupressure, assessment, and blood collection. The assistants will also be required to record treatment on a designed log, with date, start and end time, treatment duration, the category of the person delivering the session (investigator, research assistant, or student research assistant), number of missed and completed sessions, and

adverse events. The principal investigator (PI) and coordinator will regularly review the logs to find potential issues that could cause discontinuation.

Clinical assessment: Assessment will be conducted at baseline and thereafter once bimonthly, totalling 7 times. The primary outcome will be evaluated using HK-MoCA, which contains visuospatial, language, concentration, working memory, memory recall, and orientation domains, for a total possible score of 30 points (Nasreddine et al., 2005; Yeung et al., 2014). The secondary outcomes include HK-MoCA domains and the Digital Span Test (forward and reverse) for cognitive function, the Quality of Life in Alzheimer's Disease (QoL-AD) scale for quality of life, the Chinese Lawton Instrumental Activities of Daily Living Scale (IADL-CV) and the Chinese version of the Modified Barthel Index (MBI-C) for functional independence. The 15-item Geriatric Depression Scale (GDS-15) and the Pittsburgh Sleep Quality Index (PSQI) will be used to assess depression and sleep, as older adults living with dementia often have comorbid mood and sleep disorders. A nested economic evaluation will additionally be conducted to examine whether the 12-month CAE intervention is cost-effective compared with LAC, using health-related quality of life measured by the 5-level EQ-5D version (EQ-5D-5L) to derive QALYs.

Digit Span is a measure of working and short-term memory, and is evaluated in two formats, Forward Digit Span and Reverse Digit Span, with a total possible score of 14 points, respectively. The Digit span test is a simple test to further evaluate subjects' attentional function, short-term memory, and working memory (Jones & Macken, 2015).

QoL-AD is a 13-item questionnaire that is rated by both self and caregivers to measure physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores, ability to do things for fun, money and life as a whole. Response options include 1 (poor), 2 (fair), 3 (good) and 4 (excellent), for a total score of 13–52, with higher scores indicating better QoL (Logsdon et al., 1999;2002; Torisson et al., 2016).

IADL-CV a validated clinical assessment tool used evaluate complex daily living skills required for older adults to maintain independence in the community. IADL-CV covers 9 specific functional areas, i.e., ability to use a telephone, mode of transportation, shopping, food preparation, housekeeping, household maintenance, laundry, responsibility for own medications, ability to handle finance, with a 3-point ordinal scale per item. IADL-CV score ranges from 0 to 18, with a higher score indicating a higher level of independence (Lawton & Brody, 1969; Tong & Man, 2002).

MBI-C is a validated outcome measure to evaluate the functional status and dependency of patients. MBI-C consists of 10 items, i.e., feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation, and stair climbing, to score with a five-step scoring system. MBI-C score ranges from 10 to 50, with a higher score indicating a higher level of independence (Shah et al., 1989; Leung et al., 2007).

GDS-15 consists of 15 questions in which subjects are asked to respond by answering yes or no in reference to how they felt over the past week. Of the 15 items, 5 items (question numbers 1, 5, 7, 11, 13) indicate depression when answered negatively, while the rest of the questions indicate the presence of depression when answered positively. The GDS-15 score is interpreted as follows: normal (0-4), mild depression (5-8), moderate depression (9-11), and severe depression (12-15) (Yesavage et al., 1982; Chiu et al., 1994). GDS can be used in older adults with mild to moderately cognitive impairment (Feher et al., 1992).

PSQI is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval, with an overall score ranging from 0 to 21, and lower scores indicate a better sleep quality (Buysse et al., 1989).

The EQ-5D-5L is a generic, preference-based measure of health-related quality of life comprising five dimensions (mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression), each with five response levels, together with a visual analogue scale (EQ VAS) on which respondents rate their health today from 0 (the worst health you can imagine) to 100 (the best health you can imagine). The Traditional Chinese (Hong Kong) interviewer-administered version will be used and will be delivered to participants by a trained research assistant at all seven assessment time points, following the standardised interviewer instructions supplied by the EuroQol Research Foundation; administration requires approximately 5 minutes. Responses will be converted into a single utility index using the Hong Kong value set (Wong et al., 2018). Unlike the QoL-AD, which is retained as a condition-specific measure of quality of life, the EQ-5D-5L is preference-based and is therefore required to derive QALYs for the economic evaluation.

