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Clinical Study

Developing Interventions for Frailty

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Frailty is a well-recognised, complex syndrome, predominantly affecting older people. Currently, there are two main conceptualizations of frailty: the phenotypic and the accumulated deficit models, with the phenotypic model being more widely applied in clinical research. Based on these models, we contend that a number of the phenotypic frailty components (weakness, slowness, and low energy expenditure) are potentially reversible. This paper outlines the results of a frailty research program. It summarizes the initial frailty treatment model and reports its effectiveness. Briefly, the effect of a twelve-month individually tailored multifactorial, interdisciplinary intervention targeting frailty was compared with usual care. The intervention reduced phenotypically defined frailty and improved mobility. Further, it is contended that there is evidence of substantial unmet need due to treatment fragmentation and the absence of a comprehensive approach for this population. Our paper then outlines the current stage of our research in which the model is now being extended to prefrailty. Interventions aimed at reversing the frailty syndrome or its consequences are only in their early stages. There is significant scope for future research to identify optimal management programs for frail older people.

1. Introduction

1.1. The Concept of Frailty. In the first century, the final stage of life was identified by Ptolemy as being from 68 years to death, with Aristotle characterising it as a period of decline [1]. It was not till 1908 that Metchnikoff [2] identified the importance of understanding the pathology of aging so that it could be better managed.

By the early 1990s, with the increase in life expectancy in industrialized countries, geriatricians had recognized a clinical presentation characterized by a multisystem reduction in physiological capacity which was not necessarily related to a specific single disease process. A variety of terms have arisen to describe this or similar syndromes [3], but frailty is the most commonly used term. Frailty in community-dwelling adults was first characterised as a physical phenotype by Fried et al. [4] on the basis of five physical components: weight loss, exhaustion, weakness, slow gait speed, and low levels of physical activity. People who meet none of these criteria are classified as "robust," those who meet one or two criteria as prefrail, and those who meet three or more criteria as frail, which is predictive of poor outcomes including institutionalization and death. In contrast, frailty can also be diagnosed using models counting deficits across multiple domains such as the Frailty Index [5]. Rockwood et al. [6] defined frailty as a complex, multidimensional disorder related to accumulated deficits, involving the loss of reserves, including energy, physical ability, cognition, and health, increasing an individual's vulnerability. The phenotypic model of frailty (also termed the Fried model, or Cardiovascular Health Study model), with its underlying physiological base and easily measurable components, makes it straightforward to both comprehend and use. In comparison, the Rockwood Frailty Index, designed to reflect the syndrome's complexity, has proven difficult to operationalize in a clinical setting [7]. Consequently, the Fried technique has been more widely applied in clinical research settings [8], despite its exclusion of mood and cognition indices [7].

There is agreement that the biological basis of frailty is multifactorial; it involves dysfunction across various physiological systems; its risk increases in a nonlinear pattern with the number of physiological systems impaired; and it is independent of chronic diseases and chronological age. Further, Fried et al. [9] suggested that whilst each individual dysfunction on its own might be minor, it was the summation and interactive effects that created the syndrome. Frailty affects quality of life, morbidity, and mortality and results in considerable medical and public spending expense [10] such that it is now seen as one of the major challenges for health services. The criteria applied for frailty diagnosis in clinical practice continue to remain a challenge primarily because the causes of frailty are not fully understood.

Frailty is a common biological syndrome occurring in five to seventeen percent of community-dwelling older people [11]. It may be initiated by disease, lack of activity, inadequate nutritional intake, stress, and/or the physiologic changes of aging [12]. Frailty develops slowly with increments of decline marked by acute events. It is manifested as a loss of skeletal muscle mass (sarcopenia), abnormal function in inflammatory and neuroendocrine systems, and poor energy regulation [13]. People who are frail have a 1.2- to 2.5-fold increase in the risk of falls, institutionalization, and mortality [4] and there is a decreased ability in the body's physiologic response to maintain homeostasis in times of acute stress. In essence, frailty is a product of "excess demand imposed upon reduced capacity" [14]. Once a person has become frail, there is often a rapid, progressive, and self-perpetuating downward spiral toward failure to thrive and death [15].

