ATTRITION, MISSING DATA, AND FEASIBILITY TRIALS IN OLDER ADULTS

METHODOLOGICAL AND INTERVENTIONAL ISSUES AND CONSIDERATIONS IN STUDIES OF OLDER ADULTS: ATTRITION, MISSING DATA, AND FEASIBILITY TRIALS

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LAY ABSTRACT

The number of people who are old is increasing by the day and so is the need to understand how to ensure they are aging well. Old age makes people more prone to diseases. The risks of becoming ill could make the efforts to generate knowledge that can help them thrive challenging. They could drop out of a study making it difficult to collect enough information for data analysis.

For some older adults who are frail and have higher risk for diseases, there is little known about how to design programs that will enable them stay active and healthier during the COVID-19 pandemic or before they have hip or knee replacement surgery.

This thesis contributes to the knowledge on how to improve the quality of research involving older adults and bridge the gap in the knowledge about how to support those who are frail among them.

ABSTRACT

Older adults are a rapidly growing segment of the population with unique healthcare needs. As people age, they are more likely to become susceptible to diseases and develop complex health conditions that require tailored strategies to address. These vulnerabilities could also impact different stages of the research process to generate evidence that promote healthy aging and better quality of life for this population.

Attrition and missing data are some of the common methodological challenges in research with older adults. These issues could affect the quality of evidence generated if not properly addressed. There is also limited evidence to guide the development of interventions in specific populations of older adults with frailty, who have reduced function and are at higher risk for poor health outcomes.

Across six chapters, this thesis addresses these methodological and interventional gaps in research with older adults. Using different research methodologies including a systematic literature survey, secondary data analysis of a cohort study, and two randomized feasibility trials, this thesis provides some important considerations for practice. In particular, we (i) evaluated the magnitude, pattern, and factors associated with attrition in the Global Longitudinal Study of Osteoporosis in Women (GLOW) Hamilton cohort of older adults; (ii) performed a systematic survey of the reporting and handling of missing data in longitudinal observational studies of older adults; (iii) conducted a randomized controlled feasibility trial of the Geras virtual frailty rehabilitation program to build resilience in vulnerable older adults during the COVID-19 pandemic; and (iv) evaluated the feasibility of the FitJoints randomized controlled trial of a multimodal intervention in frail older patients with osteoarthritis awaiting hip and knee replacement.

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DEDICATION

This thesis is dedicated to the memory of my dear father, Prince Fan Ayeh Osuala (†11/07/2021), a champion of education, and my dear maternal grandmother, Ezinne Martha Emeziaka Ogu (†12/08/2022); both of whom passed away from age-related diseases during my PhD journey, and whose memories make this thesis work meaningful and fulfilling.

TABLE OF CONTENTS

LIST OF TABLES

Chapter 2

Chapter 3

Chapter 4

Chapter 5

LIST OF FIGURES

LIST OF ABBREVIATIONS

COVID	Coronavirus disease
GLOW	Global Longitudinal Study of Osteoporosis in Women
RE-AIM	Reach Effectiveness Adoption Implementation and Maintenance
SD	Standard deviation
CI	Confidence interval
BMI	Body mass index
HRQoL	Health-related Quality of Life
EQ5D5L	European Quality of Life 5-dimension 5-level
FI	Frailty index
SE	Standard errors
Q1	Quartile 1
Q3	Quartile 3
n/N	Number
LTFU	Lost to follow-up
HR	Hazard ratio
MCAR	Missing completely at random
MAR	Missing at random
MNAR	Missing not at random
IQR	Interquartile range
BMC	BioMed Central
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
5XSST	Five times sit-to-stand test
DASS	Depression, Anxiety, and Stress Scale
ITT	Intention to treat
PP	Per protocol
aMD	Adjusted mean difference
ANCOVA	Analysis of covariance
HiREB	Hamilton Integrated Research Ethics Board
STOPP	Screening Tool of Older Person's Prescriptions
START	Screening tool to alert to right treatment
OA	Osteoarthritis
CONSORT	Consolidated Standards of Reporting Trials
MSK CIAC	Musculoskeletal Central Intake and Assessment Centre
RJAP	Regional Joint Assessment Program
RCT	Randomized controlled trial
APP	Advanced Practice Physiotherapists
YMCA	Young Men Christian Association
RA	Research assistant
TiDier	Template for Intervention Description and Replication
SPPB	Short Physical Performance Battery
REDCap	Research Data Capture
FITT	Frequency, Intensity, Type and Time

DECLARATION OF ACADEMIC ACHIEVEMENT

This is a "sandwich" thesis comprising of four individual manuscripts (chapters 2 – 5), three of which have been published and the last one prepared for publication. I declare that the thesis is an original work conducted by me between Fall 2019 and Summer 2023 with the help of my supervisor, supervisory committee members, and other collaborators. Details of each co-author's contribution can be found at the end of each chapter.

In brief, I, Chinenye Okpara, am the first author in all the manuscripts and my contributions include: conception of research idea, design of study, analysis of data, interpretation of results, writing of first and final drafts of manuscripts, submission of manuscripts to journals, and responding to comments from reviewers.

The co-authors contributed to the conception of research idea, design of study, acquisition of dataset, recruitment of participants, data management, and critical revision of drafts of manuscripts.

CHAPTER 1

INTRODUCTION

The global population of older adults (persons aged 60 years or beyond) is increasing rapidly, with a projected growth from 1 billion in 2020 to 2.1 billion by 2050[1]. In Canada, approximately 25% of the overall population is 60 years or older, which translates to 1 older adult in every 4 persons[2]. A 2017 report predicts that the share of senior's population (≥65 years) in the country will rise by 68% over the next two decades[3]. This 'population ageing' is substantial as older adults possess unique health care needs that require tailored strategies to address them both now and in the future[1,4].

Old age may be marked by the manifestation of complex health conditions including frailty, osteoporosis, osteoarthritis among many others [1,5,6]. As people grow older, they are more likely to experience multiple physiological changes in their bodies that increases their susceptibility to diseases[7]. The presence of age-related conditions could impair the ability for healthy and independent living in older adults, thus increasing the need for care and support[4,5]. The average cost of healthcare for seniors in Canada is more than four times the spending for those below the age of 65[8]. In the face of the growing numbers of elderly persons, these attendant health conditions could further place substantial demands on healthcare systems[9]. Consequently, the need for research in this population to understand the aging process, identify interventions that promote healthy aging, improve quality of life, reduce the burden of age-related illnesses, and minimize costs to health and social care continues to increase.

Research in older adult population still face several methodological and interventional challenges. Due to the serious vulnerability to poor health, different stages of the research process, including recruitment, retention, data collection and analysis could be severely impacted[10-13]. For example, an older person with cognitive impairment or who develops this condition during follow-up may have difficulty with participation. The loss of participants during follow-up, also known as attrition, is one of the common methodological challenges and a potential source of bias in longitudinal studies of older adults[14,15]. These

losses could also lead to missing data problems[16]. Where these issues are present and not addressed appropriately, the validity, generalizability, and overall quality of evidence generated could be threatened[17,18].

In specific populations of older adults with frailty (a state of reduced function and increased vulnerability to poor health)[19,20], there is limited well-designed clinical trials to inform programs that could improve their health outcomes. During the COVID-19 pandemic, older adults with frailty were at increased risk of further decline in physical function and mental health due to pandemic-related restrictions[21-23]. Therefore, there was a critical need to develop alternatives to in-person interventions that could be delivered effectively and safely to this vulnerable group. Also, among older patients with frailty awaiting joint replacement, the risk of poor surgical outcomes is higher than their non-frail counterparts[24]. As such, it is crucial to identify strategies to prepare these patients for surgery to minimise postoperative complications.

To address these methodological and interventional issues, this thesis examined (1) participant attrition in a longitudinal cohort of older adults; (2) the reporting and handling of missing data in longitudinal studies of older adults; (3) the feasibility of a virtually-delivered multimodal frailty rehabilitation program for older adults with frailty during the COVID-19 pandemic; and (4) the feasibility of a multicomponent prehabilitation intervention for older adults with frailty awaiting joint replacement.

Issue 1: Participant attrition in a longitudinal cohort of older adults.

Longitudinal studies require repeated assessments of a predefined group of participants over time to provide information about multi-factor changes that occur in the cohort[14,25]. During the follow-up period, attrition of participants may occur for various reasons[26-28]. This could lead to bias when there are differential losses in participants' groups and variations in participants' characteristics between the initial cohort and final analytical sample[18,29]; which is also known as selective attrition[29].

Longitudinal studies of older adults are particularly prone to selective attrition[16,27]. Due to age, this population has increased vulnerability to adverse experiences such as illness, disability, hospitalization, institutionalization, and death that could negatively affect their continued participation in the study[15,16]. Drop out rates could increase by 25% for every decade increase in age[15]. Those who eventually complete the study are likely to be younger healthier and wealthier[27,30]. This risk factors for attrition may be common across cohorts or differ between them[27,31]. Additionally, the magnitude and pattern of attrition may vary depending on the study design, setting, and retention strategies employed[31,32].

This study, therefore, explored the extent, pattern, and risk factors of attrition in a new cohort of older adults from the Global Longitudinal Studies of Osteoporosis in Women. It examined different forms of attrition to provide insights into the factors that are associated with each type. Time-to-event analysis was used to investigate these associations which allows for utilization of all information contributed by each participant over the follow-up period[33]. Exploring these attrition-related issues is crucial to the analysis and interpretation of the original study and further contributes formative data for the design of future studies in similar cohorts.

Issue 2: The reporting and handling of missing data in longitudinal studies of older adults

Missing data are a common problem in longitudinal studies of older adults[16,34]. The susceptibility of this population to adverse events during follow-up increases the risk of participant non-response, drop-out and withdrawal[16,35]. Missing data leads to reduction in sample size which could introduce bias and inefficiency in estimates, therefore, undermining the validity of the study's findings[36,37]. It could also threaten the generalizability of the results if the sample analysed is different than the original[16]. As such, dealing with missing data is a critical aspect of study data analysis and interpretation.

While it may be impossible to prevent the occurrence of missing data in longitudinal studies[38], there are appropriate ways of handling them where present to strengthen the validity of the evidence[35,37,39]. These

include (1) assessing the magnitude of missing data to determine if it will have any consequences to the analysis[40]; (2) exploring the underlying mechanisms of missingness according to Rubin[41]; and (3) performing sensitivity analysis to test the robustness of the results to different missing data mechanisms[36,42]. In addition, adequate reporting of the handling of missing data in studies is equally important for transparency and replication[37,43].

The available evidence exploring how missing data are handled and reported are mostly based on randomized controlled trials[44-46] and lacked studies specific to the aging population who have high risk for participant loss[47]. Therefore, we surveyed the literature on longitudinal aging studies to assess the magnitude, reporting and handling of missing data in them. Findings from this study will contribute to the evidence for better methodological standard in aging research for authors, readers, and journal editors.

Issue 3: Feasibility of virtual rehabilitation program for vulnerable older adults with frailty during COVID-19 pandemic

Frailty is a state of is a complex condition involving multiple systems that results in impaired function and vulnerability to poor health outcomes[19,48]. Approximately, 23% of Canadians aged 65 and above are living with frailty[49], and this estimate increases to over 40% among those aged 85 or older[50]. The impact of frailty on health and social care is substantial, as older adults with frailty are heavy users of healthcare and rehabilitation services[51-53]. Those with moderate or severe frailty have a nearly 9-fold higher relative risk of institutionalization – (95% confidence interval, 4.9 – 15.2)[54].

During the COVID-19 pandemic, there were concerns regarding the well-being of vulnerable older adults who were housebound and isolated due to pandemic-related restrictions[55]. The extended period of inactivity could lead to decline in physical function, mental health, and ability to perform activities of daily living[56,57]. Total inactivity in older adults could result in a 2 – 5 % reduction in muscle strength per day[57]. Given the physical and social distancing policies in place[58] and the limited access to care then[59], there was an

immediate need to design interventions that could be delivered effectively to older adults with frailty, who were at high risk of adverse health outcomes.

To respond this need, this study evaluated the feasibility of implementing a multicomponent virtual rehabilitation program delivered in the homes of this vulnerable group, incorporating socialization, exercise, nutrition, and medication support. This multicomponent of intervention is in line with the evidence on frailty management[60-62]. However, there are limited studies on how it can be delivered remotely[63,64].

Issue 4: Feasibility of a prehabilitation program for older adults with frailty awaiting joint replacement

Joint replacement surgery is among the most frequently performed surgeries in older adults[65]. In Canada, more than 100,000 hip and knee replacements were done between the years 2020 and 2021[66]. It is estimated that around 40% of patients undergoing these surgeries are living with frailty[67], a percentage that could potentially increase due to extended wait times.

Frailty is a state of diminished physiological reserves, leading to reduced functional capacity and increased susceptibility to external stressors[19,48]. Patients living with frailty have longer recovery periods and face double the risk of serious post-operative complications compared to their non-frail counterparts[24]. Existing evidence suggests that frailty can be managed with appropriate interventions[61,62]. As such, older adults with frailty awaiting surgery could be prepared to cope with the upcoming stress of surgery by prehabilitation, consequently, reducing the risk of poor post-surgical outcomes[68,69]. However, there are limited studies examining prehabilitation interventions in this patient group. Available studies were short-term, included hip replacement patients or females only, measured short-term outcomes, and were mostly exercise-based[70-72].

To strengthen patients' physiological reserves and enhance post-surgical recovery, a comprehensive multimodal frailty intervention aligned with existing evidence for frailty management[60,62], including

exercise, protein supplementation, vitamin D, and medication optimization may be promising for improving frailty in those undergoing joint replacement surgery. This study investigated the feasibility of implementing this multimodal approach in older adults with frailty awaiting hip or knee replacement.

Outline of the thesis

This thesis is a 'sandwich' of four papers (Chapters 2 – 5) encompassing a systematic literature survey, secondary data analysis of a cohort study and two feasibility trials. Each paper separately addresses the issues described above.

Chapter 2 reports the magnitude, pattern, and factors associated with attrition in the Global Longitudinal Study of Osteoporosis in Women (GLOW) Hamilton cohort. This study examined the risk factors of different forms of attrition using survival analysis models and performed sensitivity analysis for missing baseline data.

Chapter 3 is a systematic survey of the reporting and handling of missing data in longitudinal observational studies of older adults.

Chapter 4 reports on the randomized controlled feasibility trial of the Geras virtual frailty rehabilitation program to build resilience in vulnerable older adults during the COVID-19 pandemic. We employed the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework to comprehensively assess the feasibility of the intervention based on predefined criteria for success.

Chapter 5 is the evaluation of the feasibility of the FitJoints randomized controlled trial of a multimodal intervention in frail older patients with osteoarthritis awaiting hip and knee replacement. We assessed feasibility based on pre-specified progression thresholds and examined pre- and post-surgical clinical outcomes at multiple time points.

Chapter 6 provides a summary of the key findings, limitations, implications, and future research directions based on the four studies included in this thesis.

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CHAPTER 2

Exploring participant attrition in a longitudinal follow-up of older adults: the Global Longitudinal Study of Osteoporosis in Women (GLOW) Hamilton cohort

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Exploring participant attrition in a longitudinal follow-up of older adults: the Global Longitudinal Study of Osteoporosis in Women (GLOW) Hamilton cohort

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ABSTRACT

Objective We explored the magnitude of attrition, its pattern and risk factors for different forms of attrition in the cohort from the Global Longitudinal Study of Osteoporosis in Women.

Design Prospective cohort study.

Setting Participants were recruited from physician practices in Hamilton, Ontario.

Participants Postmenopausal women aged ≥55 years who had consulted their primary care physician within the last 2 years.

Outcome measures Time to all-cause, non-death, death, preventable and non-preventable attrition.

Results All 3985 women enrolled in the study were included in the analyses. The mean age of the cohort was 69.4 (SD: 8.9) years. At the end of the follow-up, 30.2% (1206/3985) of the study participants had either died or were lost to follow-up. The pattern of attrition was monotone with most participants failing to return after a missed survey. The different types of attrition examined shared common risk factors including age, smoking and being frail but differed on factors such as educational level, race, hospitalisation, quality of life and being prefrail.

Conclusion Attrition in this ageing cohort was selective to some participant characteristics. Minimising potential bias associated with such non-random attrition would require targeted measures to achieve maximum possible follow-rates among the high-risk groups identified and dealing with specific reasons for attrition in the study design and analysis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used a large cohort with a relatively long follow-up period.
⇒ Different types of attrition were assessed, which provides an understanding of the factors associated with each type of attrition.
⇒ The cohort had limited racial and gender diversity which could affect the generalisability of the results.
⇒ The reasons for attrition were unavailable for more than one-third of the participants thus limiting further analysis.
⇒ We recommend caution in interpreting the results since data were based on self-reports.

BACKGROUND

Longitudinal studies require the repeated collection of data from participants over time, thus making them prone to attrition.[1] The loss of participants may be intermittent, where they miss one wave and return at subsequent time points, or terminal, where they drop out completely from the study.[2 3] Attrition complicates the analysis of longitudinal studies and could threaten the internal and external validity of study results if it is selective.[4 5] Selective attrition occurs when participants who are lost are different than those who remain or complete the study.[6] This could create differences in group compositions and changes in participant characteristics between the original cohort and analytical sample.[5 6]

Selective attrition is a serious concern in longitudinal ageing studies, given the increased susceptibility of older adults to adverse experiences such as illness, hospitalisation, institutionalisation, disability and death that could affect their ability and availability to respond to follow-up assessments.[7 8] In ageing studies, attrition rates as high as 77% over a 10-year follow-up[9] and up to 40% in a shorter observation period of 2 years[10] have been reported. Existing evidence suggests that the initial level or status of participants at study entry may predict how long they will remain in the study.[1 2 11 12] Non-completers compared with completers are generally more likely to be older, have poorer cognitive function, lower socioeconomic status, lower level of education and poorer socioeconomic

status.[4 13] This could be a source of bias if these risk factors for attrition are related to the risk factors for the exposure and outcome of interest.[2 9]

A 2005 systematic review of attrition in longitudinal ageing studies reported that many studies lacked sufficient details on attrition and its predictors.[4] This limited the number of studies that were eventually included in the review, thus underscoring the need for more evidence. While there has been new evidence generated from different ageing cohort studies to improve our understanding of participant loss since then,[2 9 10 14–19] it is still important to examine this issue in any new cohort. This is because attrition rates, patterns and risk factors may vary depending on study-specific factors including, setting, design features (such as frequency of follow-up, participant burden and mode of survey), available resources and the clinical subpopulation studied.[16 20] For example, the attrition rate in a cohort of patients living with Alzheimer's disease followed for 2 years[10] was as high as that of a cohort of community dwelling adults with twice the same length of follow-up.[16] Knowledge of attrition is essential to guide the analysis and interpretation of study findings, as well as inform the design of future studies in similar cohorts. In this study, we explored the magnitude of attrition, its pattern and risk factors for different forms of attrition in the cohort from the Global Longitudinal Study of Osteoporosis in Women (GLOW).

METHODS

Study design, participants and setting

The GLOW study, Hamilton cohort was a multisite prospective cohort study that examined the risk factors and management of osteoporotic fractures in more than 60 000 women aged ≥55 years, drawn from 17 sites across 10 countries.[21] The women were recruited from physician practices and were excluded for language barrier, cognitive impairment, severe illness or institutionalisation. Details of the study have been described elsewhere.[21] For the Hamilton cohort, 3985 women were recruited from 35 physician practices and enrolled between January 2007 and December 2008. Participants were followed up for 6 years and were mailed study questionnaires annually; however, there was no data collection between the fourth and fifth year. Participant completion of annual survey was captured for each year of follow-up and where there was no return, they were contacted by study personnel. Reasons for drop-out were collected where possible. Written informed consents were obtained from all participants.

Patient and public involvement

There was no patient or public involvement in the design, conduct, reporting or dissemination plans of this study.

Outcomes

Since existing evidence suggests that predictors of attrition may differ by cause,[11 18] outcomes assessed were categorised by cause and included time to all-cause, non-death and death attrition. These were defined as time from study enrolment to the last wave a participant was observed in the study regardless of the reason for attrition, for all non-death reasons including refusals, loss of contact and for losses due to death, respectively. Refusal was defined as declining to continue to participate in the study when contacted after failure to return a mailed survey or mailing a withdrawal note in place of completed questionnaire. Lost contact was defined as being unreachable through mail or phone calls after online search of obituaries were conducted to determine if they were lost contact due to death. Participants who were lost to follow-up without any documented reasons were classified as unknown. Death status was ascertained by contacting participants spouses, friends or relatives and by searching electronic databases of obituaries for entries that corresponded with the participant's full names and date of birth.

