Research

A multifactorial intervention for frail older people is more than twice as effective among those who are compliant: complier average causal effect analysis of a randomised trial

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KEY WORDS

Compliance
Adherence
Frail elderly
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Exercise

CrossMark

ABSTRACT

Question: What is the effect of a multifactorial intervention on frailty and mobility in frail older people who comply with their allocated treatment? **Design:** Secondary analysis of a randomised, controlled trial to derive an estimate of complier average causal effect (CACE) of treatment. **Participants:** A total of 241 frail community-dwelling people aged $\geq$ 70 years. **Intervention:** Intervention participants received a 12-month multidisciplinary intervention targeting frailty, with home exercise as an important component. Control participants received usual care. **Outcome measures:** Primary outcomes were frailty, assessed using the Cardiovascular Health Study criteria (range 0 to 5 criteria), and mobility measured using the 12-point Short Physical Performance Battery. Outcomes were assessed 12 months after randomisation. The treating physiotherapist evaluated the amount of treatment received on a 5-point scale. **Results:** 216 participants (90%) completed the study. The median amount of treatment received was 25 to 50% (range 0 to 100). The CACE (ie, the effect of treatment in participants compliant with allocation) was to reduce frailty by 1.0 frailty criterion (95% CI 0.4 to 1.5) and increase mobility by 3.2 points (95% CI 1.8 to 4.6) at 12 months. The mean CACE was substantially larger than the intention-to-treat effect, which was to reduce frailty by 0.4 frailty criteria (95% CI 0.1 to 0.7) and increase mobility by 1.4 points (95% CI 0.8 to 2.1) at 12 months. **Conclusion:** Overall, compliance was low in this group of frail people. The effect of the treatment on participants who comply with allocated treatment was substantially greater than the effect of allocation on all trial participants. **Trial registration:** Australian and New Zealand Trial Registry ANZCTRN12608000250336. [Fairhall N, Sherrington C, Cameron ID, Kurrle SE, Lord SR, Lockwood K, Herbert RD (2016) A multifactorial intervention for frail older people is more than twice as effective among those who are compliant: complier average causal effect analysis of a randomised trial. *Journal of Physiotherapy* 63: 40–44]

Introduction

The number and proportion of older people in the global population are rapidly rising.[1] Frailty and mobility impairment increase the risk of dependence, hospitalisation and death in older people.[2,3] Interventions that reduce frailty and improve mobility have the potential to benefit older people and society.[4]

The recommended primary approach to analysis of randomised, controlled trials is analysis by intention to treat.[5] Clinical trials in frail older people are particularly affected by variable compliance to treatment; some people randomised to the intervention group will not undertake the intended treatment and some will undertake part or all of the treatment.[6] A range of statistical techniques can provide estimates of the average causal treatment effect among compliant participants.[7,8] The framework and assumptions of these techniques have been described in detail

elsewhere.[8] Briefly, we assume that at the start of a trial all participants have an unobservable inherent trait that determines whether or not they will comply with the allocated treatment. As randomisation results in the expectation of an equal distribution of compliers and non-compliers to the intervention and control groups, we can observe the proportion of compliers and non-compliers in the treatment group and infer the proportions in the control group. Herein we use the term *complier* to describe a participant who undertakes treatment if allocated to the treatment group and does not undertake treatment if allocated to the control group. The term *treatment received* is used to describe the observed amount of treatment undertaken by trial participants.

In our randomised, controlled trial of 241 frail older people, the intention-to-treat analysis demonstrated that the multifactorial intervention caused worthwhile improvements in frailty and mobility, compared to usual care.[9] The effect of actually

undertaking the intervention in people who comply with their allocated treatment, that is, the CACE, is of interest to those seeking to implement such an intervention. Consequently we sought to estimate the CACE. Previous studies that have estimated CACEs[10–12] have dichotomised compliance to prescribed treatment. As compliance to an ongoing complex treatment is a continuous quantity, analysis of compliance as a continuous or ordinal variable may be preferable. We evaluated the CACE using instrumental variable regression, with the amount of treatment received as a continuous variable.[8,13]

Therefore, the research question for this secondary analysis of a randomised, controlled trial was:

What is the effect of a multifactorial intervention on the primary study outcomes of frailty and mobility in frail older people who comply with their allocated treatment?