Contrary to popular belief, not all people who are older are frail [16], with only 3% to 7% of persons between the ages of 65 to 75 years identified as frail [17], but the prevalence of frailty increases to more than 32% in those aged over 90 years [18]. Furthermore, once a person is prefrail, they are more likely to progress to frailty, thus depicting the downward spiral effect of the syndrome [19]. Frailty can be a primary or secondary syndrome. Notably, 7% of the people who are frail have no illness, and 25% have only one comorbid diagnosis [17]. Researchers have demonstrated that even when individuals with acute and chronic medical conditions were excluded, 7% of the population aged more than 65 years and 20% of the population aged more than 80 years are frail [16]. On the other hand, frailty may occur as a result of an acute event or the end stage of many chronic conditions [16].

Frailty has been described along a continuum, with three stages in the frailty process being described [4, 13]. People who are prefrail are more likely than the nonfrail to develop frailty and they have an increased risk of falls, institutionalization, and mortality, but not as high as for frail persons [4]. Transition from this latent phase to the clinically identifiable frail phase is usually marked by an event such as injury, acute disease, and/or psychological stress [20] resulting in slow or incomplete recovery, which highlights that the person's functional reserves are insufficient for them to attain complete recovery. Frailty, with or without comorbidity, may eventually reach an irreversible stage of functional decline, progressive indifference, and decreased appetite [21], with the end stage of the frailty continuum being failure to thrive [17] and ultimately resulting in death. Lang et al. [13] argue that the prefrail process, which is clinically silent, corresponds to the state where the individual's physiological reserves are sufficient to allow them to respond adequately to any event such as acute disease, injury, or stress, with a chance of complete recovery.

1.2. Interventions for Frailty. Despite the considerable academic interest in the frailty syndrome there is little research focusing on treating or at least ameliorating frailty. Efforts have been made to improve clinical outcomes for this group of people; however no interventions have been developed to specifically reverse the syndrome of frailty characterised by either an accepted phenotypic or accumulated deficits definition.

Previous intervention studies targeting frailty have focused on using general interventions such as comprehensive geriatric assessment [22–24] and rehabilitation models [25] with inconclusive effects on functional ability and well-being. A recent systematic review found community-based, multifactorial interventions reduce hospital admission in the frail population but do not significantly benefit physical functioning in this group [26]. However, specific interventions targeting physical activity have been shown to improve physical function [27, 28], and intervention with nutritional supplements plus exercise has resulted in increased energy intake and improved strength [28]. Pharmacological interventions have produced inconsistent results [29–31]. Further, intervention studies targeting frailty have failed to support the improvement of functioning and quality of life because the interventions were not tailored to the specific assessed needs of the individual [26]. During the course of our research we became aware of an intervention study of prefrailty that utilised an exercise program [32].

This paper reports on an ongoing program of research, commenced in 2008, that tests community-based interventions targeting frailty. We provide an overview of our work, presenting firstly the findings of the Stage One frailty study, reported in detail elsewhere, and then our subsequent Stage Two prefrailty study, which is currently in progress.

2. Method

Stage 1: Frailty Intervention Trial Study. We conducted a prospective, parallel group, assessor-blind, randomised, controlled, single centre trial, to examine the effect of a multifactorial, interdisciplinary intervention targeting frailty compared with usual care. The hypotheses were that the intervention would reduce frailty, improve mobility, and have a positive effect on a number of secondary outcome measures including disability, depressive symptoms, and health-related quality of life. Funding was received as part of a Strategic Initiative Grant awarded by the Australian National Health and Medical Research Council. The protocols for the Frailty Intervention Trial and a related mobility-related disability component were approved by Northern Sydney Central Coast Health Human Research Ethics Committee (1 November 2007 and 20 August 2008, resp.). It was registered

with the Australian New Zealand Clinical Trials Registry (ANZCTRN 12608000250336). The trial was undertaken from January 2008 to June 2011. Full details of the methods are outlined in the study protocol paper [33].