We also categorised outcomes into preventable attrition (attrition due to refusals and loss of contact which can lead to intermittent participant loss and for which the researcher may be able to mitigate with targeted strategies) and time to non-preventable attrition (attrition due to death and cognitive impairment which can lead to terminal attrition and are not modifiable by the researcher). Examining these types of is important given that attrition due to death and illness occur in both study cohort and target population while other forms of attrition are restricted to the study cohort.[15 22] Consequently, the risk factors may differ, therefore, presenting varying degree of potential bias and requiring different tailored strategies to address during study design and analysis.[15 22] Participants entered the study at enrolment and their observation time ended with an event at time of attrition, or with censoring at the end of the study.

Covariates

The covariates assessed were age, educational level, race, body mass index (BMI), falls in the past year, prior fracture, osteoporosis, polypharmacy, smoking, alcohol use, health-related quality of life (HRQoL) and frailty status. These are variables previously shown to be associated with attrition[2 4 9 13] and included other new variables available in the dataset. Prior fracture was defined as any baseline self-reported fracture that occurred since the age of 45. Polypharmacy was defined as taking or taken five or more medications at study entry. Participants who responded 'yes' to the question: 'Have your doctor or any other health provider ever told you that you had osteoporosis?' were classified as having osteoporosis. Smoking was defined as smoking at least once a week while alcohol use was defined as having seven or more drinks of alcohol per week. HRQoL was measured using the European Quality of Life 5 Dimension 5 Level (EQ5D5L).[23] Frailty status was derived from a categorisation of frailty index (FI), as computed by previous studies that utilised the same dataset.[24] Briefly, an FI composed of 34 baseline variables

(15 comorbidities, 12 activities of daily living, 6 symptoms and signs and 1 healthcare utilisation measure) was constructed by mapping each level of a categorical deficit to a value from 0 to 1 to indicate the frequency and severity of the deficit. The values of the deficits were summed and divided by the 34 deficits assessed to yield FI scores for each participant. Then, the FI was categorised into non-frail, prefrail and frail based on cut-points (0.20 and 0.35) from a previous study of the same cohort.[25] All the variables included in the analyses were based on self-reports.

Statistical analysis

Descriptive analysis of participants baseline characteristics by attrition status were presented as frequencies with percentages and means with standard deviation (SD) for categorical and continuous variables, respectively. Graphs were used to show the pattern and rate of participant loss across the waves of follow-up. The pattern of missingness created by participant loss was generally monotone, that is, a participant who missed a wave of assessment was unlikely to be available for subsequent waves[3]; therefore, time-to-event analysis was considered most appropriate regression method for the data. We performed univariate and multivariable analysis using Cox proportional hazards model with robust standard errors (SEs) to account for potential clustering within physician practices. For the multivariable analysis, all covariates were included simultaneously in the model regardless of statistical significance in the univariate analysis. Proportional hazards assumption was checked using both graphical diagnostics based on scaled Schoenfeld residuals and a statistical test.

Sensitivity analyses were performed to assess the robustness of results to and missing covariate data—educational level (13.9%), BMI (4.5%), fall (0.8%), osteoporosis (4.7%), smoking (0.73%), drinking (0.68%), hospitalisation (0.98%), HRQoL (3.6%). Multiple imputation using chained equation was used to handle missing baseline data assuming the data were missing at random. Ten imputed datasets were created, and the imputation model included all the covariates in the analytic model and Nelson-Aalen cumulative hazard estimator. All analyses were performed using Stata V.17 (Stata) and regression results were considered statistically significant at $p<0.05$. Additional sensitivity analyses were performed adjusting for multiple hypothesis testing using Bonferroni correction and results were considered significant at a lower threshold of <0.01.

RESULTS

Characteristics of the GLOW Hamilton cohort by attrition status are presented in table 1. A total of 3985 were enrolled in the study. The mean age of the cohort was 69.4 (SD: 8.9) years. At baseline, the majority of the participants were white (93.3%), non-smokers (88.7%), had high school or lower education (64.1%), no prior fracture (78.4%), osteoporosis (73.8%) and no hospitalisation in the past year (88.7%). Generally, the participants had relatively subjective good health at study entry, EQ5D5L: 0.72, frailty status: 81% non-frail or prefrail. The cohort was observed for a median of 4.59 (Q1–Q3: 3.04–4.67) years. Over the observation period, attrition occurred in 1206 (30.0%) of the participants: 1042 (86.4%) due to non-death causes and 164 (13.6%) due to death. The reasons for participant loss include loss of contact 223 (18.5%), refusal 330 (27.4%), ineligible to continue due to cognitive impairment 62 (5.1%), death 164 (13.6%) and unknown 427 (35.4%). Figure 1 shows the flow chart of participant loss due to death and non-death causes from enrolment to last wave of follow-up. The pattern of attrition which was generally terminal; approximately 99% of participants did not return after a missed survey (online supplemental table S1). In figure 2, the attrition rates were stable in the first three waves, then spiked up at the last wave for both all-cause and non-death attrition.

Table 2 shows the results of the multivariable analyses of the relationship between all-cause, non-death and death attrition and the factors examined while table 3 shows the results of the regression analyses for preventable and non-preventable causes of attrition. Increasing age (HR 1.19, 95% CI 1.12 to 1.25, $p<0.001$), smoking (HR 1.69, 95% CI 1.47 to 1.95, $p<0.001$), hospitalisation (HR 1.24, 95% CI 1.03 to 1.49, $p=0.022$) and being prefrail (HR 1.36, 95% CI 1.16 to 1.59, $p\leq0.001$) or frail (HR 1.82, 95% CI 1.46 to 2.26, $p<0.001$) were associated with increased hazards of all-cause attrition. Conversely, higher educational level attrition (HR 0.81, 95% CI 0.70 to 0.94, $p=0.006$) and higher HRQoL (HR 0.66, 95% CI 0.46 to 0.94, $p=0.022$) were associated with lower hazards of all-cause attrition. These relationships were comparable to the results of the non-death attrition analysis. For attrition due to death, increasing age (HR 1.59, 95% CI 1.38 to 1.83, $p<0.001$), smoking (HR 2.29, 95% CI 1.44 to 3.64, $pe\leq0.001$) and being frail (HR 3.11, 95% CI 1.59 to 6.08, $p<0.001$) were the only factors significantly associated with attrition. The results of the analyses for preventable attrition were similar to the analyses for all-cause and non-death attrition. For the non-preventable causes of attrition, the results were comparable to the analyses of attrition due to death but differed in the magnitude of the hazard ratios of the risk factors identified and with an additional statistically significant factor, race (HR 2.22, 95% CI 1.12 to 4.39, $p=0.022$). The proportional hazard assumptions were satisfied. However, the results of the missing data analyses differed slightly from the primary analyses for all-cause and non-death attrition (online supplemental tables S2 and S3). Further, the results adjusted for multiple testing differed in statistical significance for two factors (hospitalisation and quality of life) in all-cause attrition and one factor (race) in the non-death attrition regression analyses (online supplemental tables S4–S6).

Table 1 Baseline characteristics of participants

Characteristic	Total n=3985	LTFU n=1206	Retained n=2779	P value
Age (years), mean (SD)	69.4 (8.9)	72.3 (9.8)	68.2 (8.2)	<0.001
Education, n (%)				
High school or less	2509 (64.1)	840 (71.7)	1669 (60.9)	<0.001
More than high school	1405 (35.9)	331 (28.3)	1074 (39.1)	
Race, n (%)				
White	3717 (93.3)	1119 (92.8)	2598 (93.5)	0.417
Non-white	268 (6.7)	87 (7.2)	181 (6.5)	
Body mass index (kg/m^2): mean (SD)	27.7 (5.8)	27.7 (6.2)	27.7 (5.6)	<0.001
Falls, n (%)				
No	2471 (62.5)	702 (59.0)	1769 (64.0)	0.003
Yes	1483 (37.5)	488 (41.0)	995 (36.0)	
Prior fracture, n (%)				
No	3123 (78.4)	899 (74.5)	2224 (80.0)	<0.001
Yes	862 (21.6)	307 (25.5)	555 (20.0)	
Osteoporosis				
No	2801 (73.8)	779 (69.4)	2022 (75.6)	<0.001
Yes	995 (26.2)	344 (30.6)	651 (24.4)	
Polypharmacy				
No	3604 (90.4)	1091 (90.5)	2513 (90.4)	0.972
Yes	381 (9.6)	115 (9.5)	266 (9.6)	
Smoking, n (%)				
No	3510 (88.7)	1009 (84.9)	2500 (90.3)	<0.001
Yes	447 (11.3)	179 (15.1)	268 (9.7)	
Alcohol intake, n (%)				
No	3441 (87.0)	1026 (85.9)	2415 (87.4)	<0.216
Yes	517 (13.0)	168 (14.1) (52.2)	349 (12.6)	
Hospitalisation, n (%)				
No	3498 (88.7)	996 (84.2)	2502 (90.6)	<0.001
Yes	448 (11.3)	187 (15.8)	261 (9.4)	
EQ5D5L, mean (SD)	0.72 (0.23)	0.66 (0.26)	0.75 (0.22)	<0.001
Frailty status (n %)				
Non-frail	1924 (48.3)	407 (33.8)	1517 (54.6)	<0.001
Prefrail	1290 (32.4)	428 (35.5)	862 (31.0)	
Frail	771 (19.4)	371 (30.8)	400 (19.4)	

%, proportion; EQ5D5L, European Quality of Life 5 Dimension 5 Level; LTFU, lost to follow-up; n, number.

DISCUSSION

This study showed a moderately high attrition rate over the 6year period of follow-up at 30%, which is comparable to population-based studies with similar duration of observation.[17 26] The pattern of attrition was inconsistent across the waves of follow-up, which we attribute to a gap in data collection between the fourth and sixth year of the study owing to funding constraints. The losses that occurred during that period, which were observed at the fourth and last wave of data collection, was double what was recorded over the three preceding waves. In previous longitudinal ageing studies, attrition rates were stable over time.[12 16] The pattern seen in our study is similar to what has been observed in studies with longer follow-up duration of up 10 years.[14] Our contrasting finding underscores the importance of consistent follow-up, as factors that increase attrition rates such as declining interest, loss of contacts and relocations could be heightened during unplanned breaks in data collection.

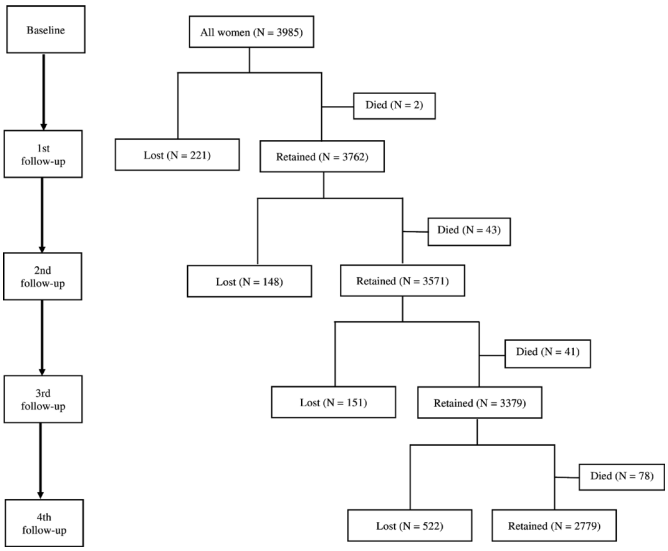

Figure 1 Flow chart of study participants.

Participants drop-out in the study was largely terminal with 99% of participants who missed a wave of data collection unavailable for subsequent follow-up. This pattern of attrition was unexpected as study personnel made efforts to recontact participants when they failed to return mailed surveys. Such reminder strategies have mostly shown favourable effects in improving retention[27 28] including postal surveys among older adults.[29] It appears a single measure was insufficient to minimise attrition in this study. Reviews of retention strategies found higher retention rates among studies where multiple methods were used.[30 31] As such, it is possible that this study could have benefited from using a combination of different retention measures.

Our study also showed that attrition was selective with respect to some participants characteristics. While increasing age, smoking and being frail were common to all forms of attrition examined, additional factors such as lower education, prior hospitalisation, lower quality of life, and being prefrail at study entry were associated with non-death attrition and preventable causes of attrition. Being white was significantly associated with greater risk of non-preventable causes of attrition. This could be explained by the fact that the cohort was largely white and that all participants who dropped out of the study due to cognitive impairment were white, which increased the number of events for this group when added to the other non-preventable cause of attrition, death. Notwithstanding, our findings are consistent with previous studies that showed that risk factors could differ by reasons for attrition.[11 17–19]

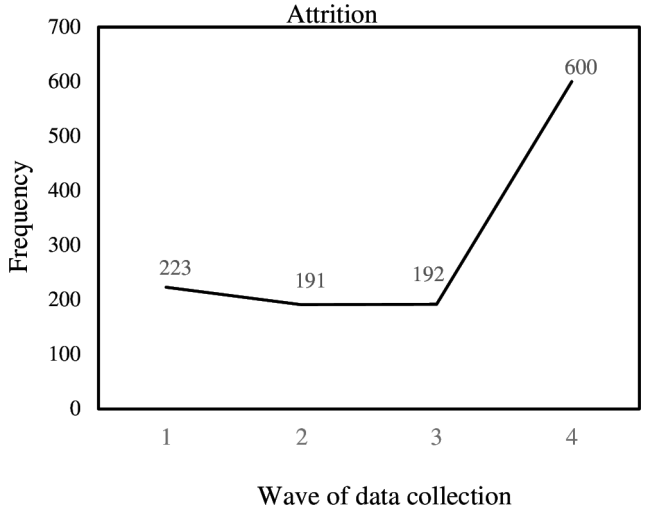

Figure 2 Graph of participants loss over the follow-up period.

Age is an established predictor of attrition[4 13] and this is further confirmed in our study with older participants having a higher risk of study loss. As participants age, they are likely to experience decline in health status and functioning, as well as death which could interfere with data collection.[7] While the ageing process is beyond the control of the researcher, some measures such as oversampling of older participants[18] and use of proxy respondents[32] could provide a buffer against attrition as participation becomes more challenging with age. Participants who had lower levels of education were also more likely to drop out of the study for reasons other than death or impairment, which is consistent with most evidence on this risk factor.[1 2 11 13 14 33] A person's level of education may influence what they know and understand about research, thus affecting their attitudes towards continued participation in the research process. Therefore, retaining participants of lower educational status could benefit from continuous targeted messaging on the value of completing the study. In addition, our study supports existing literature in which smokers were consistently less likely to complete follow-up assessments.[1 17 34] This factor remained significantly associated with attrition across all the types examined. Smoking is associated with many health risks and worsening health outcomes in older adults,[35] consequently affecting the ability of those participants to continue in the study. As such, it is important to prioritise smokers as a high-risk group in the design of retention strategies for cohort studies of older adults.

The multidimensional measures of health assessed in this study, frailty status and European Quality of Life 5 Dimension 5 Level, suggests an increased risk of attrition at poorer levels of these health variables. For frailty, which is an indicator of vulnerability to poor health outcomes,[36] participants who were prefrail or frail, that is, those who had a FI>0.20 were more likely to drop out of the study than the non-frail group for any reason. However, losses due to death and impairment were higher among frail participants. This finding was expected as higher levels of frailty are related to increased risk of morbidity and mortality,[36 37] which affects participation. The EQ5D5L index which is a measure of the participants perceived HRQoL[23] indicated that those with higher scores had greater chances of completing the study. However, it was not significantly associated with the non-preventable

Table 2 Multivariable regression analysis for all-cause, non-death and death attrition

	All-cause attrition		Non-death attrition		Death attrition	
Characteristics	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age*	1.19 (1.12 to 1.25)	<0.001	1.22 (1.14 to 1.31)	<0.001	1.59 (1.38 to 1.83)	<0.001
Education						
≥High school	0.81 (0.70 to 0.94)	0.006	0.71 (0.57 to 0.89)	0.003	0.93 (0.60 to 1.43)	0.729
Race						
White	1.19 (0.91 to 1.57)	0.199	1.08 (0.74 to 1.59)	0.685	1.69 (0.84 to 3.42)	0.142
Body mass index*	0.99 (0.95 to 1.05)	0.788	0.98 (0.91 to 1.06)	0.694	0.97 (0.87 to 1.22)	0.739
Falls						
Yes	1.06 (0.95 to 1.20)	0.302	1.07 (0.90 to 1.26)	0.466	1.21 (0.88 to 1.67)	0.240
Prior fracture						
Yes	1.08 (0.94 to 1.23)	0.263	1.03 (0.84 to 1.26)	0.759	1.33 (0.95 to 1.86)	0.098
Osteoporosis						
Yes	1.00 (0.87 to 1.15)	0.987	0.95 (0.78 to 1.16)	0.624	1.20 (0.80 to 1.78)	0.376
Polypharmacy						
Yes	0.83 (0.65 to 1.07)	0.149	0.79 (0.58 to 1.09)	0.151	1.01 (0.62 to 1.67)	0.954
Smoking						
Yes	1.69 (1.47 to 1.95)	<0.001	1.74 (1.36 to 2.24)	<0.001	2.29 (1.44 to 3.64)	<0.001
Alcohol intake						
Yes	1.06 (0.92 to 1.22)	0.406	1.12 (0.92 to 1.37)	0.257	0.98 (0.58 to 1.67)	0.939
Hospitalisation						
Yes	1.24 (1.03 to 1.49)	0.022	1.32 (1.05 to 1.66)	0.016	1.23 (0.68 to 2.20)	0.494
EQ5D5L	0.66 (0.46 to 0.94)	0.022	0.56 (0.38 to 0.85)	0.006	0.71 (0.29 to 1.70)	0.435
Frailty status						
Prefrail	1.36 (1.16 to 1.59)	<0.001	1.38 (1.12 to 1.68)	0.002	1.35 (0.79 to 2.29)	0.269
Frail	1.82 (1.46 to 2.26)	<0.001	1.73 (1.33 to 2.24)	<0.001	3.11 (1.59 to 6.08)	<0.001

*Expressed as change per five-unit increase.
EQ5D5L, European Quality of Life 5 Dimension 5 Level.

causes of attrition in contrast to previous studies.[17] Nevertheless, the results of the composite measures support existing evidence that poor health status is an important predictor of participant loss.[4 19 38 39] These health index measures could be useful for streamlining the number of individual health variables that would otherwise be too many to consider when designing strategies to minimise attrition. For example, being hospitalised in the past year was also associated with increased risk of participant loss in this study. Frailty is a known risk factor for hospitalisation among older adults.[40] Therefore, a frailty measure could be used to capture participants whose risk of attrition is related to previous or even future hospitalisation.

The differences observed in the characteristics of participants who were lost and those who completed the study extends the evidence on non-random losses in longitudinal ageing studies. While the risk factors of attrition identified in this study are unmodifiable person-level characteristics that cannot be changed by the researcher,[41] these can be accounted for in the study design. Some of the strategies that have demonstrated positive effects on retention in the ageing literature include, inclusion of proxy respondents,[32] transportation support,[11] at-home assessment,[42] financial incentives, flexible data collection schedule, provision of periodic update on study progress as well as participant appreciation.[43] Most of these measures may not be effective in addressing non-preventable attrition, that is, attrition due to death or illness which are common in ageing studies.[2 9 11 33 44] Uncommon but cost-effective measures such as substitution sampling, which involves the recruitment of new participants as replacements for losses based on shared baseline characteristics, could be used to mitigate this type of attrition.[45 46]

In designing retention strategies, it is important to consider what could constitute increased participant burden to avoid a counterproductive effect. According to a recent meta-analysis of longitudinal cohort studies, strategies that offered flexibility to participants and were less burdensome provided the greatest benefits.[47] Further, successfully retaining older adults in longitudinal studies may require reviewing the strategies periodically to determine what works best, as in the Gates *et al* study,[48] where

Table 3 Multivariable regression analyses for preventable and non-preventable attrition

	Preventable attrition		Non-preventable attrition	
Characteristics	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age*	1.18 (1.10 to 1.26)	<0.001	1.66 (1.48 to 1.85)	<0.001
Education				
≥High school	0.73 (0.58 to 0.92)	0.008	0.82 (0.56 to 1.21)	0.324
Race				
White	0.98 (0.67 to 1.44)	0.912	2.22 (1.12 to 4.39)	0.022
Body mass index*	0.99 (0.91 to 1.07)	0.781	1.03 (0.91 to 1.07)	0.655
Falls				
Yes	1.04 (0.88 to 1.24)	0.610	1.22 (0.97 to 1.54)	0.096
Prior fracture				
Yes	0.99 (0.80 to 1.22)	0.919	1.34 (0.95 to 1.87)	0.092
Osteoporosis				
Yes	0.95 (0.77 to 1.16)	0.607	1.15 (0.82 to 1.63)	0.416
Polypharmacy				
Yes	0.81 (0.57 to 1.13)	0.211	0.90 (0.58 to 1.41)	0.658
Smoking				
Yes	1.79 (1.38 to 2.31)	<0.001	2.07 (1.33 to 3.21)	0.001
Alcohol intake				
Yes	1.16 (0.94 to 1.43)	0.165	0.93 (0.61 to 1.41)	0.724
Hospitalisation				
Yes	1.48 (1.18 to 1.86)	0.001	0.98 (0.58 to 1.67)	0.943
EQ5D5L	0.58 (0.39 to 0.86)	0.006	0.68 (0.31 to 1.45)	0.306
Frailty status				
Prefrail	1.42 (1.15 to 1.76)	0.001	1.24 (0.80 to 1.90)	0.333
Frail	1.71 (1.31 to 2.21)	<0.001	2.74 (1.59 to 4.70)	<0.001

*Expressed as change per five-unit increase.
EQ5D5L, European Quality of Life 5 Dimension 5 Level.

transitioning from a long face-to-face questionnaire to a shorter postal survey increased response rates and reduced questionnaire error rates.