Method

Design

We conducted a secondary analysis of the Frailty Intervention Trial – a prospective, parallel-group, assessor-blind, randomised, controlled, single-centre trial. Participant recruitment commenced in January 2008 and finished in June 2010. The protocol and primary results have been published elsewhere.[9,14–16]

Participants

Briefly, 241 participants were recruited following discharge from the Division of Rehabilitation and Aged Care Services at Hornsby Ku-ring-gai Health Service (Sydney, Australia). Eligible participants: were aged $\geq$ 70 years; met the Cardiovascular Health Study criteria for frailty (met specified cut-offs for three or more of: slow gait, weak grip, exhaustion, low energy expenditure and weight loss);[2] did not reside in a residential aged care facility; did not have severe cognitive impairment (defined as a Mini Mental State Examination[17] score of $\leq$ 18); and had a life expectancy exceeding 12 months (estimated by a modified Implicit Illness Severity Scale score of $\leq$ 3).[18]

The trial statistician developed the group allocation schedule using a computer-generated, random number sequence that was stratified by degree of frailty (three frailty criteria versus four or five frailty criteria) using permuted blocks of random sizes. The allocation schedule was stored off-site and concealed from the staff who recruited the trial participants. Following baseline assessment, randomisation was performed by staff not involved in recruitment or assessment. Researchers who collected outcome measures, and recorded and analysed data were blinded to group allocation. Participants and treating staff could not be blinded to group allocation.

Intervention

Participants were randomised to receive usual care or a 12-month interdisciplinary, multifactorial intervention. The treatment, which has been described elsewhere,[14] was individualised to each participant based upon the frailty criteria present and incorporated the principles of geriatric evaluation and management. Delivered by a team comprised of two physiotherapists, a dietician, rehabilitation physician, geriatrician and nurse, the treatment was coordinated by a physiotherapist and involved case-conferences and case management. Participants who met the weight-loss frailty criterion received dietician assessment and management. All participants received 10 physiotherapy home visits and a home exercise program consisting of lower limb strength and balance exercises to be completed three to five times per week for 12 months. Medical management included management of chronic health conditions and medication review.

Participants were referred to services as indicated. Multiple strategies were used to maximise the amount of treatment received by participants allocated to the treatment group, such as involvement of family and carers, exercise diaries, visual cues, goal setting, and education. The strategies are outlined using the Behavior Change Technique Taxonomy[19] in a supplementary file (see Appendix 1).

The control group received the usual care provided to older residents of the area from their general practitioner and community services, which may have included medical and allied health management, and assessment and delivery of care needs.

Outcome measures

The original trial had two primary outcomes: frailty and mobility. Frailty was measured using a modification of the Cardiovascular Health Study definition of the frailty phenotype, whereby frailty was defined by the presence of at least three of five criteria (weight loss, slow walking, weakness, exhaustion, low energy expenditure).[2,9] Mobility was measured with the Short Physical Performance Battery,[20] which measures: the ability to stand for up to 10 seconds with feet side-by-side, semi-tandem and tandem; time to walk 4 m; and time to rise from a chair five times. Health professionals blinded to group allocation assessed outcomes at baseline (before randomisation) and at 3 and 12 months after randomisation.

Measurement of treatment received

At weekly case conferences and each home visit, the physiotherapist kept a written record of the treatment components prescribed and treatment received by participants allocated to the intervention group. Exercise intervention was measured by number of repetitions as recorded in the participant's exercise diary, or where the physiotherapist considered the diary inaccurate, estimated through discussion with the participant, their family or carer plus assessment of physical progress. Self-report and proxy-report was used to measure the number of dietician-recommended supplements and meals taken. Follow-up of medical conditions was measured by attendance at scheduled appointments. Service use was quantified by the hours of services accepted compared with the hours of services recommended by the service provider or physiotherapist. At 12 months, the treating physiotherapist calculated the overall amount of treatment received as a proportion of the amount of treatment prescribed. This estimate was reported on a 5-point scale that has face validity and was determined prior to analysis of study outcomes: 0%, 1 to 25%, 26 to 50%, 51 to 75%, and 76 to 100%.