Adverse events (AEs) will be systematically recorded at each session of treatments and assessments, in which AEs that first appear in the study or worsen relative to the pre-study status will be recorded at each visit, including date and time of onset, duration, severity, relationship to intervention, and action taken accordingly. Related AEs will be grouped by system organ class (SOC), if applicable, to minimize false discovery of AEs.

Fatal or life-threatening unexpected AEs will be reported to the regulatory bodies as soon as possible but no later than 7 calendar days after first knowledge by the PI that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report would include an assessment of the importance and implications of the findings, including relevant previous experience with the same or similar medicinal products. For other serious, unexpected AEs that are not fatal or life-threatening, they will be reported as soon as possible but no later than 15 calendar days after first knowledge by the PI or that the case meets the minimum criteria for expedited reporting. For non-serious AEs and serious AEs that are expected, they will be reported in a brief summary at the conclusion of the trial.

Blood sample collection and biomarker analysis: To minimize potential physical discomfort and psychological stress caused, a part-time certified phlebotomist will be employed to collect blood samples. Three 5-ml blood samples will be collected at baseline, 6 months, and 12 months, respectively. As aforesaid in **Screening and recruitment** section, the screening blood samples and analysis values will be reused for baseline if participants give informed consent for participation in the study within one month of post-screening sample collection. Otherwise, an additional 5-ml blood sample will be collected for baseline. The samples will be collected at 08:00 after an overnight fast into tubes coated with an anticoagulant. Plasma will be immediately separated via centrifugation. For screening blood samples, some plasma separated from baseline blood samples will be immediately measured for Aβ42, Aβ40, p-tau181, and p-tau217 for screening. Other plasma will be stored at -80°C until assayed. Aβ42, Aβ40, p-tau181, p-tau217, NfL, and GFAP will be measured using commercial enzyme-linked immunosorbent assay (ELISA) kits.

Maintenance of consistency and fidelity: The study will last about 3 years and be carried out at multiple sites. There also will be many different professional investigators involved in the study. To ensure and maintain high consistency and fidelity of intervention and assessment across sites and throughout 3 years of study period, training workshops will be conducted at pre-trial, the beginning of year 2 and year 3. Research team members, including research assistants and student research assistants will receive training. A training manual will be prepared for CAE and LAC procedures and clinical assessment instruments.

For intervention training, the PI and a senior Chinese medicine practitioner (CMP) will instruct and demonstrate CAE and LAC. Trainees will practice CAE and LAC with each other. Investigators and assistants who will perform CAE and LAC must obtain satisfactory training outcomes, which will be rated by the PI and a senior CMP.

For clinical assessment training, an investigator (CHAN WC) who has extensive experience in clinical assessment will instruct clinical instruments. An older adult living with dementia

will be invited to be evaluated for HK-MoCA by investigators who will be responsible for clinical assessment. An inter-rater reliability coefficient (*k* value) of >0.80 must be achieved after the completion of each training workshop.

To further ensure consistency and fidelity, the following additional measures will be taken: (1) all assessors will be deployed to each site via central allocation; (2) all assessments from baseline throughout endpoint for the same participant will be performed, if possible, by the same assessor who is blind to participants' intervention; (3) all interventions of each patient will be conducted by the same intervener, if possible.

Safety assurance and ethical consideration: The study will be carried out in accordance with the ethical principles of the Declaration of Helsinki' and its subsequent amendment. Ethical approval is being sought and must be obtained before the recruitment starts. The proposed study will be registered in www.clinicalTrials.gov, which is accessible to the public, before the onset of patient enrolment.