Attrition causes missing data problems, and our study and others have shown that this missingness could be non-random in ageing cohorts.[2 9 14–16] Notwithstanding, the common method for handling participant losses in longitudinal studies of older adults is by exclusion from analysis based on the assumption of random loss.[49] This assumption is not plausible where the probability of attrition is dependent on participant characteristics. There are statistical methods that could be used to handle missing data due to selective attrition, such as multiple imputation, joint models and mixed models,[50–52] but the discussion is beyond the scope of this paper. It is important to note that these post-hoc measures may not completely eliminate potential attrition bias, particularly when the missing data are large.[7] As the popular saying goes, 'prevention is better than cure', so it is most valuable to employ measures that ensure maximum follow-up rates possible are achieved.

LIMITATIONS

We examined potential risk factors for different types of attrition in a large, population-based sample of older adults. However, the study is not devoid of limitations. Since our study cohort was predominantly white and involved females only, the findings may not apply to more racially diverse populations and genders. In addition, we only investigated the associations between baseline characteristics and attrition; however, some of these characteristics may have changed over time which could impact attrition rates across different waves of data collection. The data were obtained in a self-reported manner and were not validated by patient clinical records. As such, there is possibility of underestimation or overestimation. Notwithstanding, the source of our death data has also been proven to be reliable.[53] Lastly, the reasons for attrition were unavailable for more than a third of the participants who did not complete the study, thus limiting our analyses and narrowing our understanding of why participants drop out which is critical to designing retention strategies.

CONCLUSION

This study extends evidence on the occurrence of inevitable and non-random attrition in ageing cohort studies, showing risk factors that are common and specific to different types of attrition. Addressing these potential sources of attrition bias will enhance our understanding of the ageing process with longitudinal data. This would require targeted measures to achieve maximum possible follow-rates among high-risk groups and dealing with specific reasons for attrition in the design and analysis of cohort studies of older adults.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was ethical approval was granted by the Western Institutional Review Board (No: 20062338) and written informed consent was obtained from all participants. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data are held by a third party and includes potentially identifying patient information, so cannot be shared publicly. However, the dataset is available on request from JA: jd.adachi@sympatico.ca, St. Joseph's Healthcare Hamilton, McMaster University, Hamilton, ON, Canada.

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Supplementary documents

S1: Patterns of missing values created by participant loss

Pattern	Missing values	Frequency
+ + + +	0	2779
+ + + -	1	593
+ + - -	2	192
+ - - -	3	191
- - - -	4	223
+ + - +	1	6
- + + +	1	1

+ present; - absent

S2: Multivariable regression analyses: all-cause, non-death and death attrition to account for missing data

	All-cause attrition			Non-death attrition			Death attrition		
Characteristics	HR	(95% CI)	p-value	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Age*	1.20	1.16 – 1.24	<0.001	1.19	1.13 – 1.26	<0.001	1.61	1.42 – 1.81	<0.001
Education									
≥ High school	0.80	0.69 – 0.92	0.003	0.74	0.59 – 0.93	0.009	0.91	0.62 – 1.33	0.613
Race									
White	1.00	0.80 – 1.25	0.999	0.84	0.62 – 1.14	0.266	1.32	0.69 – 2.52	0.397
Body mass index*	0.98	0.93 – 1.03	0.366	0.98	0.91 – 1.05	0.564	0.96	0.82 – 1.14	0.663
Falls									
Yes	1.06	0.94 – 1.20	0.324	0.98	0.83 – 1.14	0.773	1.22	0.92 – 1.61	0.165
Prior fracture									
Yes	1.02	0.90 – 1.15	0.803	1.00	0.84 – 1.18	0.958	1.22	0.88 – 1.71	0.233
Osteoporosis									
Yes	1.02	0.89 – 1.15	0.815	0.96	0.79 – 1.17	0.695	1.10	0.75 – 1.63	0.625
Polypharmacy									
Yes	0.81	0.64 – 1.02	0.073	0.78	0.58 – 1.06	0.115	0.95	0.60 – 1.51	0.823
Smoking									
Yes	1.65	1.45 – 1.89	<0.001	1.77	1.42 – 2.22	<0.001	1.98	1.27 – 3.11	0.003
Alcohol intake									
Yes	1.09	0.94 – 1.28	0.255	1.17	0.94 – 1.45	0.168	1.21	0.78 – 1.88	0.391
Hospitalization									
Yes	1.23	1.05 – 1.43	0.010	1.42	1.16 – 1.73	0.001	1.28	0.79 – 2.09	0.313
EQ5D5L	0.61	0.44 – 0.84	0.003	0.50	0.34 – 0.72	<0.001	0.58	0.26 – 1.27	0.172
Frailty status									
Prefrail	1.33	1.15 – 1.54	<0.001	1.31	1.07 – 1.61	0.010	1.54	0.94 – 2.53	0.089
Frail	1.74	1.44 – 2.10	<0.001	1.60	1.26 – 2.05	<0.001	3.29	1.82 – 5.95	<0.001

HR, hazard ratio; CI, confidence interval; EQ5D5L, measure for health-related quality of life; *expressed as change per 5-unit increase

S3: Multivariable regression analyses: preventable and non-preventable attrition to account for missing data

	Preventable attrition			Non-preventable attrition		
Characteristics	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Age*	1.19	1.13 – 1.26	<0.001	1.67	1.45 – 1.89	<0.001
Education						
≥ High school	0.74	0.59 – 0.93	0.009	0.76	0.54 – 1.07	0.118
Race						
White	0.84	0.62 – 1.14	0.266	1.78	0.94 – 3.35	0.075
Body mass index*	0.98	0.91 – 1.05	0.564	0.95	0.80 – 1.14	0.481
Falls						
Yes	0.98	0.83 – 1.14	0.773	1.21	0.96 – 1.53	0.100
Prior fracture						
Yes	1.00	0.84 – 1.18	0.958	1.20	0.89 – 1.62	0.241
Osteoporosis						
Yes	0.96	0.79 – 1.17	0.695	1.05	0.75 – 1.48	0.772
Polypharmacy						
Yes	0.78	0.58 – 1.06	0.114	0.89	0.55 – 1.45	0.647
Smoking						
Yes	1.77	1.42 – 2.22	<0.001	1.79	1.15 – 2.78	0.010
Alcohol intake						
Yes	1.17	0.94 – 1.45	0.168	1.08	0.74 – 1.58	0.680
Hospitalization						
Yes	1.42	1.16 – 1.73	0.001	1.03	0.67 – 1.58	0.887
EQ5D5L	0.50	0.34 – 0.72	<0.001	0.59	0.29 – 1.20	0.146
Frailty status						
Prefrail	1.31	1.07 – 1.61	0.010	1.45	0.98 – 2.17	0.065
Frail	1.60	1.26 – 2.05	<0.001	2.82	1.74 – 4.58	<0.001

HR, hazard ratio; CI, confidence interval; EQ5D5L, measure for health-related quality of life; *expressed as change per 5-unit increase; preventable attrition (attrition due to refusals and loss of contact) non-preventable attrition (attrition due to death and cognitive impairment)

S4: Multivariable regression analysis for all-cause, non-death and death attrition

	All-cause attrition			Non-death attrition			Death attrition		
Characteristics	HR	(99% CI)	p-value	HR	(99% CI)	p-value	HR	(99% CI)	p-value
Age*	1.19	1.12 – 1.25	<0.001	1.22	1.12 – 1.34	<0.001	1.59	1.32 – 1.91	<0.001
Education									
≥ High school	0.81	0.67 – 0.99	0.006	0.71	0.54 – 0.95	0.003	0.93	0.52 – 1.64	0.729
Race									
White	1.19	0.84 – 1.69	0.199	1.08	0.65 – 1.79	0.685	1.69	0.67 – 4.27	0.142
Body mass index*	0.99	0.93 – 1.06	0.788	0.98	0.88 – 1.09	0.694	0.97	0.83 – 1.28	0.739
Falls									
Yes	1.06	0.91 – 1.24	0.302	1.07	0.85 – 1.33	0.466	1.21	0.80 – 1.84	0.240
Prior fracture									
Yes	1.08	0.91 – 1.29	0.263	1.03	0.79 – 1.34	0.759	1.33	0.85 – 2.07	0.098
Osteoporosis									
Yes	1.00	0.84 – 1.20	0.987	0.95	0.74 – 1.23	0.624	1.20	0.71 – 2.02	0.376
Polypharmacy									
Yes	0.83	0.59 – 1.16	0.149	0.79	0.52 – 1.20	0.151	1.01	0.53 – 1.95	0.954
Smoking									
Yes	1.69	1.40 – 2.04	<0.001	1.74	1.26 – 2.42	<0.001	2.29	1.24 – 4.22	<0.001
Alcohol intake									
Yes	1.06	0.88 – 1.28	0.406	1.12	0.86 – 1.45	0.257	0.98	0.68 – 1.62	0.939
Hospitalization									
Yes	1.24	0.97 – 1.58	0.022	1.32	0.98 – 1.79	0.016	1.23	0.57 – 2.65	0.494
EQ5D5L	0.65	0.41 – 1.05	0.022	0.56	0.33 – 0.96	0.006	0.71	0.22 – 2.24	0.435
Frailty status									
Prefrail	1.36	1.10 – 1.68	<0.001	1.38	1.05 – 1.79	0.002	1.35	0.67 – 2.71	0.269
Frail	1.82	1.36 – 2.43	<0.001	1.73	1.22 – 2.44	<0.001	3.11	1.29 – 7.51	<0.001

HR, hazard ratio; CI, confidence interval; EQ5D5L, measure for health-related quality of life; *expressed as change per 5-unit increase

S5: Multivariable regression analyses for preventable and non-preventable attrition

	Preventable attrition			Non-preventable attrition		
Characteristics	HR	(99% CI)	p-value	HR	(99% CI)	p-value
Age*	1.18	1.07 – 1.29	<0.001	1.66	1.43 – 1.92	<0.001
Education						
≥ High school	0.73	0.54 – 0.99	0.008	0.82	0.50 – 1.37	0.324
Race						
White	0.98	0.59 – 1.62	0.912	2.22	0.91 – 5.43	0.022
Body mass index*	0.99	0.89 – 1.10	0.781	1.03	0.86 – 1.23	0.655
Falls						
Yes	1.04	0.84 – 1.30	0.610	1.22	0.90 – 1.66	0.096
Prior fracture						
Yes	0.99	0.75 – 1.31	0.919	1.34	0.86 – 2.08	0.092
Osteoporosis						
Yes	0.95	0.72 – 1.24	0.607	1.15	0.73 – 1.81	0.416
Polypharmacy						
Yes	0.81	0.52 – 1.26	0.211	0.90	0.50 – 1.62	0.658
Smoking						
Yes	1.79	1.27 – 2.51	<0.001	2.07	1.16 – 3.69	0.001
Alcohol intake						
Yes	1.16	0.88 – 1.53	0.165	0.93	0.53 – 1.61	0.724
Hospitalization						
Yes	1.48	1.10 – 1.99	0.001	0.98	0.49 – 1.98	0.943
EQ5D5L	0.58	0.34 – 0.97	0.006	0.68	0.24 – 1.85	0.306
Frailty status						
Prefrail	1.42	1.07 – 1.88	0.001	1.24	0.70 – 2.18	0.333
Frail	1.71	1.21 – 2.40	<0.001	2.74	1.34 – 5.57	<0.001

HR, hazard ratio; CI, confidence interval; EQ5D5L, measure for health-related quality of life; *expressed as change per 5-unit increase; preventable attrition (attrition due to refusals and loss of contact) non-preventable attrition (attrition due to death and cognitive impairment)

S6: Multivariable regression analyses: all-cause, non-death and death attrition to account for missing data

	All-cause attrition			Non-death attrition			Death attrition		
Characteristics	HR	(99% CI)	p-value	HR	(99% CI)	p-value	HR	(99% CI)	p-value
Age*	1.20	1.15 – 1.26	<0.001	1.19	1.11 – 1.28	<0.001	1.61	1.36 – 1.89	<0.001
Education									
≥ High school	0.80	0.66 – 0.97	0.003	0.74	0.55 – 1.00	0.009	0.91	0.55 – 1.50	0.613
Race									
White	1.00	0.75 – 1.33	0.999	0.84	0.56 – 1.26	0.266	1.32	0.57 – 2.09	0.397
Body mass index*	0.98	0.91 – 1.05	0.366	0.98	0.89 – 1.08	0.564	0.96	0.77 – 1.20	0.663
Falls									
Yes	1.06	0.91 – 1.24	0.324	0.97	0.79 – 1.20	0.773	1.22	0.84 – 1.76	0.165
Prior fracture									
Yes	1.02	0.86 – 1.20	0.803	1.00	0.79 – 1.25	0.958	1.22	0.79 – 1.89	0.233
Osteoporosis									
Yes	1.02	0.86 – 1.20	0.815	0.96	0.74 – 1.25	0.695	1.10	0.66 – 1.84	0.625
Polypharmacy									
Yes	0.81	0.59 – 1.10	0.073	0.78	0.53 – 1.17	0.115	0.95	0.52 – 1.74	0.823
Smoking									
Yes	1.65	1.39 – 1.97	<0.001	1.77	1.32 – 2.37	<0.001	1.98	1.10 – 3.58	0.003
Alcohol intake									
Yes	1.09	0.89 – 1.34	0.255	1.17	0.88 – 1.55	0.168	1.21	0.68 – 2.16	0.391
Hospitalization									
Yes	1.23	0.99 – 1.50	0.010	1.42	1.09 – 1.84	0.001	1.28	0.68 – 2.43	0.313
EQ5D5L	0.61	0.40 – 0.93	0.003	0.50	0.31 – 0.81	<0.001	0.58	0.21 – 1.62	0.172
Frailty status									
Prefrail	1.33	1.10 – 1.61	<0.001	1.31	1.00 – 1.72	0.010	1.54	0.80 – 2.96	0.089
Frail	1.74	1.36 – 2.22	<0.001	1.60	1.16 – 2.21	<0.001	3.29	1.51 – 7.17	<0.001

HR, hazard ratio; CI, confidence interval; EQ5D5L, measure for health-related quality of life; *expressed as change per 5-unit increase

S7: Multivariable regression analyses: preventable and non-preventable attrition to account for missing data

	Preventable attrition			Non-preventable attrition		
Characteristics	HR	(99% CI)	p-value	HR	(99% CI)	p-value
Age*	1.19	1.11 – 1.28	<0.001	1.67	1.45 – 1.89	<0.001
Education						
≥ High school	0.74	0.55 – 1.00	0.009	0.76	0.48 – 1.20	0.118
Race						
White	0.84	0.56 – 1.26	0.266	1.78	0.77 – 4.09	0.075
Body mass index*	0.98	0.89 – 1.08	0.564	0.95	0.80 – 1.14	0.481
Falls						
Yes	0.98	0.79 – 1.20	0.773	1.21	0.90 – 1.65	0.100
Prior fracture						
Yes	1.00	0.79 – 1.25	0.958	1.20	0.81 – 1.79	0.241
Osteoporosis						
Yes	0.96	0.74 – 1.25	0.695	1.05	0.67 – 1.65	0.772
Polypharmacy						
Yes	0.78	0.53 – 1.17	0.114	0.89	0.47 – 1.69	0.647
Smoking						
Yes	1.77	1.32 – 2.38	<0.001	1.79	1.00 – 3.20	0.010
Alcohol intake						
Yes	1.17	0.86 – 1.55	0.168	1.08	0.66 – 1.78	0.680
Hospitalization						
Yes	1.42	1.09 – 1.84	0.001	1.03	0.59 – 1.81	0.887
EQ5D5L	0.50	0.31 – 0.81	<0.001	0.59	0.23 – 1.51	0.146
Frailty status						
Prefrail	1.31	1.00 – 1.72	0.010	1.45	0.86 – 2.45	0.065
Frail	1.60	1.16 – 2.21	<0.001	2.82	1.49 – 5.34	<0.001

HR, hazard ratio; CI, confidence interval; EQ5D5L, measure for health-related quality of life; *expressed as change per 5-unit increase; preventable attrition (attrition due to refusals and loss of contact) non-preventable attrition (attrition due to death and cognitive impairment)

CHAPTER 3

The reporting and handling of missing data in longitudinal studies of older adults is suboptimal: a methodological survey of geriatric journals

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RESEARCH

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The reporting and handling of missing data in longitudinal studies of older adults is suboptimal: a methodological survey of geriatric journals

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Abstract

Background: Missing data are common in longitudinal studies, and more so, in studies of older adults, who are susceptible to health and functional decline that limit completion of assessments. We assessed the extent, current reporting, and handling of missing data in longitudinal studies of older adults.

Methods: Medline and Embase databases were searched from 2015 to 2019 for publications on longitudinal observational studies conducted among persons ≥55 years old. The search was restricted to 10 general geriatric journals published in English. Reporting and handling of missing data were assessed using questions developed from the recommended standards. Data were summarised descriptively as frequencies and proportions.

Results: A total of 165 studies were included in the review from 7032 identified records. In approximately half of the studies 97 (62.5%), there was either no comment on missing data or unclear descriptions. The percentage of missing data varied from 0.1 to 55%, with a 14% average among the studies that reported having missing data. Complete case analysis was the most common method for handling missing data with nearly 75% of the studies ($n = 52$) excluding individual observations due to missing data, at the initial phase of study inclusion or at the analysis stage. Of the 10 studies where multiple imputation was used, only 1 (10.0%) study followed the guideline for reporting the procedure fully using online supplementary documents.

Conclusion: The current reporting and handling of missing data in longitudinal observational studies of older adults are inadequate. Journal endorsement and implementation of guidelines may potentially improve the quality of missing data reporting. Further, authors should be encouraged to use online supplementary files to provide additional details on how missing data were addressed, to allow for more transparency and comprehensive appraisal of studies.

Keywords: Missing data, Longitudinal studies, Review, Methods, Older adults

Background

Longitudinal studies inherently suffer from missing data due to the multiple waves of data collection that increase the chance of non-response and participant attrition [1, 2]. In studies of older adults, there is high risk for missing data due to the susceptibility of this population to physical and cognitive decline, illness,

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and death [3], which may impact on completion of assessments. The likelihood of having incomplete observations increases with increasing age. For example, a review of attrition in longitudinal studies in the elderly found a 25% increased risk in drop out rates for every decade increase in age [4]. The presence of missing data in these studies could lead to biased and inefficient estimates that can threaten the validity of study inferences, especially if not properly addressed [5, 6].

The appropriateness of methods for handling missing data largely depends on the extent and mechanism of missingness [7]. The amount of missing data may be considered negligible if less than 5% [8]; however if participants with missing data differ from those with complete data, or where data for key variables are unavailable, the resulting estimates could be biased [7]. Proper handling of missing data requires exploration of the mechanisms of missingness, whereby data can be assumed to be Missing Completely at Random "MCAR", (where missingness is unrelated to the observed or unobserved data), Missing at Random "MAR" (where missingness can be explained by observed data only) or Missing not at Random "MNAR" (where missingness is dependent on unobserved data) [5, 7]. The assumptions of the mechanism of missingness made for any data entail different approaches for dealing with the missing data. However, there are no techniques that can correctly determine mechanism of missingness [5], and in practice there could be a mix of different mechanisms at play in the data [9]. As such, sensitivity analysis is recommended to test the stability of the results to different assumptions, particularly where there is a strong indication that the missing data is non-ignorable, that is, MNAR [5, 10].