As the treatment was only deliverable to participants randomised to receive it, the amount of treatment received was only measurable in the intervention group. It was assumed that the control group could not access treatment.

Data analysis

The amount of treatment received was calculated for intervention participants. We described baseline characteristics of the intervention group participants by the amount of treatment received, and reported the baseline characteristics of the control group. The intention-to-treat effect was estimated as per the original analysis; participants were analysed by group allocation, irrespective of compliance, using linear regression models with the baseline of the outcome as covariates.[9] The CACE estimates the mean effect of treatment in compliers who undertake 100% of treatment if allocated to the treatment group and 0% of treatment if allocated to the control group.[13] We estimated the CACE using instrumental variable regression[13,21] using the 'ivregress' command in Stata software[a] with the two-stage least squares estimator. The instrument was the randomly allocated treatment. The amount of treatment received was entered as a continuous

variable. To enhance the precision of the estimate, we included covariates that were significantly associated with baseline frailty in univariate regression analysis and likely to be related to amount of treatment received: baseline age, use of a walking aid, mood, cognition, and quality of life. The amount of treatment received was plotted against change in frailty and change in mobility over 12 months in the intervention and control groups, with the spline illustrating the relationship between amount of treatment and outcome.[22]

Results

### Flow of participants through the trial

Of the 241 randomised participants, 216 (90%) completed the 12-month assessment. The majority of losses to follow-up were due to death (12 in the intervention group and 10 in the control group). Three participants withdrew from the study (one from the intervention group and two from the control group). One participant in the intervention group had missing data for baseline mood and cognition, and was excluded from analyses that involved these covariates.

There was no significant association between loss to follow-up and amount of treatment received. At the 12-month follow-up, frailty and mobility data were available for 87% (60/69) of those participants randomised to the intervention group who under-took < 50% of treatment, and 92% (47/51) of the participants randomised to the intervention group who undertook > 50% of treatment (Chi-squared *p*-value = 0.37).

The median amount of treatment received was 26 to 50% of that prescribed. Sixteen (13%) of the 220 participants in the intervention group received no intervention, 34 (29%) received 1 to 25% of the intervention, 19 (16%) received 26 to 50%, 26 (21%) received 51 to 75%, and 25 (21%) received 76 to 100% (Figure 1).

Table 1 compares the baseline characteristics of the participants in the control group and participants in each of the five categories in the intervention group. There was little difference in the characteristics of the groups, although participants randomised to the intervention group who did not receive any treatment were older and had poorer function measured using the SPPB and Barthel Index.

Univariate regression analyses showed that age, walking aid, mood and quality of life were independently and significantly (*p* < 0.05) associated with frailty; however, cognition was not. The
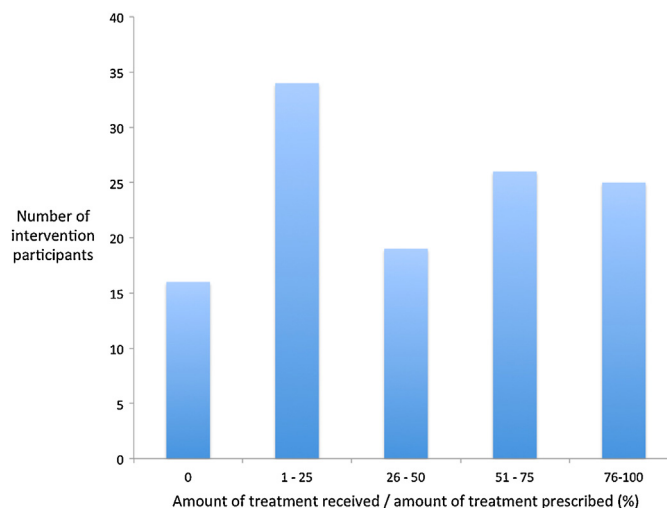
Figure 1. Amount of treatment received in the intervention group. Number of participants in each category is shown on the vertical axis (n = 120) and the amount of treatment received on the horizontal axis.

variables independently and significantly associated with mobility were age, walking aid and quality of life, but not mood and cognition. None of these variables were significantly associated with amount of treatment received on the 5-point scale.