Two written consents will be obtained: one is from potential subjects for blood collection for biomarker screening; another from participants whose eligibility is confirmed. Both participants and their guardians are required to provide written consent. Guardians are those who are participants' next of kin or legal guardians appointed by a court or via a will to make personal, medical, or financial decisions for an incapacitated adult. As participants are mild dementia, the procedure of obtaining consent will follow the international protocol (https://www.alzheimers.org.uk/dementia-professionals/dementia-experience-toolkit/howrecruit-people-dementia/consent-and-capacity). A full explanation of the study goal, procedures (including blood collection), and potential side effects and risks will be presented to each participant. The consent will also cover access to care-centre records for the purpose of recording health and residential care service use for the economic evaluation.

Informed consent and other documents provided to patients will be written in both English and Chinese. This study is conducted on Chinese patients. Patients would not receive remuneration, but treatments and biochemical assessments directly associated with the clinical trial will be provided at no cost. Upon completing all 12 months of the intervention and assessment, a transportation subsidy of HKD$500 will be given to patients to thank them for their support of this study. The issue of confidentiality is a major ethical issue, and will be solved by recording the data in a manner that does not allow the participants to be identified (i.e., using a non-recognizable code for each patient). A review of medical records that have been already recorded as part of clinical care. Therefore, this poses no physical risks.

For those who fulfil the neuropathogenic inclusion criteria but are identified as undiagnosed cases, they will be referred to a psychiatry specialist of Co-Is (CHAN WC or CHANG WC) for further confirmation of the eligibility. Their guardians are informed and a follow-up will be arranged.

Case Record Form (CRF) will be used to record each participant's assessment and treatment. Emergency contact numbers (the investigator's mobile number and a hotline number) will be provided in the informed consent in case of any AEs.

Record retention: The investigators, and their designated study team members and research staff, and the Research Ethics Committees (RECs) are responsible for overseeing this study to get access to, use, and retain subjects' personal data for the purposes of clinical study; and the relevant local or overseas regulatory bodies, e.g., the National Medical Products Administration (NMPA), can get access to subjects' personal data for the purposes of checking and verifying the integrity of study data and assessing compliance with the study protocol and relevant requirements. Subjects who have the rights of access to personal data and known study results will have access to the personal and study data if and when needed. The lead PI will be responsible for the execution of data protection.

The collected personal information and study data will be kept for 5 years after the completion of the study. After completion of the aforesaid storage period, all personal and study data will be destroyed, subject to local regulations. The collected blood samples will be destroyed after the completion of the study. To protect patient privacy, all research data will be handled in line with Hospital Authority (HA)/Hospital's policy in handling/storage/destruction of patients' medical records. They will be locked in cabinets where the department keep patient information. Electronic data will be saved in secured computer of the department with restricted access. Universal Serial Bus (USB) device will not be used for patient information nor personal data. Personal data (name, Hong Kong Identity [HKID], outpatient department / hospital numbers, address and any other personal identifiable information) will not be recorded on the project's data sheets or electronic files. A study code will be used instead. The document of electronic file containing the linkage information between the study code and the identity of the patient will contain no other information and will be kept separate from the study data files or data sheets with the same stringent security as the medical record. Any documents or electronic files containing personally identifiable information will be considered as part of the medical record and will be dealt with the same stringent regulations of security according to the HA/Hospital's policies.