For adequate handling of missing data, existing guidelines [6, 11] recommend comprehensive descriptions of the amount of missing data, reasons for missingness, methods used to deal with missing data and assumptions that were made about the missingness mechanism. Clear and detailed reporting of missing data improves transparency and allows readers to assess the validity and applicability of the study results. However, reviews of clinical and epidemiological studies have shown persistent practice of poor reporting and inappropriate handling of missing data [2, 12–17]. These reviews mostly focused on randomized controlled trials and different clinical areas. Only one review [18] has specifically investigated this issue in aging studies; however, it was limited to publications from six cohort studies. In this paper, we reviewed the extent, current reporting, and handling of missing data in longitudinal observational studies of older adults.

Methods

Data sources and search strategy

Medline and Embase databases were searched for studies published from January 01, 2015, to December 31, 2019, to assess the current practice on reporting and handling of missing data. The search strategy was developed with the help of an experienced librarian and included the following key search terms: Longitudinal studies AND Older adults. Initially, no limits were set to identify studies; however, due to the impracticability of reviewing tonnes of records identified, the search was restricted to 10 high-ranking general geriatric journals with the highest impact factor that publish clinical studies [19]. They include Age and Aging, Aging and Disease, Geroscience, Journal of Gerontology: Medical Sciences, Journal of American Geriatric Society, Journal of American Medical Directors Association, BMC Geriatrics, Aging Clinical and Experimental Research, Journal of Aging and Health, and Clinical Interventions in Aging. We also restricted the search to only articles published in English, as it is the only language shared by the reviewers. The search strategy can be found in the supplementary files (Additional file 1).

Study selection

Abstracts of the identified citations were screened for eligibility based on the following criteria (i) observational, defined as studies that did not include any intervention, (ii) longitudinal, if they had at least one wave of data collection after baseline assessment, and (iii) among older adult population, defined as persons aged 55 years or older. We excluded meta-analyses, randomized controlled trials, study protocols and simulation studies. Conference abstracts were also removed as they were considered too short to have sufficient information on missing data handling. Full texts were randomly selected for review from the pool of eligible studies until the target sample size of at least 139 articles was reached. The sample size was calculated using the formula for a single proportion at 5% precision and 95% confidence level [20], assuming that 90% of studies report missing data based on the average amount from previous reviews [2, 17, 21]. We randomly selected 150 studies per time for review, replacing excluded articles by another round of random selection. This was done twice yielding 165 studies that met the eligibility criteria. Random sampling of studies was performed using an online random number generator (available at: www.random.org).

All abstracts were screened for eligibility by one reviewer while two independent reviewers conducted the full text review and data abstraction. A pilot full text review and data abstraction were performed on 10% of the articles to assess the consistency of reporting

between the reviewers. Modifications were made to the aspects that were unclear in the inclusion criteria and data abstraction form. Discrepancies in data collected were resolved by discussion and consensus.

Data extraction and analysis

We extracted information on study identity (title, author, year of publication and journal name), study setting, study design (prospective or retrospective), duration of follow up, number of data collection waves, method of data collection, sample size, primary statistical analysis method and missing data information. The missing data component was based on the recommended guidelines by STROBE and Sterne et al. (see Table 1 for details). These included: amount of missing data, reasons for missing data, mechanism of missingness, method used to handle missing data and sensitivity analysis if performed. Where multiple imputation was used, we extracted information on whether the following were reported: variables used, number of imputations, evaluation of imputation procedure and handling of non-normal or categorical variables. The highest value of missing covariate or outcome data reported among all variables with incomplete observations were selected instead of adding them together to avoid double counting. Where the amount of missing primary outcome data was not explicitly stated, we determined that by calculating the difference between the number of enrolled participants and number included in the analysis. Online supplementary files were accessed for additional information on dealing with missing data, where it was referenced in the main article.

Data were summarised descriptively as frequencies and proportions per the reporting and handling of missing data. The review data were managed with Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, www.covidence.org), and analyses were performed using Stata 13 (Stata Corps, College Station, Texas, USA).

Results

Characteristics of included studies

Figure 1 shows the flowchart of study inclusion process. The search yielded 7032 articles and after 2818 duplicates were removed, 4214 remaining abstracts were screened for eligibility. Of these, 3010 did not meet the inclusion criteria and were excluded, leaving 1204 full-text articles. A random sample of 300 full-text studies were selected for assessment, of which 135 were further excluded. A total of 165 studies were eventually included in the review. The characteristics of the included studies are summarised in Table 2. Overall, majority of the studies were retrospective cohort 119 (72.6%) and conducted at multiple sites 130 (85.0%). Data were collected mostly via surveys 102 (63.9%), over a median of 3 waves and for a median of 44 months of follow-up. The median (IQR) sample size of included studies was 1234 (350–890,544).

Reporting of missing data

Details of the reporting of missing data are presented in Table 3. In 79 (47.9%) of the studies, there was either no mention of missing data or unclear statements about it. Among 82 (49.7%) with missing data, the proportion ranged from 0.1 to 55%, with a 14.5% average. About a quarter% ($n = 21$) of these studies stated the reasons for missing data, which were mainly due to lost to follow-up 12 (57.1%). Of the studies that reported having missing data, the majority, 64 (78.0%), described the method used to handle missing data. Only 8 (11.3%) studies specified the type of mechanism of missingness assumed in the analysis. Sensitivity analysis on the methods used for handling missing data was reported in 7 (8.5%) of the studies and the results of this analysis were presented in

Table 1 General reporting guidelines for missing data

STROBE Guideline
i State the amount of missing data for per variable and analysis step
ii Provide reasons for missing data
iii Indicate the number of individuals excluded due to missing data
iv Describe method used to handle missing data
v State the assumptions made for missing data analysis
vi Perform sensitivity analysis to examine robustness of findings
Sterne et al (for multiple imputation)
i Compare differences between individuals with and without missing data
ii Indicate number of imputed datasets
iii State the variables included in the imputation model
iv Describe how non-normally distributed and categorical variables were handled
v Evaluate multiple imputation analysis

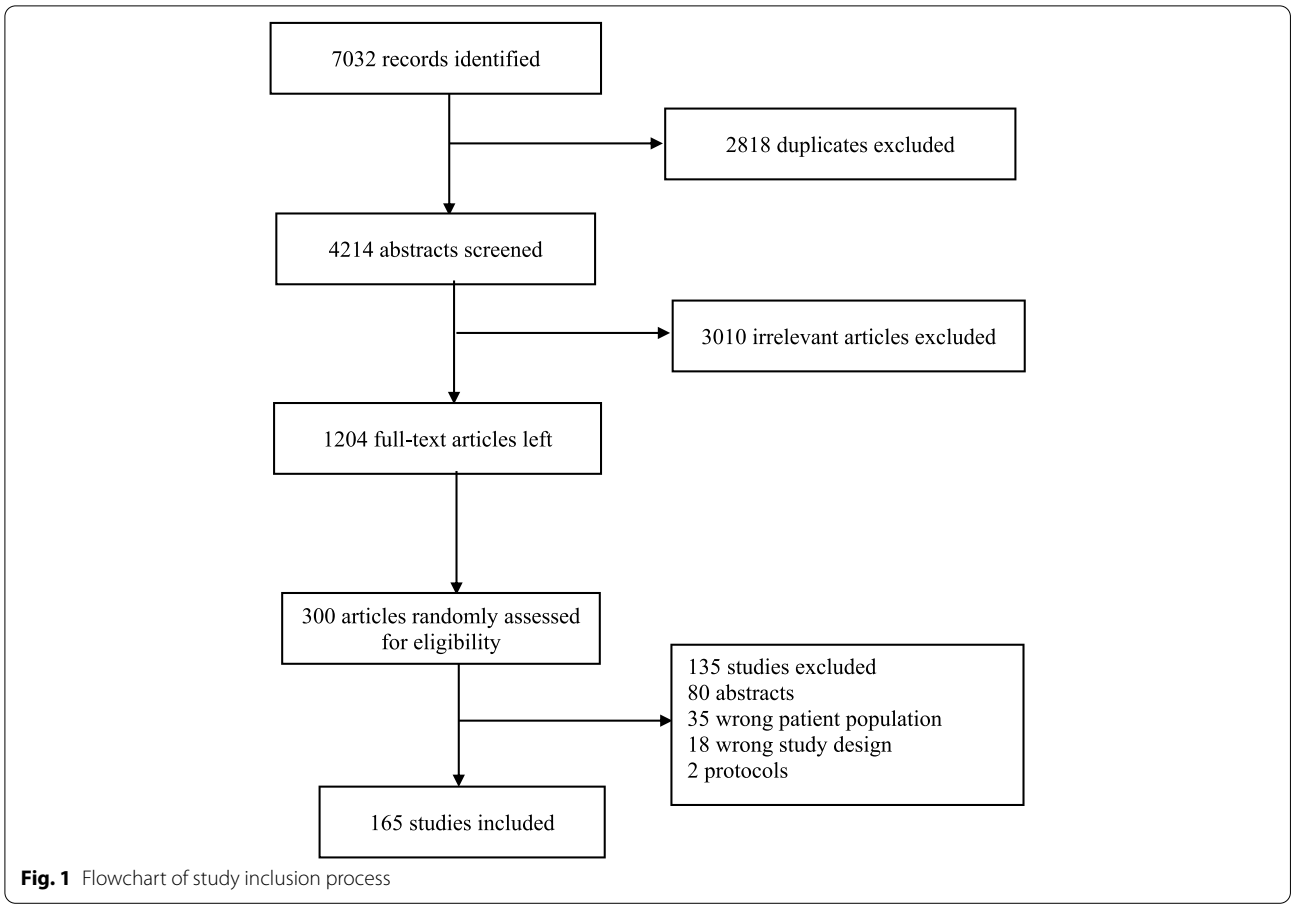

Fig. 1 Flowchart of study inclusion process

Table 2 Characteristics of included studies

Description	Total ($n = 165$)
Study design, n (%)*	
Prospective	45 (27.4)
Retrospective	119 (72.6)
Sample size, Median (IQR)	1234 (350–890,544)
Sample size, n (%)*	
< 1000	69 (43.4)
1000–10,000	65 (40.9)
> 10,000	25 (15.7)
Study site, n (%)*	
Multisite	130 (85.0)
Single site	23 (15.0)
Number of data collection waves, Median (IQR)	3 (3–5)
Duration of follow-up (months), Median (IQR)	44 (12–108)
Method of data collection, n (%)*	
Administrative data	28 (17.4)
Surveys[a]	102 (63.4.9)
Mixed	31 (19.2)

n, number; %, percent; * frequencies do not add up to 165 because some studies did not report these characteristics

[a] includes clinical report form or any study questionnaire

4 (57.1) of them. Online supplementary files were used to report additional details on missing data in approximately 3.7% ($n = 6$) of all included studies.

Handling of missing data

Table 4 shows the methods used to deal with missing data in the studies reviewed. Among studies that reported methods for dealing with missing data ($n = 70$), complete case analysis was the most common method with approximately 75% of the studies ($n = 52$) excluding individual observations due to missing data, at the initial phase as part of the inclusion criteria or at the analysis stage. Seventeen studies (26.2%) where participants were excluded based on data completeness compared those with and without missing data. Other methods used for handling missing data in order of popularity include multiple imputation 10 (14.3%), full information maximum likelihood 3 (4.3%), inverse probability weighting 2(2.8%), single imputation 2 (2.8%) and pattern mixture model 1 (1.4%). For 12 (14.6%) of the studies that reported having missing data, there was no explicit description of the analytical approach used. In eight studies that indicated the mechanism of missingness, the assumptions were MAR

Table 3 Reporting of missing data

Description	n (%)
Reported the amount of missing data ($N = 165$)	
Yes	86 (52.1)
No	57 (34.6)
Unclear	22 (13.3)
Reported reasons for missing data ($N = 82$)[a]	
Yes	21 (25.6)
No	52 (63.4)
Unclear	9 (11.0)
Reported number of individuals excluded due to missing data ($N = 66$)[b]	
Yes	55 (83.3)
No	4 (6.1)
Unclear	7 (10.6)
Described method used to handle missing data ($N = 82$)[a]	
Yes	64 (78.0)
No	9 (11.0)
Unclear	9 (11.0)
Stated the assumptions for missing data methods ($N = 71$)[c]	
Yes	8 (11.3)
No	61 (85.9)
Unclear	2 (2.8)

n/N, Number; %, percent

[a] number of studies that reported having missing data

[b] number of studies that excluded individuals based on missing data

[c] number of studies that reported methods for handling missing data

in six and MNAR in two. Of the 10 studies where multiple imputation was used, only 1 (10.0%) study followed the Sterne guideline fully, clearly specifying the variable used in the imputation model, indicating the number of imputations, evaluating the model, and reporting how non-normal and categorical variables were handled in the imputation process. Sensitivity analysis was performed in 7 (10.0%) of the studies that reported a method for dealing with missing data. Survival analysis was the most frequently used primary analysis method in 51 (31.5%) of all included studies.

Discussion

This review shows that the reporting and handling of missing data in longitudinal studies of older adults are suboptimal. Insufficient and unclear reporting, exclusion of participants with missing data, failing to assess the robustness of the missing data results are still common practices. Generally, there is poor adherence to recommended guidelines for reporting and handling of missing data. This is consistent with other reviews of missing data across different research designs and clinical areas [12, 21–24]. Considering that all the articles included in this review were published at least more than 5 years following the release of these guidelines, it was expected that the reporting standards would have improved over time. Guideline endorsement by journals could enhance compliance with standards [25], but only four of the ten included journals mentions one of the guidelines in its instructions to authors.

In some of the studies included, there was no indication of whether data were missing or fully observed. Similar to previous reviews [13, 23], it was unclear how the analytical cohort were selected and how much missing data there was, particularly in retrospective cohort studies. In the absence of comments on missing data, the reader may likely assume that the data were complete, which may either be true or false. Leaving room for speculation falls short of transparent reporting and impairs critical appraisal and replicability of the study. With the 14% average proportion of missing data observed in the studies where it was reported, there is indication that longitudinal studies among older adults are susceptible to a high amount of missing data that are non-negligible.

Where there are missing data, the common practice for dealing with them was complete case analysis, in which individuals with incomplete observations are removed. Methodological reviews of missing data since 2004 have

Table 4 Handling of missing data

Description	n (%)
Methods used for dealing with missing data ($N=70$)[a]	
Complete case analysis	52 (74.3)
Multiple imputation	10 (14.3)
Full information maximum likelihood	3 (4.3)
Inverse probability weighting	2 (2.8)
Single imputation	2 (2.8)
Pattern mixture model	1 (1.4)
Compared differences between individuals with and without incomplete data ($N=65$)[b]	
Yes	17 (26.2)
No	48 (73.8)
Performed sensitivity analysis to test robustness of results ($N=70$)[a]	
Yes	7 (10.0)
No	60 (85.7)
Unclear	3 (4.3)
For multiple imputation *($N=10$)*[c]	
Indicated number of imputed datasets	
Yes	5 (50.0)
No	5 (50.0)
Unclear	0 (0.0)
Reported variables included in imputation model	
Yes	4 (40.0)
No	5 (50.0)
Unclear	1 (1.0)
Described handling of non-normal and categorical variables	
Yes	2 (20.0)
No	8 (80.0)
Unclear	0 (0.0)
Evaluated multiple imputation analysis	
Yes	1 (100)
No	8 (80.0)
Unclear	1 (10.0)

n/N, Number; %, percent

[a] number of studies that reported methods for dealing with missing data

[b] number of studies that excluded individuals based on missing data

[c] number of studies that used multiple imputation

consistently reported similar findings [14, 16–18, 21, 23, 26]. The persistent use of this method may reflect its ease and simplicity, as well as the fact that it is the default approach in most traditional statistical software [5, 23]. Since there are no in-built mechanisms to flag missing data in these applications, they may go unnoticed. Therefore, performing an exploratory analysis to understand the extent of missing data is an important part of the first step in data analysis to address missing data problem.

When complete case analysis is used, the underlying assumption is that missing data are MCAR, implying that the missingness is unrelated to the observed or unobserved data [5, 7]. Simply put, the fully observed sample is still representative of the study population [5]. This assumption is plausible when the amount of missing data is minimal [13]. In the presence of large proportion of missing data, the resulting estimates will not only be inefficient but could be biased [7, 15]. In some of the studies, exclusion of participants with missing data occurred at the initial phase of inclusion in the study. That is, the fully observed dataset reported in these studies were due to some eligibility criteria that defined the sample based on data completeness; potentially to avoid missing data problem. The majority were retrospective cohort studies where a subset of the original population was used. Excluding participants due to missing data at any phase will have same potential for bias if the groups with or without complete data differ systematically [15].

In the context of longitudinal studies of older adults, the use of complete case analysis to deal with missing data may yield biased estimates. With extended duration of observation and multiple waves of data collection, it is unlikely that missing data will be MCAR. Elderly participants are at increased risk of events such as poor or compromised health, hospitalization, institutionalization, and death, that limit their ability to return for a follow up assessment, or complete surveys over time [3, 27]. Consequently, selective attrition may occur, where healthier older adults are more likely to remain at the end of the study [4]. For example, frail older adults are vulnerable to adverse events [28]; as a result, they are less likely to be available to complete study assessments, including frailty measures. In this case, having missing data for frailty or other measurements may be a function of how frail a participant is. Therefore, MAR or MNAR are plausible assumptions to make.

While it may not be feasible to categorically prove the mechanisms of missingness at play in a dataset [5], there are few assessments that could guide our assumptions. A comparison of the baseline characteristics of those with and without complete data could indicate whether missingness is dependent on the observed variables, if the two groups differ significantly [13]. Other methods include Little's MCAR test [29] or logistic regression to determine the variables that are associated with missing data indicators [30]. However, with MNAR, it will be impracticable to perform any evaluations for unobserved data. Assumptions typically rely on a priori biological, clinical, or epidemiological knowledge and insights on reasons for missing data [15]. Assessments of assumptions were infrequent in this review as in other reviews of observational studies [13, 23]. Regardless of the mechanism of missingness assumed or methods used, it is important to examine the robustness of the results to different alternative assumptions and methods [5, 11]. We found that

such sensitivity analysis was performed in only a limited number of studies.

In some of the reviewed studies, the principal analysis involved methods such as survival analysis that handle incomplete outcome data differently. In majority of these studies, there was no mention of missing data and how they were addressed. When participants have unobserved outcome data in survival analysis, they are typically addressed by censoring, where available data are used until the last time of observation [31]. This method may bias the results when the censoring is informative, that is, censored participants have higher or lower risk of experiencing the outcome [3]. Additionally, it could be problematic when dealing with missing covariate values in the presence of time-dependent variables and time-varying effects or when assessing proportional hazards assumptions [23]. Carrol et al. [23] provide detailed descriptions for dealing with missing covariate data when using survival analysis in observational studies.

Multiple imputation was used in very few studies to deal with missing data despite its popularity and its availability in mainstream statistical packages [5, 18]. This method is based on the MAR assumption which is considered valid in many longitudinal data contexts [32]. It involves reproducing multiple complete versions of the original dataset by replacing the missing observations with plausible values, then combining them into a single result [7, 33]. Multiple imputation reflects the uncertainty around missing data prediction compared to single imputation that does not account for the variability around the imputed estimates [6]. Unlike complete case analysis, this method allows for the use of all available data, thus minimizing the loss of precision and power [6, 13].

Where multiple imputation is used, existing guidelines recommend describing elements of the procedure to facilitate review [6], but these details were scantly presented in the studies reviewed. The only study [34] in which the method was described in full used an online supplementary file for that purpose. This allowed for a comprehensive appraisal of the missing data handling in that study. Online supplementary files provide great space for reporting additional study details that could not be presented in the main article due to word or page limits. However, its use for presenting missing data information is uncommon, with only 3% of the studies referring to it in the primary text.

In situations where data are MNAR, that is, the probability of missingness is dependent on the unobserved data [7]; modelling the missing data becomes more challenging and requires more sophisticated techniques. For example, one study that examined the association between cognitive decline and life-space mobility in community-dwelling older adults used pattern-mixture model to account for the probable non-ignorable missingness [35]. In the study, participants who dropped out had lower scores on the predictors, intermediate and predicted variables compared to those who remained, which is suggestive of non-random missingness. Pattern-mixture model allowed for modelling participants' missingness and response within each missing data pattern [36]. Selection model could also be used to handle non-random missing data by modelling the probability of participants' responses and missing values based on a common selection factor [32].

