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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
Randomised controlled trial
Exercise

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 ≥ 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

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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