Estimates of treatment effect

The estimates of the intention-to-treat effect and the CACE are shown in Table 2. Including covariates in the analysis had little effect on the results, so the unadjusted analyses are presented. The CACE was a 1.0 criterion reduction in frailty (95% CI 0.4 to 1.5) and 3.2 point increase in mobility (95% CI 1.8 to 4.6) at 12 months. The relationship between amount of treatment received and the frailty and mobility outcomes are illustrated in Figures 2 and 3, respectively.

The reduction in frailty was about 2.5 times greater with the CACE estimate of treatment effect compared with the intention-to-treat estimate (Table 2). Compared with intention to treat, the CACE estimate of the treatment effect increased from 0.4 to 1.0 for the reduction in frailty and from 1.4 to 3.2 for the improvement in mobility. The significance levels of the intention-to-treat and CACE estimates were similar.

Table 1
Baseline characteristics of participants by amount of treatment received.

Characteristic	Percentage of the multifactorial intervention received (n = 120)					
	Control (n = 121)	0% (n = 16)	1 to 25% (n = 34)	26 to 50% (n = 19)	51 to 75% (n = 26)	76 to 100% (n = 25)
Age *(yr)*, mean (SD)	83.2 (5.9)	84.9 (7.0)	83.6 (5.4)	83.6 (5.4)	83.0 (6.4)	82.6 (5.4)
Gender, n male (%)	39 (32)	5 (31)	10 (29)	8 (42)	9 (35)	7 (28)
Lives alone, n (%)	51 (42)	8 (50)	18 (53)	8 (42)	12 (46)	14 (56)
Total frailty criteria[a], n (%)						
3	79 (65)	9 (56)	19 (56)	14 (74)	15 (58)	20 (80)
4	30 (25)	7 (44)	13 (38)	3 (16)	8 (31)	2 (8)
5	12 (10)	0 (0)	2 (6)	2 (11)	3 (12)	3 (12)
Coexisting conditions[b], mean (SD)	5.9 (2.3)	5.8 (2.7)	6.3 (2.2)	6.5 (2.5)	5.2 (2.3)	5.5 (2.1)
Mini Mental State Exam[c,d], mean (SD)	25.9 (3.1)	25.4 (3.2)	27.1 (2.4)	26.4 (2.8)	26.5 (2.8)	27.1 (1.8)
Geriatric Depression Scale[c,e], mean (SD)	5.1 (3.2)	4.8 (3.2)	4.8 (2.9)	4.8 (3.8)	5.3 (3.9)	4.1 (2.3)
Short Physical Performance Battery score[f], mean (SD)	5.7 (2.1)	4.4 (1.8)	4.9 (1.7)	5.3 (2.0)	5.7 (2.0)	5.6 (1.9)
Barthel Index[g], mean (SD)	92.5 (14.3)	89.1 (15.6)	93.7 (10.1)	94.5 (9.4)	93.5 (12.4)	97.4 (8.2)
Health-related quality of life, EQ-5D[h], mean (SD)	7.8 (1.5)	8.2 (1.4)	7.7 (1.4)	7.5 (1.3)	7.6 (1.7)	7.4 (1.6)

Data presented as number (%) or mean (standard deviation).
[a] Frailty Phenotype (modified from Cardiovascular Health Study criteria).
[b] Self-reported, doctor-diagnosed medical conditions.
[c] Missing data for Mini Mental Status Examination (n = 2) and Geriatric Depression Scale (n = 1).
[d] The Mini Mental Status Examination[17] has scores between 0 and 30, with higher score indicating better cognition.
[e] The Geriatric Depression Scale (short form)[26] has scores between 0 and 15, with more depressive symptoms indicated by a higher score.
[f] The Short Physical Performance Battery[20] has scores between 0 and 12, with a higher score indicating better mobility.
[g] The Barthel Index[27] has scores between 0 and 100, with higher scores indicating better basic activities of daily living functioning.
[h] The EQ-5D[28] has scores between 5 and 15, with higher scores indicating worse health-related quality of life.