Participants were eligible if they were defined as frail according to the Cardiovascular Health Study (CHS) Frailty Phenotype [4]; were 70 years or older; had completed their rehabilitation; did not usually reside in a residential aged care facility; did not have severe cognitive impairment as defined as a Mini Mental State Examination score of 18 or less [34]; resided in the Hornsby or Ku-ring-gai local government areas; and had a score of three or less on a modified Implicit Illness Severity Scale [35] indicating a life expectancy exceeding 12 months.

The 241 participants who met the inclusion criteria and gave informed consent were randomised into intervention and control groups. The intervention is described in detail elsewhere [33]. In brief, participants in the intervention group received a multifactorial interdisciplinary intervention for one year. The intervention was tailored to each participant based upon the CHS frailty criteria present at baseline; issues identified during comprehensive geriatric evaluation; and reassessment throughout the 12-month intervention period. The interdisciplinary intervention was coordinated using case management by the treating physiotherapist and regular case conferences.

Participants who met the CHS frailty criteria of weakness, slowness, or low energy expenditure received 10 home visits from a physiotherapist and a home exercise program designed to improve mobility, increase physical activity, and prevent falls (the Weight-Bearing Exercise for Better Balance program, http://www.webb.org.au) and community participation. The program was tailored to the individuals' physical impairments, prescribed three to five times per week, and reviewed and modified regularly. Appropriate equipment items such as mobility aids were also recommended.

A dietician evaluated nutritional intake in those participants who met the weight loss CHS frailty criterion. Home-delivered meals and nutritional supplementation were offered where indicated.

If the exhaustion frailty criterion was met and the Geriatric Depression Scale [36] score was high, referral to a psychiatrist or psychologist and options to facilitate social engagement were considered.

Participants assigned to the control group received the usual care available to this group of residents of the Hornsby Ku-ring-gai area from their general practitioner (GP) and community service.

Outcomes were assessed in participants' homes by independent, blinded nurse assessors at baseline (before randomization) and at 3 months and 12 months after randomization. The primary outcomes were frailty, measured using the CHS phenotype [4] and mobility using the Short Physical Performance Battery [36]. Secondary outcomes included falls, mood (using the Geriatric Depression Scale), health related quality of life (EQ-5D) and mobility-related disability, measured at the levels of participation restriction (using the Goal Attainment Scale [37] and Life Space Assessment [38]) and activity limitation (gait speed and Activity Measure for Post Acute Care) [39].

A further component of the project involved an evaluation of family carers of FIT study participants. Details of the methods of this study are provided in Aggar et al. [40].

The results of this trial are detailed in Cameron et al. [41], Fairhall et al. [42], and Aggar et al. [40]. We also produced an evidence based guide and resources for implementing the intervention program in the clinical setting [43].

3. Results

241 participants (68% female) were recruited between January 2008 and April 2010, with an average age of 83.3 years (SD: 5.9 years). Of the 241 people randomised, 226 (94%) completed the 3-month assessment and 216 (90%) completed the 12-month assessment. The majority (22 out of 25) of losses to follow-up were due to death. Participants had poor mobility at baseline, with an average of seven medical conditions and walked at one-quarter the speed of healthy people of the same age [44]. Most had recently been discharged from an aged care and rehabilitation service and almost half did not get out of the house as much as they wanted to. There was a maximum of 2 percent of cases missing for any variable, with missing data for individual variables assigned using multiple imputations.

The two groups were similar at baseline in terms of number of comorbidities, depression and cognition scores, proportion living alone, walking speed, and disability measured using the Barthel Index. The only between group difference detected at baseline was that the control group had significantly better scores on Short Physical Performance Battery.

The intervention and control treatments were implemented as planned. The median adherence to the intervention program was in the category of 26% to 50%. Adherence was 0% for 16 participants (13%). This adherence reflects the nature of treatment in the clinical setting, where the health, physical, and social needs of these people fluctuate. Full details of the intervention delivered and compliance with trial protocol are published elsewhere [41, 42].

Two intervention group participants experienced back pain that was classified as an adverse event [45]. Both resumed exercising following modification of their exercise program.