Limitations

Our survey is limited by several restrictions applied in the search. It is possible that some studies may have been missed due to the limitations of the search to few general geriatric journals. In addition, we randomly selected studies for data abstraction as it was impractical to include all eligible articles. Notwithstanding, we expect that the practices described in this review provide a snapshot of the actual practice in the entire field. Further, we did not exclude studies from the same cohort of participants, so there may be duplication or overlap of data or reporting, particularly for retrospective cohort studies. Since this review was restricted to observational studies of older adults, the current practice in handling and reporting of missing data for other research designs, such as randomized controlled trials may differ.

Conclusion

Inadequate reporting and lack of rigour in handling of missing data are prevalent in longitudinal observational studies of older adults. The susceptibility of this population to missing data makes it imperative for the issue to be addressed adequately where present. However, authors either do not mention it or at best exclude participants with missing data. These have implications on study validity and transparent reporting. Progress in the implementation and compliance with reporting standards could be enhanced with endorsement of the recommended guidelines by journals. In addition, authors can take advantage of the underutilised online supplementary files to provide details of missing data analysis. It is worth noting that better reporting on missing data handling is associated with higher citation counts [14], which could potentially improve the utilization and contribution of these studies. Please see supplementary file 3 for guide on reporting of missing data and examples of standard reporting.

Abbreviations

MCAR: Missing completely at random; MAR: Missing at random; MNAR: Missing not at random; IQR: Interquartile range.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12874-022-01605-w.

Additional file 1.

Additional file 2.

Additional file 3.

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Authors' contributions
Study design: CO and LT. Literature search and data extraction: CO and CE. Data analysis and interpretation: CO. Writing the first draft of the manuscript: CO. Revisions of the manuscript for important intellectual content and final approval: CO, CE, GI, AP, JDA and LT.

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Declarations

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Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

Supplementary file 1: Search strategy

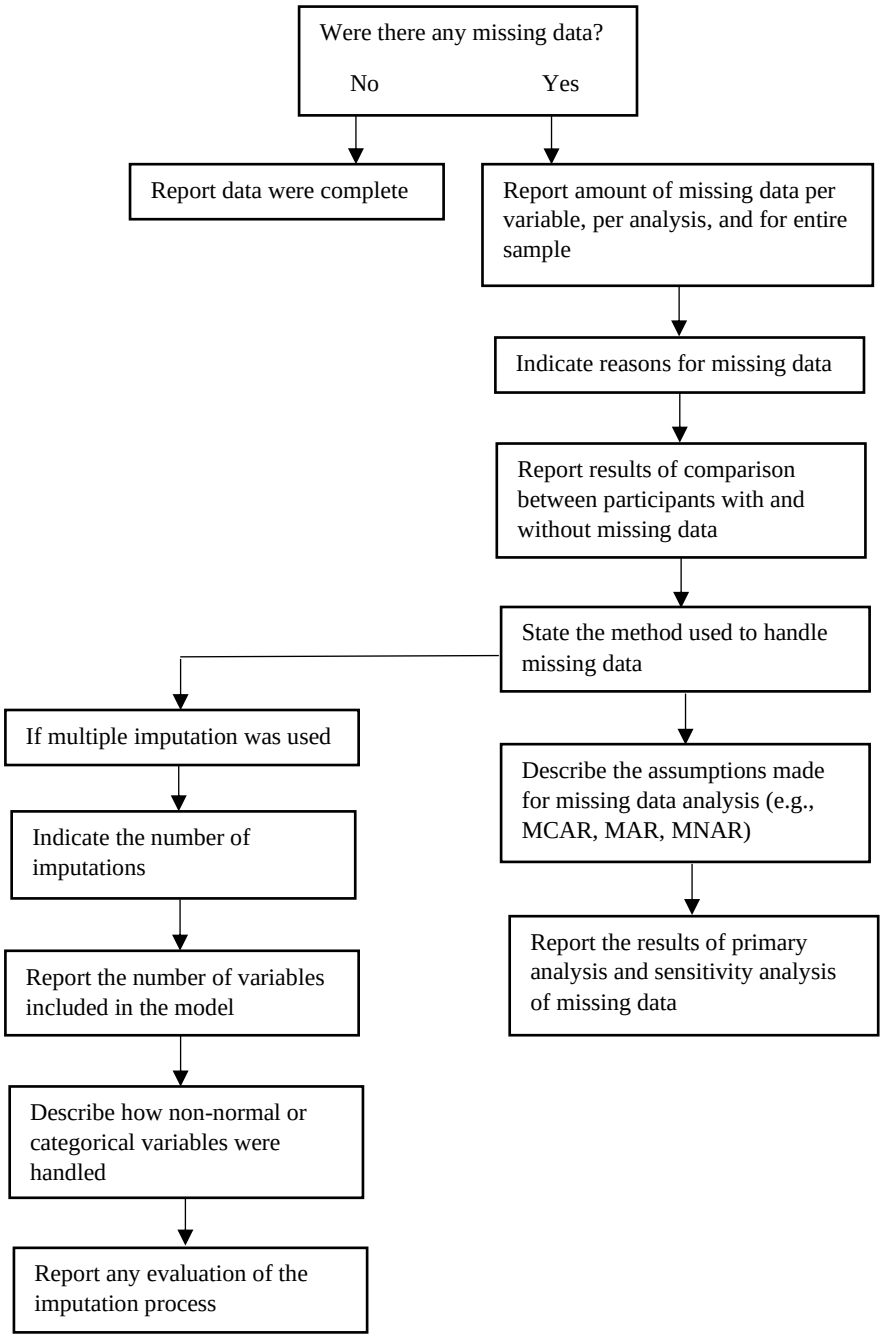
Medline Search

1	Aged/	3,337,283
2	"Aged, 80 and over"/	1,003,928
3	Aging/	243,738
4	ag?ing.ti,ab.	248,528
5	advanced years.ti,ab.	73
6	(old* adj3 (age or m?n or male** or wom?n or female* or people or adult* or population or person*)).ti,ab.	827,155
7	pensioner.ti,ab.	184
8	late?life.ti,ab.	9
9	elder*.ti,ab.	282,267
10	retire*.ti,ab.	23,794
11	senior*.ti,ab.	46,613
12	exp Geriatrics/	31,031
13	geriatric*.ti,ab.	53,523
14	post?menopausal women.ti,ab.	38,432
15	1 or 2 or 3 or 5 or 6 or 7 or 8 or 11 or 12 or 13 or 14	4,140,323
16	(exp infant/ or exp child/ or adolescent/) not exp adult/	2,032,508
17	15 not 16	4,091,570
18	exp longitudinal studies/	156,484
19	exp prospective studies/	620,071
20	exp retrospective studies/	1,007,856
21	longitudinal stud*.ti,ab.	87,125
22	retrospective stud*.ti,ab.	191,947
23	prospective stud*.ti,ab.	192,672
24	follow?up.ti,ab.	21,096
25	exp cohort studies/	2,317,275
26	cohort stud*.ti,ab.	266,653
27	Observational Study/	123,735
28	observational stud*.ti,ab.	136,895
29	cohort analysis.ti,ab.	9,116
30	Epidemiologic Studies/	9,043
31	epidemiological stud*.ti,ab.	63,255
32	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2,691,996
33	17 and 32	1,087,861
34	limit 33 to yr="2015 - 2019"	305,061
35	limit 34 to english language	297,698
36	(Age & Ageing or BMC Geriatrics or Aging & Disease or Journal of the American Geriatrics Society or Journals of Gerontology Series A-Biological Sciences & Medical Sciences or Geroscience or Journal of the American Medical Directors Association or Journal of Aging & Health or Clinical Interventions in Aging or Aging-Clinical & Experimental Research).jn.	48,297
37	35 and 36	3,580

Embase Database

1	aged/	3,323,061
2	elder*.ti,ab.	398,796
3	elderly care/	41,582
4	ag?ing.ti,ab.	313,317
5	aging/	287,177
6	geriatrics/	32,097
7	geriatric*.ti,ab.	84,336
8	advanced years.ti,ab.	100
9	(old* adj3 (age or m?n or male** or wom?n or female* or people or adult* or population or person*)).ti,ab.	1,188,542
10	senior*.ti,ab.	65,372
11	pensioner*.ti,ab.	1,331
12	late?life.ti,ab.	110
13	post?menopausal women.ti,ab.	54,159
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	4,548,987
15	(exp infant/ or exp child/ or adolescent/) not exp adult/	2,323,648
16	14 not 15	4,470,674
17	longitudinal study/	169,682
18	prospective study/	754,272
19	retrospective study/	1,219,298
20	longitudinal stud*.ti,ab.	112,286
21	retrospective stud*.ti,ab.	304,280
22	prospective stud*.ti,ab.	291,565
23	follow up/	1,815,591
24	follow?up stud*.ti,ab.	1,537
25	cohort analysis/	821,031
26	cohort stud*.ti,ab.	385,666
27	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	3,917,899
28	16 and 27	1,203,084
29	limit 28 to yr="2015 - 2019"	418,813
30	limit 29 to english language	412,038
31	(Age & Ageing or BMC Geriatrics or Aging & Disease or Journal of the American Geriatrics Society or Journals of Gerontology Series A-Biological Sciences & Medical Sciences or Geroscience or Journal of the American Medical Directors Association or Journal of Aging & Health or Clinical Interventions in Aging or Aging-Clinical & Experimental Research).jn.	39,526
32	30 and 31	3,452

Supplementary file 3: Missing Data Reporting



Flow Chart for Reporting of Missing Data[1,2]

[1]Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. PLoS Med. 2007;4(10):1628–54.

[2]Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. BMJ. 2009;339(7713):157–60.

Example 1: Study with no missing data (1)

"The complete data represent 188 full observations of 60 variables (no missing data)".

Example 2: Study with missing data (2)

Main article

Missing data per variable were reported in the table describing the sample characteristics.

"Multiple imputation using a full conditional specification model (chained equation) in the analysis was used to account for missing data, which was mainly due to the interview being conducted through a proxy or the 1905 cohort member being physically or mentally unable to perform the tests.22 Online Appendix S1 describes the multiple imputation in detail".

Supplementary file

"Multiple imputation was performed using a full conditional specification model (chained equation) with ten iterations of the burn-in period. It was examined whether the ten iterations were adequate for the chain to converge to a stationary distribution. To minimize the Monte Carlo error, 50 imputation sets were generated. In this procedure a series of regression models are run whereby each variable with missing data is modeled conditional upon the other variables in the data. This means that each variable can be modeled according to its own distribution. In the imputation model of each variable all the other measures were used to impute the missing value including the remaining life span which was log transformed. The imputation model was performed separately for each gender, i.e. not assuming similar association between the measures and mortality for both genders. Multiple imputation has the advantage that it only requires the data to be missing at random (MAR) to give an unbiased result whereas using complete case analysis assumes missing completely at random or at least that the missing data are caused only by the measure (exposure) itself.15, 16 However, since mortality (outcome) adjusting for the measure still predicts the missing data, complete case analysis would give a biased result. Besides the measures and mortality, additional (auxiliary) variables from the health survey were also used in the imputation model to address the assumption that the data are missing at random which is the assumption of multiple imputation. Auxiliary variables are variables that are predictive of the missingness of the variable in question. Since the missing data was due mainly to the interview being through a proxy, variables which were both found in the non-proxy and proxy interviews were most important to find to address the MAR. The auxiliary variables were mainly found by automated stepwise procedure. All 6 variables were given the same attention in the imputation model, however since the variables about socioeconomic factors, disease, medication, and activity of daily living had very few missing data the imputation will have little impact on the analysis of these variables. Hence, we will in the following turn our attention to the imputation of the variables about physical performance, cognition and general and mental health perception. Missing values of the chair stand were imputed using an ordered logistic regression and some of the auxiliary variables which were used were information about if they could wash their lower part of their body, if they have had a fracture of their femur or if they used a wheel chair or walker. Missing values of grip strength were imputed using a linear regression with a bound between 1 and 60 to be sure to create valid imputations. Some of the auxiliary variables used in the imputation of the grip strength were information about if they lived in a nursing home or if they had visit from a home care service. Missing information of being able to walk was imputed by a logistic regression and auxiliary variables such as information if they used a wheelchair, a walker or a cane. Missing values of the walking speed were imputed by a linear regression

with a bound between 2 and 30 seconds. It was only imputed if being able to walk was imputed as yes and information about if they had fallen within the last 6 month or if they used a walker was some of the variables used as auxiliary variables. Before the imputation, walking speed was transformed to be more normally distributed and after the imputation model it was transformed back by the inverse function. Missing values of the MMSE were imputed using a linear regression with a bound between 0 and 30 and MMSE scores were transformed to be more normally distributed. Auxiliary variables such as information about if they had a hobby, if they had visit from a home care service, or if they were senile was used in the imputation. Information about senility of the 1905 cohort member was either 7 informed from the proxy or from the interviewer who recorded if the interview was to some degree difficult to perform because the respondent seemed to be senile. Missing values for the five tests which comprises the cognitive composite score was imputed separately and from this the cognitive composite score was formed. Appropriate regression model was used for the five tests and auxiliary variables used for these tests were almost the same as those used in the imputation model for MMSE."

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CHAPTER 4

The Geras virtual frailty rehabilitation program to build resilience in older adults with frailty during COVID-19: a randomized feasibility trial

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Pilot and Feasibility Studies

RESEARCH

Open Access

The Geras virtual frailty rehabilitation program to build resilience in older adults with frailty during COVID-19: a randomized feasibility trial

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Abstract

Background The Coronavirus (COVID-19) pandemic has exacerbated the risk for poor physical and mental health outcomes among vulnerable older adults. Multicomponent interventions could potentially prevent or reduce the risk of becoming frail; however, there is limited evidence about utilizing alternative modes of delivery where access to in-person care may be challenging. This randomized feasibility trial aimed to understand how a multicomponent rehabilitation program can be delivered remotely to vulnerable older adults with frailty during the pandemic.

Methods Participants were randomized to either a multimodal or socialization arm. Over a 12-week intervention period, the multimodal group received virtual care at home, which included twice-weekly exercise in small group physiotherapy-led live-streamed sessions, nutrition counselling and protein supplementation, medication consultation via a videoconference app, and once-weekly phone calls from student volunteers, while the socialization group received only once-weekly phone calls from the volunteers. The RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework was used to evaluate the feasibility of the program. The main clinical outcomes were change in the 5-times sit-to-stand test (5 × STS) and Depression, Anxiety and Stress Scale (DASS-21) scores. The feasibility outcomes were analyzed using descriptive statistics and expressed as frequencies and mean percent with corresponding confidence intervals (CI). Analysis of covariance (ANCOVA) was used for the effectiveness component.

Results The program enrolled 33% ($n = 72$) of referrals to the study ($n = 220$), of whom 70 were randomized. Adoption rates from different referral sources were community self-referrals (60%), community organizations (33%), and healthcare providers (25%). At the provider level, implementation rates varied from 75 to 100% for different aspects of program delivery. Participant's adherence levels included virtual exercise sessions 81% (95% *CI*: 75–88%), home-based exercise 50% (95% *CI*: 38–62%), protein supplements consumption 68% (95% *CI*: 55–80%), and medication optimization 38% (95% *CI*: 21–59%). Most participants (85%) were satisfied with the program. There were no significant changes in clinical outcomes between the two arms.

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Conclusion The GERAS virtual frailty rehabilitation study for community-dwelling older adults living with frailty was feasible in terms of reach of participants, adoption across referral settings, adherence to implementation, and participant's intention to maintain the program. This program could be feasibly delivered to improve access to socially isolated older adults where barriers to in-person participation exist. However, trials with larger samples and longer follow-up are required to demonstrate effectiveness and sustained behavior change.

Trial registration ClinicalTrials.gov NCT04500366. Registered August 5, 2020, https://clinicaltrials.gov/ct2/show/NCT04500366

Keywords Older adults, Frailty, Feasibility studies, COVID-19, Virtual rehabilitation

Key messages regarding feasibility

- There is limited evidence on how multicomponent interventions to address frailty can be delivered remotely to older adults where there are health-related, geographical, or logistical barriers to access.
- We found that the Geras virtual multicomponent frailty rehabilitation program was feasible with respect to the reach of participants, adoption across referral settings, adherence to implementation protocol, and intention to maintain from participant's perspective.
- A large-scale trial with longer follow-up is required to provide evidence of effectiveness and sustained behavioral change. Future trials should consider the potential for differences in feasibility of implementation in non-COVID-19 context, recruiting from multiple sources using different strategies for a wider reach of participants, providing devices for participation and optimal training of participants on how to navigate technology, and designing effective strategies to improve adherence to unsupervised home exercises, participant's implementation of medication review recommendation, and retention of volunteers.

Introduction

Frailty can be one of the challenging consequences of aging and is characterized by a decline in reserve and function across multiple body systems [1, 2]. In Canada, approximately 1.5 million older adults are frail, and this estimate is predicted to increase to more than 2 million within the next 10 years as the population ages [3]. Older adults living with frailty account for a large proportion of users of rehabilitation programs and home care services [4, 5]. Their decreased capacity to resist the negative impact of stressors increases the risk of experiencing adverse health outcomes, with costs to health and social care [6].

The COVID-19 pandemic presents a major stressor to vulnerable older adults. This population had the highest infection risk, illness severity, and case fatality [7]; consequently, they received the strictest public health preventive measures. Emerging evidence on the impact of the pandemic on older adults suggests decreased physical activity [8–11], increased sedentary behavior [12, 13], poor mental health [9, 10, 13, 14], and increased incidence of frailty [15, 16]. There are also indications of a negative impact on the nutritional behavior of this population with increased risk of undernutrition or overnutrition [17]. These factors could potentially exacerbate the risk of adverse consequences on their overall health and well-being. Therefore, interventions are critically needed to build resilience, preserve functional abilities, prevent frailty, and reverse or slow decline in older adults isolated at home.

International guidelines recommend the use of multidimensional rehabilitation approach including exercise, protein-calories supplementation, reduction of polypharmacy, and vitamin D3 supplementation to address frailty [18, 19]. Rehabilitation interventions are essential for building resilience, preserving functional capacity, and supporting recovery [20, 21]. Most trials on multicomponent frailty interventions were implemented before the COVID-19 pandemic [22, 23]. These trials were either conducted in-person or were hybrid (including in-person and virtual delivery or assessement) [24]. Face-to-face programs were not feasible with the early pandemic restrictions, thus necessitating innovative models of care that could be delivered remotely and safely.

Virtual rehabilitation offers a potentially viable alternative [24]; however, the evidence is sparse [25, 26]. Only 7% of the included studies in a recent scoping review of digital interventions investigated rehabilitation interventions [25]. While a recent meta-analysis found small positive effects on physical function and quality of life, the authors noted that there were insufficient details on implementation factors that could influence intervention outcomes [26]. Now that virtual care use is increasing [27–29], studies on virtual rehabilitation are needed to understand how best to deliver this service to older adults living with frailty. This evidence will contribute to improving equitable access to care, where there are

barriers to participation in in-person programs. Our study reports the feasibility of a virtual multicomponent frailty rehabilitation program which was designed to build resilience among seniors living with frailty during the COVID-19 pandemic compared with a socialization-only intervention.