Table 2
Intention-to-treat and CACE estimates of treatment effect at 12 months.

Outcome	Intention-to-treat estimate[a]		CACE estimate[b]	
	Mean treatment effect (95% CI)	*p*-value	Mean treatment effect (95% CI)	*p*-value
Frailty[c]	−0.4 (−0.1 to −0.7)	0.004	−1.0 (−0.4 to −1.5)	0.002
Mobility[d]	1.4 (0.8 to 2.1)	< 0.001	3.2 (1.9 to 4.7)	< 0.001

[a] Based on a linear regression model adjusted for baseline score.
[b] Based on an instrumental variable regression model, adjusted for baseline score.
[c] Measured using modification of Cardiovascular Health Study criteria[2] (range 0 to 5).
[d] Measured using Short Physical Performance Battery[20] (range 0 to 12).
CACE = complier average causal effect.
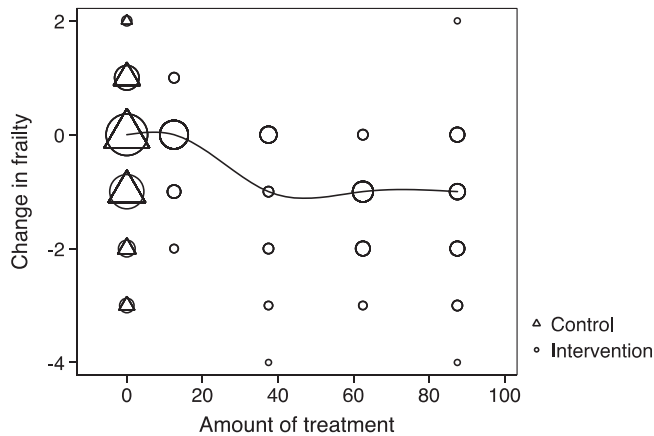
Figure 2. Amount of treatment received and change in frailty over 12 months in intervention and control groups. Frailty was measured using modified Cardiovascular Health Study Criteria (range 0 to 5). Negative change indicates a reduction in frailty. The symbol area is proportional to the number of participants. The line is a median spline.
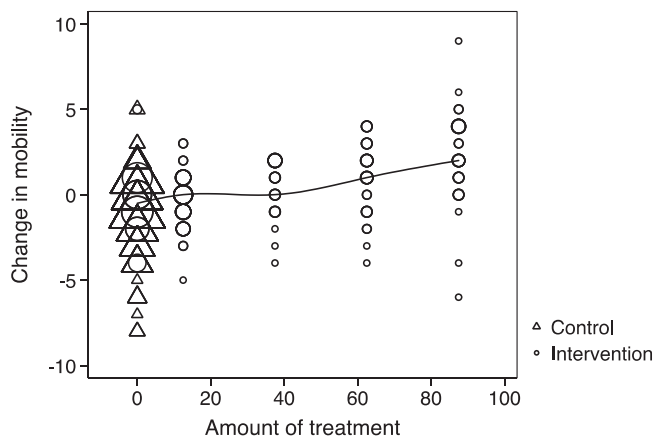
Figure 3. Amount of treatment received and change in mobility over 12 months in intervention and control groups. Mobility was measured using the Short Physical Performance Battery (range 0 to 12). Positive change indicates an increase in mobility. The symbol area is proportional to the number of participants. The line is a median spline.