Overall, the intervention resulted in a lower prevalence of frailty in the intervention group compared with the control group at 12 months (absolute difference 14.7%; 95% CI: 2.4%, 27.0%; $P = 0.02$; number needed to treat = 6.8). This highlights that treating frailty is a realistic therapeutic option. Further, we found that mobility was significantly better (both statistically and clinically), in the intervention group in terms of the Short Physical Performance Battery score and gait speed. In terms of community participation, the intervention group were significantly more likely to reach their self-selected mobility goals than the control group and had significantly greater life space (defined as how often people mobilised in the home and community, how far they went, and their degree of independence). However, there

were no major differences between the groups with respect to the secondary outcomes measured by the Barthel Index, the Geriatric Depression Scale, and the EQ5D VAS. [41]. The intervention had no effect on falls, although some falls risk factors improved significantly as a result of the intervention [46]. The effect of the intervention on carers has been evaluated with some positive outcomes [40]. An evaluation of the cost-effectiveness of the intervention is being conducted but is not yet published.

More detailed descriptions of the results can be found in Cameron et al. [41] and Fairhall et al. [42].

The findings of Stage 1 gave rise to the question whether people who are prefrail may have the potential to benefit more from intervention than those with established frailty. Theoretically, prefrail people should require less input with regard to service provision compared with those who are frail, therefore resulting in more intervention resources being available for targeting specific CHS frailty criteria. Prefrail people also should have less difficulty with basic activities of daily living, so there is potential to prevent both disability and the accompanying requirement for care. Consequently, we hypothesise that the FIT intervention could be applied to the prefrail population, in order to delay or avoid transition to frailty. To determine the impact of the FIT intervention on frailty progression and mobility, a clinical trial targeting people who are prefrail is currently underway. We now report briefly on this trial.

Stage 2: Prefrailty Intervention Trial (Pre-FIT) Study Design. A single centre randomized controlled trial and economic analysis to determine the effectiveness and cost-effectiveness of a multifactorial, interdisciplinary intervention for people diagnosed as prefrail. Pre-FIT was registered with the Australia New Zealand Clinical Trial Registry (ACTRN12613000043730) and commenced in January 2013. This trial aims to recruit 230 people with prefrailty over an 18-month period from members of this target group living in the Hornsby and Ku-ring-gai local government areas in New South Wales, Australia. Eligible participants will be prefrail (one or two of CHS frailty criteria present); will be aged 70 years or over; will have mild or no cognitive impairment (defined as a Mini Mental State Examination score of more than 23); will not be living in a residential aged care facility; will have an estimated life expectancy of greater than 12 months; and must not be receiving treatment from a rehabilitation facility. Assessment occurs prior to randomization (baseline) and at 4 and 12 months after randomization, plus telephone contact is also made at 8 months to record service utilization. As with the FIT intervention, demographic detail and health information are being collected and cognitive function is assessed; the CHS criteria are being used to measure frailty and the Short Physical Performance Battery to measure mobility. In addition, adverse events are being monitored, and quality of life is measured using the EQ-5D (EuroQol) and depression using Geriatric Depression Scale-5.

Participants in the intervention group receive a 12-month multifactorial, interdisciplinary treatment program targeting the frailty criteria present at baseline. The intervention is the same as that delivered in the FIT study [33] with modification of the exercise program to enable more challenging endurance and balance training as required by the prefrail group. Participants in the control group receive the usual healthcare available in the Hornsby Ku-ring-gai area from their GP and community services.

As of mid-October, the planned sample size of 230 participants had been recruited and randomized into the intervention and control groups. Initial impressions are that the intervention is feasible in people identified as prefrail and that the exercise program is the main component of the prescribed intervention.

4. Discussion

To our knowledge, this is the first trial that has identified a community-based intervention that can reduce frailty in this target group. For stage 1, we have found that a 12-month multifactorial, interdisciplinary, frailty targeted program is more effective than usual care in reducing frailty, improving mobility and reducing mobility-related disability. In particular, the effect of the intervention on mobility and activity outcomes is consistent with previous trials, which have shown that gait speed and composite activity measures are able to be improved through a prolonged period of regular multicomponent training [47]. However, the findings regarding community mobility and goal attainment in this group are novel as previous research into the effect of exercise and geriatric evaluation and management on functional outcomes [47–49] have primarily reported function in terms of body structure and/or function and activity, with participation outcomes having been largely unreported. Further, whilst the intervention increased gait speed, the extent of mobility in the home and community, and the likelihood of meeting participation goals, some statistically significant improvements may not be clinically meaningful and require continued exploration.