Methods

Study design, participants, and setting

This study was reported in accordance with the CONSORT extension for pilot and feasibility studies [30]. The Geras virtual multicomponent frailty rehabilitation study was a parallel group randomized controlled feasibility trial among community-dwelling older adults aged 65 years and above. The study was conducted between August 2020 and November 2021 during the peak of the pandemic in Canada and ended after the last cohort of participant completed the intervention. Participants were recruited from three referral sources: (1) healthcare providers, (2) community organizations, and (3) self-referrals from the community through advertising. Clinicians at the referral sources identified potentially eligible participants opportunistically during consultation using a clinical pre-screening checklist. The patients were asked for their permission to share their names, contact information (phone and email), caregiver information (name and phone number), and the pre-screening information with the Geras research team and for a member of the study team to collect their pre-screening information and contact them. Patients who consented were formally assessed for eligibility by the research team. For community organizations, potential participants were recruited pre-pandemic for the original study at the centers run by the organizations. They were referred by the center coordinators and had given permission to be contacted by the study team. When the study was adapted to virtual delivery, they were recontacted for consent, and those who consented to participate were assessed for eligibility. Self-referrals were interested individuals in the community who contacted the research staff by themselves through emails or phone call with the contact information provided on advertised materials. To be eligible for the study, participants had to (a) have a clinical frailty scale score of 4 to 6 indicating mild to moderate level of frailty [1], (b) ambulate independently with or without walking aid, and (c) have no other physical limitations to exercise evident by average resting heart rate of 50–100 bpm and average resting blood pressure $\leq$ 160/90 mmHg or for self-referrals have a clearance to exercise from their family physician. They were excluded if they (a) could not speak or understand English or had no caregiver for translation, (b) had difficulty following two-step instructions (assessed by asking if they could do that in a group exercise), (c) were receiving palliative care, (d) had unstable angina or heart failure, (e) would be unavailable for more than 20% of the duration of the study due to travel plans, and (f) were currently involved in a group exercise program. Potential participants were mailed study information document after an initial telephone contact to confirm interest. This was followed by an eligibility screening and consent visit for interested participants over the phone or via Zoom for Healthcare. Given that the study was completely virtually, verbal informed consent was obtained from participants following an in-depth discussion of study details with each person, which was then documented on a consent process form prior to participation in the study. Research assistants enrolled participants in cohorts of 10 and then randomly allocated to either the multimodal or socialization study arm with a 1:1 ratio based on a computer-generated block randomization sequence generated. Only the researcher who was not involved in the study had access to the computer-generated allocation list. Outcome assessors, analysts, and investigators were blinded to the participant group assignments. It was not possible to blind other study intervention personnel and the participants due to the nature of the intervention. Ethical approval for this study was obtained from the Hamilton Integrated Research Ethics Board (HiREB).

Intervention development

The virtual frailty rehabilitation was originally designed as an in-person multicomponent community-based model of care to manage frailty which was adapted to a virtual delivery during the height of the COVID-19 pandemic. The modifications were based on existing evidence and discussions with stakeholders, including a team of researchers and healthcare providers to identify relevant and practicable solutions within the COVID-19 context. The exercises were informed by a systematic review on exercise interventions for frail older adults [31] and a meta-analysis on fall prevention in older adults [32]. The studies suggest that a combination of strength and endurance training performed at a moderate weekly frequency may improve muscle hypertrophy, strength, and power in frail older adults [31]. In addition, exercise performed for a minimum of 180 min/week with a high challenge to balance provides the greatest benefits for fall prevention [32]. The nutrition component aligned with recommendation for protein supplementation in older adults with frailty to enhance the gains of physical exercise [19]. Medication review was based on evidence that improving the appropriate use of polypharmacy in older adults can be obtained using the Beers' criteria and Screening Tool of Older Person's Prescription (STOPP)/Screening Tool to Alert to Right Treatment (START)

[33]. The socialization component was initially designed as a group-based social engagement for better mental and physical health [34] but was modified due to the prevailing social and physical distancing measures during the pandemic.

Intervention description

Multimodal arm

Participants randomized to the multimodal group received an intervention package comprising of exercise, medication support, nutrition, and socialization for 12 weeks. The intervention components are reported in accordance to the TIDieR guidelines [35].

Physical exercise

One-hour-long small group live exercise sessions delivered virtually via Zoom for Healthcare to participants at their homes were conducted twice weekly per cohort of participants assigned to the multimodal arm. The exercise classes were facilitated by physiotherapists with a participant-physiotherapist ratio of 5:1 per class. The physiotherapists were trained via videoconferencing by a physiotherapist co-investigator with expertise in exercise and rehabilitation for frail older adults and were provided with a manual developed by the expert. The exercises comprised of functional movements to build strength and balance and followed a sequence of 5-min warm-up exercises, 10-min aerobic activities, 20-min functional strength exercise, 20-min balance training, and 5-min warm down and stretching exercises. All multimodal participants were provided with an exercise safety sheet that included tips for exercise preparation, materials required, and safety considerations. They were also given safety cues for correct posture, body position, and equipment safety during the virtual sessions. Participants were allocated time at the beginning of the class to report any concerns or injuries. They were given additional tailored home-based exercises to be performed for at least 1 h in order to achieve the minimum 3 h/week of exercise required for fall prevention [32]. The home-based exercises were developed from what was taught during the virtual exercise sessions and were routinely reviewed for safety and level of challenge appropriateness by the study physiotherapists.

Nutrition support and protein supplementation

For the nutrition component, multimodal participants had an individualized virtual nutrition assessment and coaching session on how to improve their nutrition with a research assistant who was trained by a dietitian. The nutrition counselling was developed with the guidance of geriatric nutrition experts. In addition, the participants received oral protein supplements and protein intake adherence tracking logs via contactless delivery. Participants were either provided commercially available protein drink or powder depending on their preference, and those who were diabetic were given suitable alternatives. During the nutrition counselling and review session, participants who had concerns about the protein supplement were recommended to speak with their family physician about it. The nutrition supplement contained 360 cal and 14 g of protein per serving to be taken daily with a meal or within 3 h of exercise.

Medication review consultation

The medication support intervention included a one-on-one virtual visit with the trained study pharmacist. The visit involved the review of participants medical record and medication list, followed by providing recommendations to their family physician or pharmacist where necessary. Optimization of medications was conducted using STOPP/START [36] and Beers criteria [37]. Participants were asked to review the recommendations with their primary care provider. A follow-up check-in occurred at their 12-week appointment to determine whether the medication recommendations were implemented.

Participants in the multimodal arm received the same socialization intervention as those in the socialization arm described below. All study personnel — blinded assessors, nutrition counsellor, pharmacists, physiotherapist, and social call volunteers, were trained on study protocols by the research team before study implementation and were provided with relevant study materials.

Socialization arm

Social calls

The socialization component involved a once-weekly phone call from trained volunteers to participants in both socialization and multimodal arms to mitigate the impact of social isolation during the pandemic. The volunteers consisted of undergraduate, graduate, and medical school students. They were each assigned to a maximum of two participants. The conversations were unstructured; however, volunteers were provided with prompts that covered topics related to COVID-19, wellness, and life experiences including family, hobbies, and work. All volunteers received an hour-long synchronous and asynchronous training on communication with older adults by a study research assistant.

At the end of the study, participants in the socialization arm were offered the opportunity to participate in a 2-week long virtual exercise program post-intervention period.

Technology use

Persons who indicated interest in the study but did not have devices or internet connection were given iPads and internet service. Participants were oriented to the use of the devices during a brief phone conversation with study research staff and were provided with tip sheets on how to navigate the devices. Technical challenges regarding connectivity, audio, or visuals were addressed earlier in the study during baseline assessments or in the first week of the exercise classes.

Sample size estimation

Enrolment rateThe sample size is based on the implementation feasibility success threshold of 75% adherence to intervention components. Considering a 10% drop-out rate, we needed a sample size of 70 participants (35 participants in the multimodal intervention group and 35 participants in the socialization group) to produce a two-sided 95% confidence interval with a width equal to ± 11%. This sample size was large enough to provide useful information regarding feasibility that will inform a larger multicenter trial. The sample size calculation was conducted using PASS software (Kaysville, Utah).

Evaluation and analysis of program feasibility

The RE-AIM framework [33] was used to evaluate the feasibility of the program. The framework considers five elements (Reach, Effectiveness, Adoption, Implementation and Maintenance) that could influence the implementation success and impact of a program [38]. RE-AIM has been used in the evaluation of the feasibility and implementation of similar health programs [39–41]. Given the unique COVID-19 implementation context and novelty of the intervention, the framework allows for the use of multiple indicators to broadly assess and understand the factors that could impact future study outcomes. Table 1 outlines how we applied the RE-AIM framework in this study including component definitions, outcome measures, and criteria for success. Briefly, *Reach* was defined as recruitment of target population. It was assessed by enrollment rate (percentage of all referrals enrolled in the study) and by the examination of participant demographics. The feasibility threshold for this component was set at an enrolment rate of ≥ 10%, derived from previous studies on digital intervention in frail older adults [42, 43]. *Effectiveness* was assessed by comparison of physical function using the five times sit-to-stand test (5XSST) [44], psychological distress using the Depression, Anxiety and Stress Scale (DASS-21) [45] and adverse events between the multimodal and socialization arm. *Adoption* was measured by the percentage of participants enrolled from each referral source. Success for this domain was defined as having each referral sources contributing ≥ 10% of enrolled participants for representativeness of settings. *Implementation* was assessed by adherence to each component of the intervention either at participant or provider (i.e., study research team) level. For the exercise component, implementation was evaluated by the percentage of virtual exercise sessions attended out of total number of sessions and percentage of home exercises completed out of total number expected. For the nutrition element, the measures were based on percentage of participants whose protein shipment was successfully delivered at provider level and percentage of protein supplements consumed out of total supplements at participant level. We assessed medication review as percentage of participants who received medication consultation from the study pharmacists at provider level and percentage of participants who implemented medication recommendation at participant level. The socialization component was measured by the percentage of calls made per participant out of the total calls at provider level. Success was defined as achieving ≥ 75% adherence and ≥ 75% implementation for participants and providers, respectively. *Maintenance* was defined as intention to sustain the intervention. Since the study duration was short, we were unable to measure actual sustainability or long-term effects of the intervention; as such, proxy measures based on program satisfaction survey were used. This was assessed by the percentage of participants who would recommend the program (≥ 7/10 rating on the question how likely are you to recommend the program?) and percentage of participants who reported that the program met their expectations. Maintenance was considered a success if ≥ 75% participants were satisfied with or would recommend the program.

Data collection

Data collection was conducted virtually via Zoom for Healthcare or the telehealth through Clinicmaster, at baseline and 12 weeks of follow-up by blinded assessors with rehabilitation training. Outcome assessors were trained and observed by research staff to standardize the assessments and ensure it was done appropriately.

Clinical outcome measures

Physical function

Five times sit-to-stand was used to assess lower limb strength [44]. It is a feasible, reliable, and valid measure for mobility and falls [46] with moderate sensitivity to change over time [45].

Psychological distress

Depression, Anxiety and Stress Scale (DASS-21) is a short version of the DASS-42 used to assess negative

Table 1 RE-AIM assessment of program feasibility

			Results	
RE-AIM component	**Outcome measure**	**Criteria for success**	**Outcome**	**% (95% CI)**
Reach	**Recruitment**			
Recruitment of target population	Proportion of persons who were enrolled out of all referrals (participation rate)	10% of all referrals enrolled in the study	Enrolment rate	72 (33)*
	Assessment of participants' characteristics			
Effectiveness				
Positive and adverse effect of intervention	5XSST	-	Please see Table 3	
	DASS 21	-		
	Adverse events	-		
Adoption	**Referral sources and settings**			
Representativeness of settings	Proportion of participants enrolled from different sources	≥10% of participants from each source enrolled in the study	**Referral sources**	
			Health provider	42 (25)*
			Self-referral	28 (60)*
			Community organization	2 (33)*
Implementation	**Adherence to intervention**			
Successful delivery of intervention, fidelity, and modifications to interventions	**Social calls**	**Social calls**	**Social calls**	
	Percentage of weekly calls made per participant out of the total calls	75% of the participants received all weekly calls	Percentage calls volunteers made per participant	78 (71 – 84)
	Exercise	**Exercise**	**Exercise**	
	Percentage of virtual exercise sessions attended	Group: ≥75% of class attendance	Average virtual exercise sessions attended	81 (75 – 88)
	Percentage of home exercises completed	Home: ≥75% of home exercise completion	Average home-based exercises completed	50 (38 – 62)
	Nutrition	**Nutrition**	**Nutrition**	
	Percentage of participants who received protein supplements	≥75% of the participants received their protein supplements	Received protein supplements	97 (80 – 100)
	Percentage of protein supplements consumed	≥75% of the participants had daily protein supplements	Average daily protein supplements consumption	68 (55 – 80)
	Medication review	**Medication review**	**Medication review**	
	Percentage of participants who received medication review	≥75% received a medication review consultation	Received medication review	33 (100)*
	Percentage of participants who implemented recommendations	≥75% implemented the recommendations	Implemented recommendation	38 (21 – 59)
	Outcome assessment			
	Average time to complete assessment of outcomes			
	Project devices			
	Percentage of participants who required project iPad device			
	Intervention personnel			
	Number of volunteers who were trained and dropped out			
Maintenance	**Satisfaction survey**			
Intention to sustain intervention	Percentage of participants who completed end-of-study surveys			
	Percentage of participants who were satisfied with the program	≥75% of participants would recommend the program (≥7/10 rating)	Satisfied with the program	86 (71 – 94)
	Percentage of participants who will recommend the program	≥75% of participants are satisfied with the program (that is program met their expectations)	Would recommend the program	76 (61 – 87)

DASS-21, Depression Anxiety and Stress Scale, *5XSST* Five times sit-to-stand; ≥, greater than or equal to; *count (percentage)

emotional status [47]. It has good psychometric properties and wide applicability to different populations [48].

Other measures

These include participants' baseline demographics, adherence to intervention, and satisfaction survey. Participant's attendance at each virtual exercise session was recorded by study physiotherapists, and participants tracked their adherence to prescribed home-based exercise on an exercise log. Study personnel performed biweekly phone check-ins to monitor adverse events and track protein supplementation distribution and use. Adverse events collected include exercise related (fall, fracture, pain with exercise, dizziness, muscle strain, sprain, respiratory, and cardiac adverse events) and nutrition related (constipation, diarrhea, upset stomach, severe weight loss and gain, and renal adverse events). Participants who had medication recommendations were reminded by study staff to review the recommendations with their primary care provider. Information regarding the implementation of recommendations were collected during the last two phone check-ins with the participants. Attendance and duration of the socialization phone calls were recorded by the volunteers. To obtain feedback about the program, participants and study implementation personnel completed an online satisfaction survey anonymously.

Statistical analysis

Participant's baseline characteristics were described as means with standard deviation and frequencies with percentages for continuous and categorical variables respectively. The feasibility outcomes were analyzed using descriptive statistics and expressed as frequencies, mean percent with corresponding confidence intervals (CI). Effect of the intervention was assessed using between-group analysis of covariance (ANCOVA) adjusting for baseline scores and was based on intention-to-treat (ITT) principle. Multiple imputation using chained equation was used to account for missing values assuming the data were missing at random. A sensitivity analysis based on per-protocol (PP) cohort, that is, participants who completed the trial and who had complete data, was performed to assess if there were any difference in effects for those who completed the trial. Results are presented as pre- and postintervention means, adjusted mean differences with associated 95% confidence interval (CI). All analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA).

Table 2 Baseline characteristics of participants

Characteristics	Total $n=67$	Socialization arm $n=32$	Multimodal arm $n=35$
Age, mean (SD)	77.3 (6.5)	76.4 (5.8)	78.2 (7.0)
Age *n* (%)			
65–74	24 (35.8)	13 (40.6)	11 (31.4)
75–84	33 (49.3)	16 (50.0)	17 (48.6)
85 +	10 (14.9)	3 (9.4)	7 (20.0)
Gender *n* (%)			
Male	15 (22.4)	9 (28.1)	6 (17.1)
Female	52 (77.6)	23 (71.9)	29 (82.9)
Living arrangement *n* (%)			
Lives alone	27 (39.7)	11 (33.3)	16 (45.7)
Lives with others	41 (60.3)	22 (66.7)	19 (54.3)
Educational level *n* (%)			
≤ 12th grade	10 (14.7)	2 (6.2)	8 (22.9)
High school	12 (17.7)	6 (18.8)	6 (17.1)
College	23 (33.8)	11 (34.4)	12 (34.3)
University	22 (33.8)	13 (40.6)	9 (25.7)
Smoking status *n* (%)			
Current	2 (3.0)	0 (0.0)	2 (5.7)
Former	15 (22.4)	5 (15.6)	10 (28.6)
Never	50 (74.6)	27 (84.4)	23 (65.7)
Frailty status			
Non-frail	16 (23.9)	9 (28.1)	7 (20.0)
Prefrail	39 (58.2)	16 (50.0)	23 (65.7)
Frail	12 (17.9)	7 (21.9)	5 (14.3)
Falls in the past year *n* (%)			
No	32 (47.8)	16 (50.0)	16 (45.7)
Yes	35 (52.2)	16 (50.0)	19 (54.3)
Walking aid use *n* (%)			
No	34 (50.8)	16 (50.0)	18 (51.4)
Yes	33 (49.2)	16 (50.0)	17 (48.6)
Previous fractures[1] *n* (%)			
No	39 (58.2)	16 (50.0)	23 (58.2)
Yes	28 (41.8)	16 (50.0)	12 (41.8)
5XSST mean (SD)	15.6 (7.0)	13.5 (4.9)	17.5 (8.0)
DASS-21 depression, mean (SD)	6.7 (6.6)	7.4 (5.7)	6.2 (7.3)
DASS-21 anxiety, mean (SD)	5.2 (4.8)	5.4 (4.1)	5.0 (5.5)
DASS-21 stress, mean (SD)	8.1 (6.8)	9.6 (6.8)	6.7 (6.6)
Frailty index, mean (SD)	0.26 (0.09)	0.25 (0.10)	0.27 (0.08)
EQ-5D-5L index, mean (SD)	0.77 (0.15)	0.78 (0.12)	0.76 (0.17)

[1] Fracture since the age of 50 years; *n*, number of participants; %, percentage; *SD*, standard deviation; *DASS-21*, Depression, Anxiety and Stress Scale; *5XSST*, five times sit-to-stand; EQ-5D-5L, measure for health-related quality of life

Results

Participant characteristics

The study enrolled participants between September 2020 and July 2021. Table 2 presents the baseline characteristics of participants by study arm. Of the 70 randomized

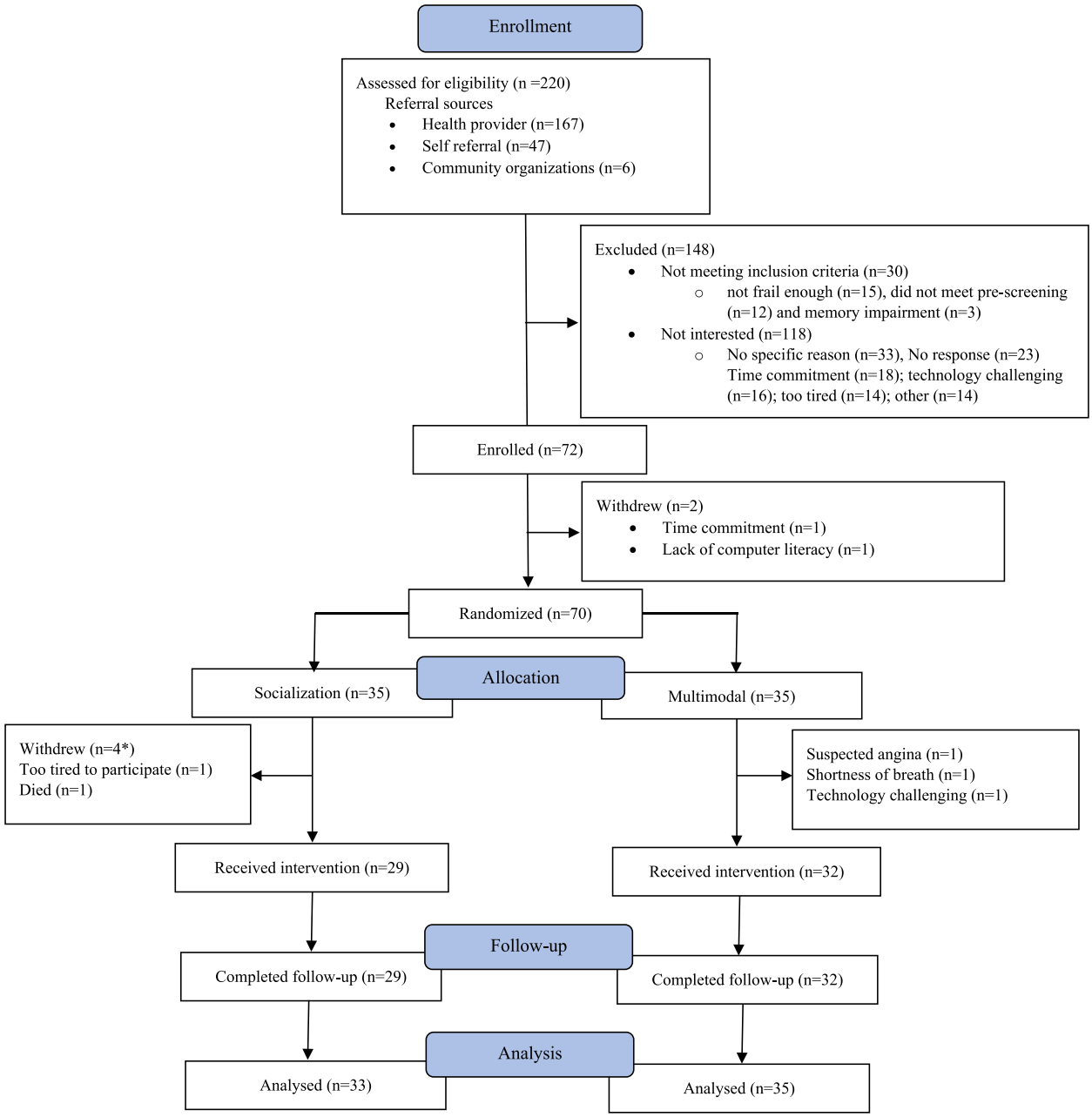

Fig. 1 CONSORT flow chart of participants. *Data removed as requested by participant (*n*=2)

participants, 67 had a baseline assessment, 32 in the socialization, and 35 in the multimodal study arms. The average age of the participants was 77.3 (*SD*: 6.4), of whom 12 (18%) were frail, 29 (58%) were prefrail, and 16 (24%) were non-frail (based on a frailty index categorization[49]). The majority of participants were females 53 (77%), had college or university education 46 (68%), and lived with others 41 (60%). The mean time to complete 5XSST was 15.6 (*SD*: 7.0) s, and mean frailty index score was 0.26 (0.09). The mean scores for depression, anxiety and stress were 6.7 (*SD*: 6.6), 5.2 (*SD*: 4.8), and 8.1 (*SD*: 6.8), respectively. Figure 1 shows the CONSORT flowchart of study participants.