Data processing and analysis: The analysis will be carried out on the intention-to-treat (ITT) population, defined as participants who complete baseline and at least one post-treatment evaluation. A linear mixed-effect model will be applied to compare the primary outcome (changes in the total HK-MoCA score from baseline) and secondary outcomes (HK-MoCA domains, Digital Span test, QoL-AD, EQ-5D-5L, MBI-C, GDS-15, and PSQI) between the two groups. The model will be established using time and group as categorical fixed factors and random intercepts within a scaled identity covariance matrix. Although stratified randomization is expected to minimize confounding effects of gender, age and baseline HK-MoCA, all confounders, including gender, age, baseline HK-MoCA, baseline amyloid and tau levels, medication, routine care, and study sites, will be controlled by including them in the outcome analysis as covariates. Subgroup analysis will be conducted to compare outcomes by gender (female and male), age (60–74 years and 75–85 years), care setting types (care and attention homes for the elderly and elderly activity centres), and baseline HK-MoCA (16th–9th percentile group and <9th–2nd percentile group) to detect whether these factors are associated with outcomes. Two-way repeated measures analysis of variance (ANOVA) will be used to detect significant differences in blood biomarkers (Aβ42/Aβ40 ratio, p-tau181, p-tau217, NfL and GFAP) between the two groups. Linear regression will be conducted to examine inter-correlations between clinical outcomes and biomarker levels. Independent-samples t-test will be used to detect differences in continuous baseline variables and biomarker levels between the two groups. Categorical baseline variables, including discontinuation and incidence of AEs will be analysed using Chi-square test. Statistical significance is defined as a two-tailed $P < 0.05$.

A within-trial cost-utility analysis will be conducted from the perspective of the healthcare payer. QALYs will be estimated by the area-under-the-curve method from EQ-5D-5L utility values measured at the seven assessment time points, with baseline utility included as a covariate; no discounting will be applied given the 12-month time horizon. The cost of delivering CAE and LAC will be estimated by micro-costing, using the treatment logs to obtain, for each participant, the number of sessions completed, the duration of each session, and the category of staff delivering it, valued at the corresponding salary rates inclusive of on-costs; the costs of training workshops and supervision will be apportioned across participants. Participants' use of health and social care services in the preceding 6 months will additionally be recorded at baseline, month 6, and month 12 from the service records maintained by the participating centres, verified with the participant, their caregiver, or centre staff by the research assistant, and valued using published Hong Kong unit costs. Costs

arising solely from research procedures, including blood sampling and biomarker assays, will be excluded, as they would not be incurred if the intervention were delivered in routine practice. The incremental cost-effectiveness ratio, expressed as the incremental cost per QALY gained, will be calculated, and uncertainty will be characterized by non-parametric bootstrapping, with results presented on the cost-effectiveness plane and as cost-effectiveness acceptability curves. Missing utility and cost data will be handled by multiple imputations.

Termination criteria:

Premature termination or suspension of study: The study will be completed as planned unless the following criterion are satisfied that require temporary suspension or early termination of the study: new information or other evaluation regarding the safety or efficacy of the procedure that indicates a change in the known risk/benefit profile, such that the risk/benefit is no longer acceptable for subjects participating in the study.

Premature termination or suspension of investigational sites: A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of protocol or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

Procedures for premature termination or suspension: In the event that the PI, an institutional review board (IRB) / REC or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the PI; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

Criteria for discontinuation or withdrawal of a subject: (1) pretreatment event or AE: the subject has experienced a pretreatment event or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pretreatment event or AE; (2) major protocol deviation: the discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health; (3) lost to follow-up: the subject does not return to the clinic and attempts to contact the subject are unsuccessful; (4) withdrawal of consent: the subject wishes to withdraw from the study; (5) study termination: the PI, IRB, REC, or regulatory agency terminates the study.

Procedures for discontinuation or withdrawal of a subject: The investigator may terminate a subject's study participation at any time during the study when the subject meets the study termination criteria. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination would be recorded. Subjects who discontinue the study during the treatment period will visit the site as soon as possible for clinical assessment if applicable. To ensure participants' safety, those discontinued because of severe side effects or hospitalization due to any reason will be given individual clinical treatment. Discontinued or withdrawn subjects will not be replaced.

Potential pitfalls and contingency plans

Our several previous studies and the aforementioned randomized controlled trials have well validated the feasibility and the short-term effectiveness of CAE in older adults living with dementia. This provides a direct and solid basis to ensure the success of the proposed long-term intervention study. We expect that CAE could produce better outcomes than LAC in improving cognitive deterioration, functional dependence, mood, sleep, blood amyloid and tau markers. In addition, we expect that this acupressure intervention is cost-effective, which

may help elderly service providers and policymakers decide whether it should be made more widely available. More importantly, related collaborative networks, protocols, and the research team have been well established in the previous study. It is therefore very unlikely that impassable obstacles will be encountered in the proposed studies.