This intervention study has also provided insights into issues that influence the effectiveness of a treatment approach for people who are frail. The complex mix of health and functional and service related issues present in this group make intervention delivery challenging. Further, there is evidence of substantial unmet need due to service fragmentation and the absence of a comprehensive management approach for this population.

Frailty frequently develops as a consequence of major illness and the management approach required in this situation is unclear. Yet our work has required participants to have a (relatively) stable health status and to not be receiving current services from an aged care health and rehabilitation program. In a number of countries, including Australia, subacute or postacute services are utilized by people who are older following hospitalization, with many of these clients likely to be frail. In the Australian subacute casemix system there are two categories of "reconditioning" where specific organ system impairment is not applicable. This is a prevalently used category, with 18% of rehabilitation episodes in 2008 recorded under this classification [50], with

most of these people being frail and the most effective forms of rehabilitation undetermined.

5. Conclusion

The geriatric assessment and management literature has shown mixed results for trials that have focused on people who are frail and have reduced functioning with regard to improvements in disability. Our work adds to previous research by demonstrating that it is possible to identify those with frailty for inclusion in a randomized trial and that frailty and mobility disability can be successfully treated using an interdisciplinary multifaceted treatment program.

There is a lack of understanding regarding disability in this group due to their systematic exclusion from trials [51] along with the narrow definitions of disability that are frequently employed. This paper provides evidence that there is the potential to reduce disability in community-dwelling people who are frail, in both the participation and activity domains. Our work also highlights that it is difficult to separate frailty from disability because these two states coexisted in almost all of the study's participants, such that improvements in frailty were paralleled by improvements in mobility disability, and both were similar in magnitude with medium effect sizes. Specifically, the FIT intervention reduced the degree of frailty and improved mobility outcomes in this population. However, the benefits of the intervention were not identifiable at three months but were evident at twelve months, indicating that an intervention treating frailty must be prolonged. Further, the FIT analyses indicated that participants who had higher levels of adherence to the intervention had better results.

The strengths of our study program reside in the use of a validated definition of frailty, broadly generalizable to recently hospitalized community-dwelling people who are frail; the small losses to follow-up that were similar in both groups; and adherence to sound trial design and methodology. The intervention, which was delivered in the setting of an existing health service by an interdisciplinary team experienced in aged care, is similar to treatment that can be provided in routine clinical practice. However the clinical trial did have limitations. The FIT study participants could not be blinded to group allocation; adherence to the program was variable; there was no frequency matched social intervention for the control group so the impact of social aspects of the program cannot be excluded; and group status was inadvertently disclosed by 51 percent of participants at the 12-month follow-up.

Interventions that reduce frailty and disability in the frail population may impact on morbidity, hospitalization, and admission to residential care facilities. This body of research has shown that treating frailty is a realistic therapeutic goal, and there is significant scope for future research into the optimal management programs for this population. Further, the inclusion of carers in trials targeting frailty may assist in the identification of at-risk carers and facilitate the provision of information and support that will assist them in their role. Research, which explores the features of frailty interventions and their impact on the caregiving experience, would therefore be beneficial.

Finally, with regard to the Pre-FIT study, the early indications are that similar principles can be used but, because those who are prefrail experience fewer comorbidities, less disability, and less need for service provision, the focus of the intervention is a progressive exercise program for most intervention group participants.

6. Limitations and Future Research

Our study has been conducted in a relatively affluent country with well-developed health and community support services and with participants who had relatively stable health conditions and no severe cognitive impairment. Accordingly, the findings of the Frailty Intervention Trial must be confirmed and extended. We acknowledge that frailty is a complex syndrome and the groups that we have chosen to target for our intervention studies are not necessarily representative of frail older people more broadly.

Future studies need to include a longer follow-up period to determine if the benefits of the intervention are sustained after 12 months. The intervention should also be evaluated using a multicentre trial with a larger sample size, and generalizability should be evaluated for residents of rural areas and for people with more marked cognitive impairment [52]. We note that research continues to be undertaken into the characterization and causes of frailty, which may assist with the development of more targeted future interventions. Additionally, research must also involve identifying the attributes of those most likely to benefit from intervention, along with an evaluation of the cost-effectiveness of intervention.