Feasibility

Reach

We had a total of 345 referrals, of whom approximately 36% ($n=125$) were waitlisted for another study after the required sample size was attained. The remaining 220 referrals were assessed for eligibility; of these,

Table 3 Clinical outcome analyses

	Socialization		Multimodal			
	Pre	Post	Pre	Post	aMD	95% *CI*
ITT						
5XSST	13.7	14.0	17.8	15.3	−0.59	−3.507–2.326
Depression	7.4	7.4	6.2	6.0	−0.66	−3.615–2.285
Anxiety	5.4	4.9	5.0	5.1	0.49	−1.411–2.398
Stress	9.6	9.2	6.7	7.6	0.38	−3.285–4.047
PP						
5XSST	13.6	14.0	16.3	14.6	−1.28	−4.007–1.454
Depression	7.7	7.7	5.4	5.7	−0.76	−3.484–1.969
Anxiety	5.4	5.0	5.4	5.1	0.08	−1.634–1.794
Stress	10.1	9.8	6.5	7.1	−0.56	−4.076–2.958

ITT Intention to treat, *pp* Per protocol, *aMD* Mean difference between socialization and multimodal arm adjusted for baseline score, *CI* Confidence interval, *5XSST* Five times sit-to-stand

72 were enrolled, representing a reach of 32.7%. The major reasons for exclusion were as follows: refusals to participate without any specific reason 33 (22%), not meeting inclusion criteria 30 (20%), and no response when contacted by study personnel 23 (16%).

Effectiveness

As shown in Table 3, there was no statistically significant difference between the groups in either the intention-to-treat and the per-protocol analyses for time to complete 5XSST (ITT: $aMD = -0.59$, $CI: -3.51–2.33$; PP: $aMD = -1.28$, $CI: -4.01–1.45$), depression (ITT: $aMD = -0.66$, $CI: -3.62–2.29$; PP: $aMD = -0.76$, $CI: -3.48–1.97$), anxiety (ITT: $aMD = 0.49$, $CI: -1.41–2.40$; PP: $aMD = -0.08$, $CI: -1.63–1.79$), and stress (ITT: $aMD = 0.380$, $CI: -3.29–4.05$; PP: $aMD = -0.0559$, $CI: -4.08–2.96$). There were 45 exercise or nutrition-related adverse events reported with no difference between the multimodal and socialization arm (25 (78%) vs 20 (69%)). The adverse events were largely exercise related 43 (96%), and most were falls 23 (54%). Only 2 (4%) nutrition-related adverse events were reported. Both study arms had about the same number of falls [multimodal 12 (36%) vs socialization arm 11 (38%)] over the course of the study. One death occurred in the socialization arm before baseline assessment and intervention started.

Adoption

Of the 220 people referred for enrollment, 167 were from health providers of whom 42 (25%) were enrolled in the study. Forty-seven people contacted the study themselves, of whom 28 (60%) enrolled. Six people were referred from community organizations of whom 2 (33%) enrolled in the study. Of the 72 study participants enrolled in the study, 42 (58%) were referred by health providers, 28 (39%) were self-referrals, and 2 (3%) were from community organizations.

Implementation

Twenty-four virtual exercise sessions were conducted per cohort of participants in the multimodal group. The average class attendance was 81% (95% *CI*: 75–88%), and adherence to the home-based exercise was 50% (95% *CI*: 38–62%). No difference was observed in adherence between participants who had their own device and those who were given study device for participation (81% vs 82%). There were no major deviations from the protocol. For the socialization component, 78% (95% *CI*: 71–84%) of expected calls were made, and the mean call duration was 21 min (*SD*: 10.4) in both groups. The major challenges were the organization and attrition of the pool of trained student volunteers for the social calls. A total of 47 volunteers was trained, of whom 12 (26%) dropped out before assignments. In some instances, when volunteers dropped out or were unavailable for the calls, another volunteer was assigned to the participant. Regarding the nutrition supplementation, 97% (95% *CI*: 80–100%) of the participants received the first shipment of protein supplements, while 27 (84%) received all their protein supplements. The 5 participants (16%) who did not receive all the protein supplements opted out for personal reasons including feelings of self-sufficiency with nutrition. The average consumption rate for the protein supplements over the 12-week intervention period was 68% (95% *CI*: 55–80%). All 33 intervention participants had a consultation with the study pharmacist representing 100% implementation. Twenty-six out of 33 (79%) had a recommendation to optimize their medication, and only 38% (95% *CI*: 21–59%) of these participants

implemented the recommendations. Among those who had a recommendation, 13 (57%) reviewed the recommendations with their family physician but did not implement them.

Maintenance intention

Forty-two (60%) of the participants, 30 (71%) multimodal, and 12 (29%) socialization arm responded to the end-of-study satisfaction survey. Among them, 85% (95% *CI*: 71–94%) were satisfied with the program, and this differed between the two groups (multimodal 28 (93%) vs socialization 8 (67%)). Thirty-two 76% (95% *CI*: 61–87%) would recommend it with no difference between the multimodal 24 (80%) and socialization 8 (67%) arm. Of the 29 participants in the socialization arm who received the intervention, 19 (66%) engaged in the post-study exercise intervention. The reasons for nonparticipation include technology challenge, vacation, and no interest.

The average time to complete outcome assessments virtually per participant was 51 (*SD*: 9.0) min. There were no adverse events reported during the assessments. Ten participants (14%) were provided an iPad device for outcome assessment and the virtual exercise sessions. Of the 72 participants enrolled, 61 (85%) completed the study. Please see Table 1 for details of feasibility results.

Discussion

The RE-AIM evaluation showed that the Geras virtual frailty rehabilitation program was feasible in terms of reach, adoption across different referral settings, adherence to implementation, and intention to maintain based on the predefined criteria for success. However, the pandemic context may have added a layer challenge to some aspects of the program including slow adoption in some settings and participants' adherence to some intervention components. While these findings are promising, a larger trial with longer follow-up is required to determine effectiveness and sustained behavior change.

In terms of reach, the participation rate was satisfactory and comparable to similar studies conducted in-person or hybrid (online and face to face) before the pandemic [50–52]. Enrollment of eligible participants was slow for the most part of the recruitment phase but increased dramatically towards the end. The major facilitator to recruitment was the dissemination of stories of participants enrolled earlier in the study through print and broadcast media. Conversely, the use of targeted social media advertising yielded lower response rates. Emerging evidence suggests that online recruitment strategies could be effective [53, 54]; however, it may most likely benefit persons who are already familiar with and have access to these digital tools and platforms [55]. A combination of strategies may be better at reaching a wider range of potential participants including technology-familiar and naïve persons. To maximize representativeness and equity in the study, we extended eligibility criteria to include persons without access to a device for participation, and approximately 15% of enrolled participants did not have their own devices and internet service. Despite these efforts, there were fewer males, persons with limited education, and the oldest-old enrolled in the study. These population tend to have lower participation in digital health research [56–58]. As such, further studies are required to understand potential strategies to improve equitable participation among these underrepresented groups.

Given that the study was not powered to detect a difference in effects between groups, we cannot make conclusive interpretations about the effectiveness of the intervention. Although the 5XSST measure of physical function showed a meaningful clinical reduction of 2.5 s in time to completion in the multimodal group [45], the difference was not statistically significant when compared to the socialization arm and adjusted for baseline scores. Notwithstanding, faster times could translate to gains in functional independence and ability to perform activities of daily living [59]. For the measures of psychological well-being (depression, anxiety, and stress), the observed differences were either in the negative or positive direction for both multimodal and socialization arms but were not significant clinically important effects. A larger trial could provide definitive evidence on the benefits of virtual rehabilitation.

In terms of safety, there were no adverse events related to the intervention as both multimodal and socialization arms had about the same number of events. In addition, no falls occurred during the virtual exercise sessions, and no adverse events were reported during the virtual outcome assessment. This finding suggests that virtual rehabilitation for frail older adults could be safely implemented; however, more research is needed to demonstrate its safety as this has not been well-reported in the literature [26].

Adoption threshold was met for the three referral settings but was not as high for healthcare settings and community organizations. Decreased access to care [60], shifts to virtual care [28, 29], and fear of contracting the virus during hospital visits [61, 62] may have affected patients' decisions to seek care as they would normally do in pre-pandemic times. Additionally, most patients who were seen during that period were very ill [61] and were probably too weak to participate in the study as indicated in the reasons for declining. We speculate that a combination of these pandemic-related factors could have contributed to the lower than anticipated enrolment rates

recorded from healthcare settings. Similarly, the small number of persons reached and enrolled from community organizations could be attributed to the prevailing pandemic restrictions that hindered access to the pool of older adults, who hitherto attended in-person services at the seniors' centers run by these organizations before the pandemic. However, it is possible that our targeted media recruitment strategy, which generated a high yield, may have captured some potential participants, who had been missed from this source through self-referrals from the community.

Implementation outcomes were promising for the delivery of all intervention components with adherence rates varying from 75 to 100% and no major modifications. Given the challenging context of implementation, the observed adherence to program delivery is encouraging for future virtual rehabilitation interventions. The virtual exercise class attendance rate was comparable to the adherence rates reported in systematic reviews of technology-based exercise programs in older adults [63, 64]. Being able to deliver exercise sessions virtually to 5 persons per physiotherapist per time is promising for rehabilitation care in Canada given the long wait times for home care services [65]. It is important to note that the virtual exercise adherence rate was similar between those who had their own devices and those who received study devices and internet service to participate in the program. This suggests that disadvantaged groups (persons without access to technology) could benefit from digital health research with same level of adherence as their counterparts even with the minimal training on the use of these devices that was provided by the study. Conversely, adherence rate to the structured homework exercise was not as optimal, which is consistent with existing research [66, 67]. This could result in decreased gains from the supervised physical therapy program [68] and decreased attainment of therapeutic goals [69], as the homework exercises were intended to complement the virtual exercise sessions for the fulfillment of the minimum exercise requirements for fall prevention [32]. More research is required to understand how to sustain behavior change among older adults in unsupervised exercise programs. Regarding the nutrition component, participants' adherence to protein supplements was lower than rates reported in recent systematic reviews of nutrition interventions (68% vs > 90%) [70, 71]. It is important to note that the studies included in these reviews were conducted pre-pandemic times. It is possible that pandemic-induced circumstances not captured in this study may have influenced participants' nutrition compliance [17]. Adherence to the medication review recommendations was especially poor. Participants reported having difficulties with booking appointments with their family physician to make the recommended changes to their prescriptions, after the consultation with the study pharmacist. The limited access to healthcare services during the pandemic [60] could have hindered the next step in the study's medication optimization process. The reasons are not known for participants who consulted with their family physician but did not implement the study pharmacist's medication review recommendations.

Overall, feedback about the program was largely positive with high ratings for satisfaction and recommendations by majority of the participants, suggesting that future virtual rehabilitation programs for vulnerable older adults may be well-received. However, it is important to note that these measures were used as a proxy for assessing intention to maintain, and as such may not reflect acceptance in a world without pandemic restrictions, where there are options for in-person programs. Maintenance would be more appropriately evaluated in a study with a longer duration and post-intervention follow-up period that includes both participants and providers perspectives [38, 72].

Strengths and limitations

This feasibility study has several strengths. First, the inclusion criteria extended to disadvantaged groups who have no device for digital interventions, thus promoting equity in access to care. The study was purely virtual, as all study implementations including outcome assessment were done remotely. We used the RE-AIM framework which allowed for a comprehensive evaluation of all aspects of the program at both participant and provider levels. Despite these strengths, this study has some limitations to consider. Most data were based on self-reports, so there is possibility of underestimation or overestimation of measures. Our study lacked data on assessment of fidelity to delivery of the intervention components which is important for future trials. The effectiveness analyses were exploratory as our study was not sufficiently powered to detect statistical significance; therefore, the results should be interpreted with caution. We were not able to objectively assess the maintenance domain of the RE-AIM framework in this short-term feasibility study; as such, the finding may not reflect actual sustainability. Additionally, the majority of respondents were from the multimodal arm which could have systematically influenced the outcomes measured through the satisfaction survey.

Conclusion

Our study demonstrates that a virtual rehabilitation program for socially isolated, community-dwelling older adults could be feasibly implemented. Considering that it was conducted in the early phases of COVID-19

pandemic when public health restrictions were in place, feasibility outcomes may be different post COVID-19, when there are no social and physical distancing restrictions. Notwithstanding, the virtual mode of rehabilitation presents a promising option that could complement in-person programs in the immediate and post-COVID 19 era, particularly, where access to these interventions may be challenging, for example, due to mobility impairments, shortage of services, and/or long wait times. However, larger definitive trials are required to provide evidence of effectiveness and sustained behavior change. These trials may need to consider recruiting from multiple sources using different strategies for a wider reach of participants. Also, continuously monitoring and adapting recruitment strategies as well as highlighting and sharing participants' success stories to motivate potential participants and enhance the visibility and credibility of the study could increase the chances of reaching intended sample size. We suggest providing devices and optimal training on how to navigate the technology to potential participants who do not have access to these resources to promote access and equitable participation in digital health research. Future trials should consider strategies on how to improve adherence to unsupervised home exercises, optimize medication review process, and retain social call volunteers.

Abbreviations

COVID-19	Coronavirus disease
RE-AIM	Reach, Effectiveness, Adoption, Implementation, and Maintenance
5XSST	Five times sit-to-stand test
DASS	Depression, Anxiety and Stress Scale
ITT	Intention to treat
PP	Per protocol
aMD	Adjusted mean difference
SD	Standard deviation
ANCOVA	Analysis of covariance
CI	Confidence intervals
HiREB	Hamilton Integrated Research Ethics Board
STOPP/START	Screening Tool of Older Person's Prescriptions and Screening Tool to Alert to Right Treatment

Authors' contributions

Study conception and design, AP, GI, CK, SM, JDA, DM, KDW, BM, TW, CP, DA, SB, and PH. Data acquisition, AP, AR, TW, PB, RB, MW, CP, BM, JDA, JBS, and KP. Data analysis and interpretation, CO, GI, LT, and AP. Manuscript drafting, CO. Manuscript revision for important intellectual content, AP, GI, LT, JDA, PH, JL, CM, CK, AR, TW, PB, RB, MW, ST, DM, SM, DA, CP, SB, KDW, SM, and BM. All authors approved the final version of the manuscript.

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Availability of data and materials

The data are held by a third party and include potentially identifying patient information so cannot be shared publicly. However, the dataset is available upon request from the principal investigator Dr. Alexandra Papaioannou: papaioannou@hhsc.ca, Geras Centre for Aging Research, Hamilton, Health Sciences, Hamilton, ON, Canada.

Declarations

Ethics approval and consent to participate

Ethics approval for the trial was obtained from the Hamilton Integrated Research Ethics Board (HiREB) (file no. 11408). All participants provided a documented verbal informed consent before participating in the trial.

Consent for publication

Not applicable.

Competing interests

Jonathan D. Adachi, grants/research support — Amgen and Radius; speaker bureau/honoraria — Amgen, Gilead, GSK, and Paladin; consulting fees — Amgen, Gilead, GSK, and Paladin; and past president of Osteoporosis Canada. David Armstrong, co-founder, chief innovation officer, and medical advisory member — A.I. VALI; board member of Canadian Digestive Health Foundation; medical advisory board member of Cinclus Pharma; speaker honorarium — Fresenius Kabi and Takeda; research funding — Nestlé Health Sciences; treasurer of International Working Group for the Classification of Oesophagitis; medical advisory board member of Phathom Pharma; and Douglas family chain in nutrition research. The other authors declare that they have no competing interests.

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Publisher's Note

Getting fit for hip and knee replacement: the Fit-Joints multimodal intervention for frail patients with osteoarthritis – a pilot randomized controlled trial

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Abstract

Background: Older adults with frailty have high risk of poor postoperative outcomes and might benefit from interventions to improve their health status prior to undergoing joint replacement surgery. This pilot randomized controlled trial (RCT) evaluated the feasibility of a multimodal prehabilitation program in older adults with frailty awaiting hip or knee replacement.

Methods: This parallel two-arm pilot trial took place in Ontario, Canada between September 2016 and October 2019. Participants were community-dwelling older adults with frailty awaiting joint replacement aged ≥ 60 years. They were recruited from the Musculoskeletal Central Intake and Assessment Centre (MSK CIAC), Ontario and randomized to either a multicomponent intervention or usual care arm. Intervention participants received tailored exercise prescriptions, protein and vitamin D supplements, and a one-time medication optimization consultation prior to their surgery while control participants received usual care. Feasibility was assessed based on predefined progression criteria that were reported as frequencies and mean percentages with confidence intervals for recruitment, retention, data completion and adherence to intervention components. Clinical outcomes including Oxford knee and hip scores, frailty index, short performance physical battery and health-related quality of life were collected at baseline, 1-week preoperative, 6-weeks and 6-months postoperative and were evaluated using generalized linear mixed models for repeated measures.

Results: A total of 69 participants was enrolled and randomized out of 195 hip or knee replacement patients, indicating a recruitment rate of 35%. The mean age of the participants was 74 (SD: 7.5) of whom 51% were prefrail and 40% were frail. The mean period of intervention was 5.2 months (standard deviation (SD):3.0). Participant retention (81%), data completion (≥80%), adherence to strength, 4 days (95% confidence interval (CI): 3 – 5 days/week), balance, 3 days (95% CI: 2 – 4

days/week) and flexibility, 3 days (95% CI: 3 – 4 days/week) exercises, adherence to vitamin D intake 82% (95% CI: 73 – 92%), and medication review consultation 86% (95% CI: 68 – 95%) met the target values for feasibility success. The Oxford knee score at 6 months postoperative 8.78 (95% CI: 0.40 – 17.16) showed a clinically meaningful and statistically significant difference between treatment groups. There were also indications of clinically relevant changes for function, frailty and quality of life post-surgery.

Conclusion: This trial provides strong evidence of feasibility and indications of improvements in knee pain, function, frailty and quality of life in a prehabilitation program in older adults with frailty awaiting joint replacement. Challenges to implementation and adherence were identified that can inform modifications to study design for future trials.

Trial registration: ClinicalTrials.gov NCT02885337. Registered August 31, 2016. https://classic.clinicaltrials.gov/ct2/show/NCT02885337

Keywords: Feasibility, Frailty, Arthroplasty, Knee replacement, Hip replacement, Osteoarthritis, Rehabilitation, Exercise, Older adults

Key Messages on Feasibility

- There are limited well-designed and generalizable trials on how to prehabilitate older adults with frailty scheduled for hip or knee replacement surgery to improve postoperative outcomes.
- The FitJoints pilot trial demonstrated that participant retention, data completion, adherence to strength, balance and flexibility exercises, adherence to vitamin D supplement intake and medication review consultation are feasible.

- There were also signals of benefits for knee pain, physical function, frailty, and quality of life with the intervention
- Future trials should consider strategies to improve participant recruitment and exercise accountability, protein supplements tailored to participant preference and current dietary needs, as well as measures to optimize the implementation of medication review recommendation.