Assuming a linear relationship between amount of treatment received and the effect of the treatment on frailty, the size of the effect on frailty is a reduction by 1.0 frailty criterion (95% CI 0.4 to 1.5) for a person who receives 100% of the intervention, 0.5 (95% CI 0.2 to 0.8) for a person who receives 50% of the intervention, and 0.2 (95% CI 0.1 to 0.4) for a person who receives 25% of the intervention. The size of the effect on mobility is an increase of 3.2 points on the SPPB (95% CI 1.9 to 4.7) for a person who receives 100% of the intervention, 1.7 (95% CI 1.0 to 2.3) for a person who receives 50% of the intervention, and 0.8 (95% CI 0.5 to 1.2) for a person who receives 25% of the intervention.

Discussion

To our knowledge this is the first trial to examine the effect of an intervention program targeting frailty on people who comply with allocated intervention. Consideration of both the intention-to-treat and CACE analyses provides a more complete understanding of the effects of the intervention. It has been argued that CACE estimates have greater clinical relevance and are more indicative of the effect of undertaking treatment.[11]

The method used to estimate the CACE is subject to limitations. First, there is no established approach to identify compliers and non-compliers to multifactorial interventions. We estimated the amount of uptake of the intervention on a 5-point scale; however, a performance-based method of quantifying intervention would have been more precise. Second, although access to the multifactorial intervention was limited to people randomised to the intervention group, it is conceivable that the treatment effect was underestimated because some participants randomised to the control group undertook components of the intervention.[11] Third, a key assumption of CACE analysis is exclusion restriction, which implies that the offer of treatment affords no additional benefit to non-compliers randomised to the intervention group compared with non-compliers randomised to the control group.[8] In this study there was potential for placebo effects, which could have caused the exclusion restriction to be violated and bias the CACE; however, such placebo effects would bias both the intention-to-treat estimate and the CACE estimate. Fourth, the two-stage least squares approach to instrumental variable regression estimates the 'weighted average of causal responses to a unit change in treatment'.[13] Thus, we have implicitly assumed that the effect of intervention scales linearly with the proportion of the intervention actually received. Finally, there were no data for the 22/241 participants who died (9%). The number of deaths was similar in the intervention and control groups, so missingness due to death was ignored in the analysis.

People who comply with allocated intervention experience a clinically meaningful improvement in mobility and reduction in frailty. The mean increase in mobility of 3.2 points on the SPPB exceeded the suggested cut-off of 1.3 for a substantial, meaningful change in a sample of older people with a higher level of functioning,[23] so is likely to be clinically significant in this comparatively frail group. The implications of reducing frailty by one criterion are not yet clear, due to the limited research in this area. However, this reduction is likely to be meaningful to the older person and those allocating healthcare resources, as it represents a 20% reduction in the 5-point Cardiovascular Health Study criteria for frailty and participants, on average, benefited by being stronger, walking faster, being more active, not feeling exhausted, or being better nourished. Cost-effectiveness analysis previously showed that the intervention provided better value for money than usual care, particularly for the very frail, in whom it had a high likelihood of being cost saving and effective.[24]

The amount of intervention undertaken was less than in most trials of exercise interventions in frail older people.[6,25] The comparatively low uptake in this trial may be explained by the multifaceted intervention and comparatively long 12-month duration, during which frail older people are likely to experience fluctuating health, physical and social needs. Further studies are needed to determine methods to increase uptake of interventions among frail older people.

We previously estimated the effect of allocation to a multifactorial intervention targeting frailty and concluded the effect was clinically worthwhile. In this paper we estimated the effect of the intervention in compliers and found a more than two-fold greater effect of treatment in this group. It is recommended that future studies of frail older people record and evaluate the amount of treatment received and estimate effects of intervention in compliant participants.

What was already known on this topic: Multifactorial intervention can improve frailty and mobility in older people; however, frail older people were poorly compliant with a multifactorial intervention in a large controlled trial.
What this study adds: The data from the large trial were re-analysed to determine the effect of the treatment among participants who comply with whichever treatment they are allocated. This re-analysis identified an effect of the intervention that was more than two-fold greater than the effect among all trial participants.

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