Ongoing work is similarly required to determine how to best embed the intervention into existing health service settings. Notably, the transdisciplinary role of the coordinating physiotherapist and their access to other health practitioners requires translation into a model suitable for routine clinical practice [43]. It is our view that such a model could be readily implemented because it utilizes clinical practitioners already working with this group. But the challenge lies in embedding it within the routine work of a regional aged care health service and securing funding to support its operation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] T. Cole, *The Journal of Life*, Cambridge University Press, New York, NY, USA, 1997.

[2] H. Gourko, D. I. Williamson, and A. I. Tauber, *The Evolutionary Biology Papers of Elie Metchnikoff*, Kluwer Academic Publishers, 2000.

[3] D. M. Buchner and E. H. Wagner, "Preventing frail health," *Clinics in Geriatric Medicine*, vol. 8, no. 1, pp. 1–17, 1992.

[4] L. P. Fried, C. M. Tangen, J. Walston et al., "Frailty in older adults: evidence for a phenotype," *Journals of Gerontology*, vol. 56, no. 3, pp. M146–M156, 2001.

[5] K. Rockwood, K. Stadnyk, C. MacKnight, I. McDowell, R. Hebert, and D. B. Hogan, "A brief clinical instrument to classify frailty in elderly people," *The Lancet*, vol. 353, no. 9148, pp. 205–206, 1999.

[6] K. Rockwood, P. Stolee, and R. A. Fox, "Use of goal attainment scaling in measuring clinically important change in the frail elderly," *Journal of Clinical Epidemiology*, vol. 46, no. 10, pp. 1113–1118, 1993.

[7] R. E. Hubbard, M. S. O'mahony, and K. W. Woodhouse, "Characterising frailty in the clinical setting—a comparison of different approaches," *Age and Ageing*, vol. 38, no. 1, pp. 115–119, 2009.

[8] S. A. Sternberg, A. W. Schwartz, S. Karunananthan, H. Bergman, and A. Mark Clarfield, "The identification of frailty: a systematic literature review," *Journal of the American Geriatrics Society*, vol. 59, no. 11, pp. 2129–2138, 2011.

[9] L. P. Fried, Q.-L. Xue, A. R. Cappola et al., "Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment," *The Journals of Gerontology Series A Biological Sciences and Medical Sciences*, vol. 64, no. 10, pp. 1049–1057, 2009.

[10] F. Landi, M. Cesari, G. Onder, F. Lattanzio, E. M. Gravina, and R. Bernabei, "Physical activity and mortality in frail, community-living elderly patients," *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, vol. 59, no. 8, pp. M833–M837, 2004.

[11] R. M. Collard, H. Boter, R. A. Schoevers, and R. C. O. Voshaar, "Prevalence of frailty in community-dwelling older persons: a systematic review," *Journal of the American Geriatrics Society*, vol. 60, no. 8, pp. 1487–1492, 2012.

[12] N. Ahmed, R. Mandel, and M. J. Fain, "Frailty: an emerging geriatric syndrome," *The American Journal of Medicine*, vol. 120, no. 9, pp. 748–753, 2007.

[13] P.-O. Lang, J.-P. Michel, and D. Zekry, "Frailty syndrome: a transitional state in a dynamic process," *Gerontology*, vol. 55, no. 5, pp. 539–549, 2009.

[14] C. Powell, "Frailty: help or hindrance?" *Journal of the Royal Society of Medicine*, vol. 90, no. 32, pp. 23–26, 1997.

[15] L. A. Lipsitz, "Dynamic models for the study of frailty," *Mechanisms of Ageing and Development*, vol. 129, no. 11, pp. 675–676, 2008.

[16] J. F. Wilson, "Frailty and its dangerous effects might be preventable," *Annals of Internal Medicine*, vol. 141, no. 6, pp. 489–492, 2004.