Despite this, according to our previous studies, slow recruitment progress often happened due to unpredictable causes. If the recruitment could not reach the goal as per the proposed timetable frame at the end of the first year, additional study sites will be sought in local areas and the Hong Kong University - Shenzhen Hospital.

3. Existing Facilities and research members

(i) Through the aforesaid trial, we have established an extensive collaboration network with local elderly care centres. The study will be conducted firstly in the following 9 care and attention homes for the elderly and elderly activity centres" which accommodate about 1,000 elderly. This provides sufficient subjects to ensure the recruitment in a timely manner. Based on our aforesaid trial, 188 subjects are expected to be recruited within 18 months, with approximately 10-11 subjects recruited per month, such that all the interventions and assessments are expected to be completed in 30 months.

(ii) ELISA analysis of biomarkers will be conducted in the Laboratory of the School of Chinese Medicine, where necessary and sufficient equipment and reagents are provided.

(iii) Research team and recruitment criteria of research assistants: core members and their roles are listed below:

Core members of research team

Name	Position and affiliation	Role and duties
ZHANG, Zhang-Jin	Professor, School of Chinese Medicine, the University of Hong Kong (HKU)	PA: foresee, design, supervise and monitor the entire project.
CHAN, Wai Chi	Clinical Professor, President of Chinese Dementia Research Association, Department of Psychiatry, HKU	Co-A: Screening, clinical and biomarker diagnosis of AD, and post-termination management
CHANG, Wing Chung	Clinical Professor and Chairpersion, Department of Psychiatry, HKU	Co-A: Screening, diagnosis of AD, and post-termination management
LI, Lei	Principal Professional Practitioner, School of Chinese Medicine, HKU	Co-A: supervise CAE and training workshop.
CHAN, Mei Yan	Postdoctoral Fellow, School of Chinese Medicine, HKU	Co-A: coordination, recruitment, and treatment

Caregivers, general physicians and social workers in the care centres will help identify potential subjects who may be eligible for the study and refer them to the research team. We will employ research assistants (RAs) and 2 student research assistants. One RA will perform screening and clinical assessment; another RA will be responsible for laboratory analysis and data analysis. Two student RAs will perform treatment. Psychiatry specialists of Co-Is (CHAN WC and CHANG WC) will be responsible for the confirmation of eligibility if an

ambiguity occurred. The Co-I Chan MY will serve as the coordinator responsible for the coordination of the study, recruitment, and performing treatment.

The recruitment criteria of the RA for screening and clinical assessment are at least a bachelor's degree in psychology, neuroscience, or a related field, with at least 3 years of clinical/research assessment experience, particularly in elderly or cognitively impaired populations. The recruitment criteria of the RA for laboratory analysis and data analysis are bachelor or master's degree in biomedical science or related field with at least 3 years of experience in laboratory work and data analysis. The recruitment criteria of the two student RAs for treatment are undergraduate students studying Chinese medicine (BChinMed), medicine (MBBS) or nursing (BNur) or postgraduate students with clinical medicine.

4. Justification of Requirements:

This is a three-year multi-site clinical trial with 188 subjects. There will be approximately 30,000 sessions of CAE and LAC, 1,316 sessions of clinical assessments, and 564 blood samples for analysis of 4 biomarkers. Two student research assistants and two research assistants are therefore needed to pursue these tasks.

5. Plan to Disseminate Research Findings to End Users:

Upon the completion of this proposed study, the following disseminations will be taken:

1. Distribute the CAE brochures with video to local community elderly care facilities and nursing homes, and hold regular training workshops for their caregivers and family members.
2. Make a CAE video clip and post it onto social media, including YouTube, TikTok, WeChat, and Little Red Book.
3. Introduce CAE to AD patients and their caregivers in public hospitals of the HA and nursing homes of the Social Welfare Department.

6. Funding

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