[17] L. P. Fried, J. Darer, and J. Walston, "Frailty," in *Geriatric Medicine: An Evidence-Based Approach*, C. Cassel, R. Leipzig, H. Cohen, E. Larson, and D. Meier, Eds., pp. 1067–1074, Springer, New York, NY, USA, 4th edition, 2003.

[18] J. Walston, M. A. McBurnie, A. Newman et al., "Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study," *Archives of Internal Medicine*, vol. 162, no. 20, pp. 2333–2341, 2002.

[19] T. M. Gill, E. A. Gahbauer, H. G. Allore, and L. Han, "Transitions between frailty states among community-living older persons," *Archives of Internal Medicine*, vol. 166, no. 4, pp. 418–423, 2006.

[20] K. Bandeen-Roche, Q. L. Xue, L. Ferrucci et al., "Phenotype of frailty: characterization in the Women's Health and Aging Studies," *The Journals of Gerontology—Series A Biological Sciences and Medical Sciences*, vol. 61, no. 3, pp. 262–266, 2006.

[21] R. G. Robertson and M. Montagnini, "Geriatric failure to thrive," *American Family Physician*, vol. 70, no. 2, pp. 343–350, 2004.

[22] H. J. Cohen, J. R. Feussner, M. Weinberger et al., "A controlled trial of inpatient and outpatient geriatric evaluation and management," *New England Journal of Medicine*, vol. 346, no. 12, pp. 905–912, 2002.

[23] R. J. F. Melis, M. I. J. van Eijken, S. Teerenstra et al., "A randomized study of a multidisciplinary program to intervene on geriatric syndromes in vulnerable older people who live at home (Dutch EASYcare Study)," *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, vol. 63, no. 3, pp. 283–290, 2008.

[24] S. G. Leveille, E. H. Wagner, C. Davis et al., "Preventing disability and managing chronic illness in frail older adults: a randomized trial of a community-based partnership with primary care," *Journal of the American Geriatrics Society*, vol. 46, no. 10, pp. 1191–1198, 1998.

[25] K. Ollonqvist, R. Grönlund, S.-L. Karppi, U. Salmelainen, L. Poikkeus, and K. Hinkka, "A network-based rehabilitation model for frail elderly people: development and assessment of a new model," *Scandinavian Journal of Caring Sciences*, vol. 21, no. 2, pp. 253–261, 2007.

[26] A. D. Beswick, K. Rees, P. Dieppe et al., "Complex interventions to improve physical function and maintain independent living in elderly people: a systematic review and meta-analysis," *The Lancet*, vol. 371, no. 9614, pp. 725–735, 2008.

[27] T. M. Gill, D. I. Baker, M. Gottschalk, P. N. Peduzzi, H. Allore, and A. Byers, "A program to prevent functional decline in physically frail, elderly persons who live at home," *The New England Journal of Medicine*, vol. 347, no. 14, pp. 1068–1074, 2002.

[28] M. A. Fiatarone, E. F. O'Neill, N. D. Ryan et al., "Exercise training and nutritional supplementation for physical frailty in very elderly people," *The New England Journal of Medicine*, vol. 330, no. 25, pp. 1769–1775, 1994.

[29] S. T. Page, J. K. Amory, F. D. Bowman et al., "Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T," *The Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 3, pp. 1502–1510, 2005.

[30] G. Percheron, J.-Y. Hogrel, S. Denot-Ledunois et al., "Effect of 1-year oral administration of dehydroepiandrosterone to 60- to 80-year-old individuals on muscle function and cross-sectional area: a double-blind placebo-controlled trial," *Archives of Internal Medicine*, vol. 163, no. 6, pp. 720–727, 2003.

[31] G. Onder, B. W. J. H. Penninx, R. Balkrishnan et al., "Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study," *The Lancet*, vol. 359, no. 9310, pp. 926–930, 2002.

[32] M. Drey, A. Zech, E. Freiberger et al., "Effects of strength training versus power training on physical performance in prefrail community-dwelling older adults," *Gerontology*, vol. 58, no. 3, pp. 197–204, 2012.

[33] N. Fairhall, C. Aggar, S. E. Kurrle et al., "Frailty intervention trial (FIT)," *BMC Geriatrics*, vol. 8, article 27, 2008.

[34] M. F. Folstein, S. E. Folstein, and P. R. McHugh, "'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[35] J. Holtzman and N. Lurie, "Causes of increasing mortality in a nursing home population," *Journal of the American Geriatrics Society*, vol. 44, no. 3, pp. 258–264, 1996.

[36] J. M. Guralnik, E. M. Simonsick, L. Ferrucci et al., "A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission," *Journals of Gerontology*, vol. 49, no. 2, pp. M85–M94, 1994.

[37] T. Kiresuk, A. Smith, and J. Cardillo, *Goal Attainment Scaling: Applications, Theory, and Measurement*, Erlbaum Associates, Hillsdale, NJ, USA, 1994.

[38] P. S. Baker, E. V. Bodner, and R. M. Allman, "Measuring life-space mobility in community-dwelling older adults," *Journal of the American Geriatrics Society*, vol. 51, no. 11, pp. 1610–1614, 2003.

[39] S. M. Haley, W. J. Coster, P. L. Andres, M. Kosinski, and P. Ni, "Score comparability of short forms and computerized adaptive testing: Simulation study with the activity measure for post-acute care," *Archives of Physical Medicine and Rehabilitation*, vol. 85, no. 4, pp. 661–666, 2004.

[40] C. Aggar, S. Ronaldson, and I. D. Cameron, "Reactions to caregiving during an intervention targeting frailty in community living older people," *BMC Geriatrics*, vol. 12, article 66, 2012.

[41] I. D. Cameron, N. Fairhall, C. Langron et al., "A multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial," *BMC Medicine*, vol. 11, no. 1, article 65, 2013.

[42] N. Fairhall, S. E. Kurrle, C. Sherrington, S. R. Lord, K. Lockwood, and I. D. Cameron, "Effect of a multifactorial interdisciplinary intervention on mobility-related disability in frail older people: randomised controlled trial," *BMC Medicine*, vol. 10, article 120, 2012.

[43] N. Fairhall, C. Langron, C. Sherrington et al., "Treating frailty-a practical guide," *BMC Medicine*, vol. 9, article 83, 2011.

[44] R. W. Bohannon, "Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants," *Age and Ageing*, vol. 26, no. 1, pp. 15–19, 1997.

[45] N. K. Latham, C. S. Anderson, A. Lee, D. A. Bennett, A. Moseley, and I. D. Cameron, "A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the frailty interventions trial in elderly subjects (FITNESS)," *Journal of the American Geriatrics Society*, vol. 51, no. 3, pp. 291–299, 2003.

[46] N. Fairhall, C. Sherrington, S. R. Lord et al., "Effect of a multifactorial, interdisciplinary intervention on risk factors for falls and fall rate in frail older people: a randomised controlled trial," *Age and Ageing*, vol. 43, no. 5, pp. 616–622, 2013.

[47] O. Theou, L. Stathokostas, K. P. Roland et al., "The effectiveness of exercise interventions for the management of frailty: a systematic review," *Journal of Aging Research*, vol. 2011, Article ID 569194, 19 pages, 2011.

[48] M. J. M. C. A. Paw, J. G. Z. van Uffelen, I. Riphagen, and W. van Mechelen, "The functional effects of physical exercise training in frail older people: a systematic review," *Sports Medicine*, vol. 38, no. 9, pp. 781–793, 2008.

[49] R. Daniels, E. van Rossum, L. de Witte, G. I. J. M. Kempen, and W. van den Heuvel, "Interventions to prevent disability in frail community-dwelling elderly: a systematic review," *BMC Health Services Research*, vol. 8, article 278, 2008.

[50] Australian Rehabilitation Outcomes Centre, "AROC Impairment Specific Outcome Target Benchmarking," 2014, http://ahsri.uow.edu.au/aroc/benchmarking/index.html#recon.

[51] I. Ridda, R. Lindley, and R. C. MacIntyre, "The challenges of clinical trials in the exclusion zone: the case of the frail elderly," *Australasian Journal on Ageing*, vol. 27, no. 2, pp. 61–66, 2008.

[52] K. Rockwood, "Making mobility-related disability better: a complex response to a complex problem," *BMC Medicine*, vol. 10, article 121, 2012.