Introduction

Joint replacement is one of the most common surgeries among older adults[1]. With the growing aging population, the demand for orthopedic surgical services is rising[2,3]. Recent estimates in Canada show approximately 110,000 hip and knee replacements were performed between 2020 and 2021, despite cases cancelled due to the COVID-19 pandemic[4]. Estimates from the USA indicate a projected rise in the number of total hip and knee arthroplasties of 71 and 85% respectively by 2030[5]. These major surgeries provide substantial improvements in pain, physical function, and quality of life for patients with osteoarthritis (OA)[6,7]. However, the presence of pre-existing conditions, such as frailty, may reduce the benefits of a joint replacement surgery, increase the risk of surgical complications, and impair recovery[8,9].

Frailty is characterized by low physiological reserve and decreased function arising from an accumulation of age and disease-related deficits[10,11]. Persons living with frailty have weakened resilience and increased vulnerability to stressors[10,11]. Therefore, the stress of a major surgery may induce the deterioration of physiological reserve, leading to poor surgical outcomes[8]. Frailty has been linked with increased risk of mortality, post-operative complications, prolonged length of stay, discharge to institutional care, functional decline, new disability, lower quality of life and discharge to institutional care following surgery[3,9,12-16]. In major, elective, non-cardiac surgeries including arthroplasty, healthcare costs and resource use are considerably higher in older adults with frailty[15,17] with a 1.5-fold increase in the cost of post-operative care in the year after surgery[18]. These issues underscore the need for preoperative interventions to manage frailty and minimize adverse post-operative outcomes in this population.

Multimodal interventions including physical exercise and nutrition supplementation have been shown to be beneficial in managing frailty[19-21] and may potentially lead to better surgical outcomes

in patients with frailty[22]. Prehabilitation can enhance the functional and adaptive capacity of patients with frailty to cope with upcoming stressors by improving physiological reserve[22,23]. Recent systematic reviews and meta-analyses examining the effectiveness of prehabilitation interventions in orthopedic surgical patients have reported varying conclusions regarding the preoperative and postoperative benefits[24,25]. In the frail general surgical population, the evidence supporting prehabilitation is also unclear[26]. Most studies evaluated in these reviews were among younger or healthier populations while studies specifically examining the high-risk population of older adults with frailty awaiting joint replacement are lacking. The few trials[27-29] available in this patient group have some methodological and interventional limitations to consider including, short duration of intervention (3 – 6 weeks), inclusion of hip replacement patients or females only, and assessment of short-term outcomes. More well-designed studies are essential to inform the perioperative management of these older patients for better health outcomes. As the first step to a larger definitive trial, we conducted a pilot study to assess the feasibility of implementing a multimodal intervention in older adults with frailty scheduled to undergo total hip or knee replacement.

Methods

Study design

The FitJoints pilot study is a two-arm, parallel group, randomized controlled trial (RCT) evaluating the feasibility and effectiveness of multimodal frailty intervention compared to usual care among prefrail/frail older patients awaiting elective total hip or knee replacement. The trial was registered with ClinicalTrials.gov NCT02885337. The reporting of this study adheres to the CONSORT

extension for pilot and feasibility studies statement[30]. We provide a summary of the study design, setting, population, recruitment, intervention and control arm description, study outcomes, and data analysis. Full details of the study methods can be found in the published study protocol[31].

Study setting

The study was conducted between September 2016 and October 2019. Participants were recruited from Musculoskeletal Central Intake and Assessment Centre (MSK CIAC) formerly Regional Joint Assessment Program (RJAP) at Juravinski Hospital – a tertiary care hospital in Hamilton, Ontario, Canada. The MSK CIAC program caters to individuals with arthritis who are recommended by their primary care provider to be assessed for hip or knee replacement. This assessment is conducted by orthopedic surgeons and advanced practice physiotherapists (APPs)[32] with specialized orthopedic training.

Study population and recruitment strategy

Inclusion criteria for participants were: (a) ≥ 60 years old; (b) prefrail (score of 1 – 2) or frail (score of 3 – 5) based on Fried frailty phenotype[11]; (c) awaiting elective unilateral hip or knee replacement; and (d) scheduled for a surgery with wait time between 3 – 10 months. Exclusion criteria included: self-reported renal insufficiency, neuromuscular disorder, active cancer, or any inflammatory arthritis. Orthopedic surgeons and APPs assessed patients referred for hip or knee surgery, then APPs invited potential participants deemed as surgical candidates and screened them for eligibility. Potential participants were given a study information sheet to guide their decision about participation and were later contacted by a research assistant (RA) to confirm participation. Those who indicated interest to participate provided written informed consent. Study staff randomized participants to the intervention or usual care group on a 1:1 ratio based on a computer-

generated stratified block randomization list generated and kept securely by a research staff external to the study. The stratification was based on the orthopedic surgeon conducting the surgery, age and joint type. Baseline assessments were conducted after randomization by blinded outcome assessors and the first intervention visit by the study kinesiologist was scheduled for the intervention group participants. Those blinded to the intervention were outcome assessors, data entry personnel, data analysts, clinical administrators who assigned participants' surgery dates, the investigative team, and steering committee. Due to the nature of the study, it was not possible to blind other intervention personnel and participants.

Intervention development

The FitJoints intervention was designed to address the complex nature of frailty using multi-modal interventions as in the Australian FIT trial[33]. The components of the intervention were informed by existing evidence including a systematic review on exercise interventions in prefrail and frail older adults[34], protein supplement recommendations by guidelines[35,36], available evidence on vitamin D including a trial on oral vitamin D in a similar population conducted by the investigators of this study[37] and a meta-analysis that demonstrated benefits with vitamin D on muscle strength and balance in older adults[38], and explicit criteria and guidelines for medication appropriateness in older adults[39,40]. A team of researchers, healthcare providers and stakeholders met to discuss the relevance, application, and adaption of existing evidence to the study context and population.

Multimodal arm

Participants in the intervention group received a multimodal intervention comprising physical exercise, protein supplement and dietary counselling, vitamin D supplement for 3 – 10 months

between randomization and surgery, as well as a one-time medication review consultation. The description of the intervention follows the TIDIER guideline[41].

Exercise: The study kinesiologist performed an introductory fitness assessment and goal setting with intervention participants at their homes based on the tools for assessing physical fitness of older adults by Jones and Rikli[42]. The kinesiologist developed tailored exercise programs for each participant and conducted bi-weekly appointments to review participant progress and adjust exercise programs as required. The exercise prescription was based on the recommendations from the Canadian Physical Activity Guidelines for older adults ≥65 years[43]and included aerobic, strength, flexibility and balance components. Participants were encouraged to exercise 3 times/week for 45 – 60 minutes[34] either at home or at a local YMCA with fitness and pool classes designed for individuals with joint issues of their preference. They were given a logbook to track their exercise activities which included frequency of balance, flexibility, and strength exercises, as well as frequency and duration of aerobic exercises.

Protein supplement: Participants received a commercially available protein supplement containing 20g protein/serving to be taken twice daily with a meal or on activity days within 3 hours of exercise. The supplements were delivered by the kinesiologist during routine visit to participants who were also provided with a dietary intake log for tracking frequency of supplement consumption.

Vitamin D: All intervention participants were supplied with vitamin D3 (1000IU/day tablets) to be taken once daily.

Medication review: The study pharmacist reviewed the medications of participants in the intervention group using the Screening Tool of Older Person's Prescription STOPP/ Screening

Tool to Alert to Right Treatment START criteria[39] and Beers criteria[40]. Based on this review, they provided written recommendations to the participant's family physician. Participants were encouraged to follow up with their family physician to review and implement the recommendations which were faxed or mailed to the physicians. The medication review consultation was conducted once per participant during the intervention period.

Control arm

Participants in the control group received usual care which may have included recommendations by their surgeon to attend a physical exercise program or improve fitness before surgery. However, the study kinesiologist provided no additional fitness support or advice.

Study outcomes

Feasibility outcomes: The primary outcome was feasibility assessed by (1) recruitment rate (percentage of patients enrolled out of all patients eligible for hip or knee replacement), (2) retention rate (percentage of participants who completed intervention phase and completed the study) and (3) data completion (percentage of participants with complete clinical outcomes data at the 6 months postoperative timepoint). The predetermined criterion for progression was set at 80% for all of these measures. Participant's adherence to each component of the intervention was also assessed as part of the feasibility outcomes. The exercise component with corresponding feasibility targets were (1) strength (≥2 days/week), (2) aerobic (≥150 mins/week), (3) balance (≥2 days/week), and (4) flexibility (≥2 days/week). The expected frequency or duration of the exercise types was based on the Canadian Physical Activity Guidelines for older adults ≥65 years[43]. Other aspects of the intervention were assessed as follows: protein supplement (percentage of daily protein supplements consumed), Vitamin D (percentage of daily Vitamin D consumed), and

medication review (percentage of participants who received medication review and the percentage who implemented the review recommendations). Adherence ≥80% was considered adequate for the nutrition component.

Clinical outcomes: The clinical outcomes evaluated include (1) Oxford hip and knee score – patient-reported outcome used to assess functional ability and pain in patients undergoing total hip or knee replacement with high validity, reliability and responsiveness[44-46] (2), Frailty – assessed using the Geras Fit-Frailty app which is based on the frailty index of deficit accumulation[47] (3) Short physical performance battery (SPPB) – validated tool for assessing functional mobility with good internal consistency and sensitivity to change[48], and (4) European Quality of Life 5 Dimension 3 Level (EQ5D3L) for the assessment of patient's health-related quality of life[49]. Higher scores for EQ5D3L (range: 0 – 1), Oxford hip and knee scores (range: 0 – 48) indicate better outcomes while higher scores for frailty index (range: 0 – 1) and SPPB (range: 0 – 12) suggests poorer outcomes.

Adverse events: Adverse events were self-reported unfavourable experiences during the study period. Fatal or life-threatening events were considered serious adverse events and were reported to the Research Ethics Board. An independent Data Safety and Monitoring Board reviewed the trial data for safety.

Data collection and management

Study outcomes were collected at baseline, 1 week preoperative, 6 weeks postoperative and 6 months postoperative by blinded assessors who were trained by the research coordinator. Trained research assistants conducted monthly visits to track intervention adherence and monthly phone

check-ins to all participants to monitor adverse events. Study data were managed using REDCap database[50].

Data analysis

Participants baseline characteristics were summarised as means with standard deviation and frequencies with percentages for continuous and categorical variables respectively. The feasibility outcomes were analysed descriptively and presented as mean score with corresponding 95% confidence interval (CI). The clinical outcomes were analysed on an intention-to-treat basis using generalized linear mixed-effects modeling for repeated measures and included time, treatment group, and time by treatment group interaction as independent variables. The estimated between-group treatment effects and associated 95% CI were obtained for each of the three study follow-up visits. Per protocol analyses were also performed in the same way and were restricted to participants with complete data at all time points. All analyses were performed using Stata version 17 (StataCorp, College Station, TX)[51].

Sample size estimation

The sample size was based on the feasibility outcomes of 80% for screening, retention, data completion, and adherence with the intervention components. A sample size of 62 patients was estimated to produce a two-sided 95% confidence interval with a width equal to ± 10% for 80% progression criterion. The estimation was conducted using PASS software (Kaysville, Utah)[52].

Ethical considerations

All participants provided signed written informed consent before enrollment. The study was approved by the Hamilton Integrated Research Ethics Board (file #2017 – 1565).

Results

Participant demographics

Participant enrolment occurred from September 2016 to January 2018. Figure 1 shows the CONSORT flow chart of participants and Table 1 shows the baseline characteristics of participants by study arm. A total of 69 participants was enrolled and randomized: 34 in the control and 35 in the intervention arm. The mean age of the participants was 74 (SD: 7.5) of whom 51% were prefrail and 40% were frail. The majority of the participants was female (68%), had high school diploma or lower (61%) and lived with others (71%). The mean Oxford hip and knee scores were 20 (SD:7.3) and 21 (SD:7.7) respectively.

Feasibility

The feasibility results are shown in Table 2. A total of 1017 patients were referred to the Musculoskeletal Central Intake and Assessment Centre. The patients were assessed by the orthopedic surgeons and APP, of whom 195 (19%) were considered candidates for hip or knee surgery and who were then screened for study eligibility. Of these, 69 (35%) were enrolled in the study. Among potential participants excluded, 84 (67%) were not interested and 42 (33%) did not meet eligibility criteria for several reasons shown in Figure 1. The retention rate for both intervention phase and study completion was 81%. Data completion ranged from 80% (95% CI: 68 – 88%) for frailty index to 85% (95% CI: 73 – 93%) for Oxford hip score at the 6 months postoperative follow-up visit. The reasons for incomplete data were withdrawal 8 (57%), missed appointment 5 (36%), and unknown 1 (7%).

The average intervention period for participants was 5.2 months (SD: 3.0). The mean adherence for physical exercise types were strength 4 days (95% CI: 3 – 5 days/week), aerobic 92 minutes

(95% CI: 64 – 121 minutes/week), balance 3 days (95% CI: 2 – 4 days/week), flexibility 3 days (95% CI: 3 – 4 days/week). On average, participants consumed 67% (95% CI: 55 – 78%) of protein supplements and 82% (95% CI: 73 – 92%) of Vitamin D per month. For medication review, 86% (95% CI: 68 – 95%) received a consultation and 41% (95% CI: 25 – 60%) met with their family physician who reviewed the study pharmacist's recommendations.

Clinical outcomes

Table 3 shows the effects of the intervention on Oxford hip score, Oxford knee score, SPPB, frailty index and EQ5D3L health-related quality of life at the three follow-up timepoints. At the 6 months postoperative visit, the intervention group had a significantly higher score, 8.78 (95% CI: 0.40 – 17.16) for knee replacement patients. There were also a clinically relevant but not statistically significant change in the oxford knee score at 6-weeks post-surgery, 9.11 (95% CI: -2.66 – 20.87). Other clinical outcomes including SPPB, -0.38 (95% CI: -1.57 – 0.82) and frailty score, -0.04 (95% CI: -0.10 – 0.01) at 6 months post-surgery and health-related quality of life, 0.04 (-0.04 – 0.12) at 6-weeks postoperatively showed clinically meaningful differences in favor of the intervention. The results of the complete case analyses (supplementary table 1) were similar to those of the intention-to-treat analyses.

Adverse events

There were 54 adverse events reported – 30 (56%) in the control vs 24 (44%) in the intervention arm. The events occurred in 44 participants – 23 (52%) in the control and 21 (48%) in the intervention arm and included pain 13 (24%), fall 11 (20%), diarrhea 3 (6%), fracture 2 (4%), and others 25 (46%). Most of the adverse events 41 (81%) were unrelated to the intervention. The fractures reported were not associated with the intervention and only 2 (19%) of the falls and 4

(31%) of pain were either possibly or probably linked to the intervention. Six serious adverse events were reported but they were not related to the intervention.

Discussion

This study provides evidence of feasibility on participant retention, data completion, and participant adherence to intervention components including exercise, Vitamin D supplement intake, and medication review consultation in the Geras FitJoints multimodal prehabilitation program for older adults with frailty awaiting total hip or knee replacement. Participant recruitment, adherence to protein supplements and aerobic exercise as well implementation of medication review recommendations did not meet the prespecified criteria for feasibility success. The evaluation of clinical outcomes showed that Oxford knee scores at 6-months post surgery was significantly better than in the intervention group. Also, there were signals of benefits for physical performance, frailty status and quality of life postoperatively. Only a few self-reported adverse events were potentially attributable to the intervention.

Recruitment of participants is critical to the success of any trial[53]; as such, it is a key indicator of feasibility of reaching planned sample size for future larger trials[54]. The recruitment rate did not meet the targeted progression cut-off of 80% due to reasons such as patients not having the minimum 3-month wait time before surgery, being below 60 years, and unavailable when contacted. In retrospect, we consider the blanket criterion for success of 80% applied to most feasibility outcomes in this study too high for the recruitment measure. A specific target informed by previous studies in similar populations and the current study context would have been more realistic. Recruitment rates from previous studies ranged from 34 – 79%[27-29], averaging around

60%. Based on the existing data, our study's recruitment rate of 35% is at the low end. Considering the long duration of recruitment and low number of potential participants screened to attain this rate, achieving higher recruitment rates for a larger sample size in future trials would require some modifications of the current study design including recruiting from multiple sources.

Generally, recruitment of older adults living with frailty is challenging due to poor health and mobility issues that may limit their inclusion or participation in studies[55,56]. Additionally, the patient group for the study may not be considered for surgery due to the high risk for unfavourable outcomes[57], thus affecting recruitment. More flexibility with time and space of study[55], use of virtual platforms for intervention delivery [58], and engagement of family caregivers[55] could accommodate for the health and mobility barriers. Also, close monitoring of the recruitment process and a flexible protocol could allow for the adjustment of strategies to reach required numbers[56]. Overall, the insights gained from this study could be used to better inform recruitment in future studies.

As a definite positive finding, the retention target was achieved and is comparable to previous trials[27-29]. With a follow-up duration of 9 – 16 months, the study's retention rate of 81% for both completion of intervention phase and the entire study is encouraging for future trials. The data completion measure was equally comparable to retention, with few participants having incomplete outcome data due to missed appointments or withdrawal.

Adherence to all exercise components was optimal except for aerobic exercises. On average, participants performed 38% below the recommended 150 mins/week of moderate to vigorous aerobic exercise per the guideline used in the study[43]. Although, higher levels of exercise adherence have been reported in systematic reviews in the general orthopedic surgical patient population[24,25], it is not clear if the exercises were aerobic. We noted during adherence tracking

that participants reported difficulty completing aerobic exercises due to pain given that it required a longer duration to perform. It is possible that the exercises may have been challenging for this patient population since the prescription was based on exercise guidelines designed for health older adults.

Aerobic exercise was the only exercise type where frequency and time were reported while only frequency was reported for other components in this trial. The evidence regarding the FITT (Frequency, Intensity, Time and Type)[59] of exercise that is most effective for frailty prevention and management is inconclusive[60]. More studies are required to demonstrate the FITT of exercises that is feasible and effective for older adults with frailty. This will not only help in the prescription, assessment, and reporting of physical exercise but will potentially improve adherence in future studies. Given that study participants had the choice of where, when, and how they exercised, stepping up accountability through supervised group exercise sessions could potentially improve exercise adherence as shown in our recent study[58]. Further, future trials should consider the use of objective measures of physical activity such as accelerometers for more reliable and valid measurements [61].

Nutrition adherence was met for Vitamin D but not for protein supplements, albeit the results fall within the range (50 – 100%) reported in recent systematic reviews[62,63]. It is possible that the observed lower compliance with protein supplements (67%) compared to Vitamin D supplements (82%) was due to participants reports of limited options of the flavours of protein supplement provided and fear of gaining weight with the recommended twice-daily protein supplements. Excess weight could impair post-surgical recovery [64,65] and patients who are obese are typically advised to lose weight prior to surgery for better outcomes[64]. We did not assess baseline dietary protein to provide specific recommendation for protein supplements. Tailoring prescribed

nutrition supplements to participant's current dietary needs, clinical profile, and preferences could improve adherence in future studies.

Adherence to the implementation of medication review recommendations was low. Given the high prevalence of polypharmacy (currently taking ≥ 5 or more drugs) in the study (75%) which increases the risk of taking potentially inappropriate medications and drug-drug interactions[66], review for potential deprescribing, medication optimization, and harm reduction is needed[67]. The reasons for low adherence to the medication recommendations were not explored in our study, as such, it presents an area of investigation for future of studies in order to enhance the success of this intervention component.

The exploratory analyses of clinical outcomes showed clinically meaningful[68] and statistically significant difference for knee pain at 6 months postoperative timepoint, and only clinically meaningful changes for physical function[69], frailty[70], and health-related quality of life[71]. Although, our study was not powered for statistical tests of efficacy, these results provide indications of benefits that could be demonstrated in larger definitive trials. Recent meta-analyses in the general arthroplasty patient population[24,25] suggests varying effects for both preoperative and postoperative outcomes. Therefore, future adequately powered trials in older adults with frailty are required to provide firm conclusions about the efficacy of the prehabilitation intervention in the short and long term perioperatively. Overall, the data on adverse events suggests that the intervention is safe with minimal risks to participants.

Strengths and limitations

This study addressed the limitations of previous studies including generalizability (it included patients regardless of the type of joint surgery or gender), longer duration of intervention,

multimodal intervention, and assessment of short- and long-term outcomes. However, the results should be interpreted in the context of these limitations. First, there were no measures to validate participant's self-reported adherence to intervention components, so there is a possibility of under-reporting or over-reporting of outcomes. Second, the trial was single-blinded; as such, participants behaviour and responses may have been influenced by the knowledge of their group assignment. Third, the efficacy analyses were only exploratory as our study was not sufficiently powered to detect differences in effects.

Conclusion

Our study provides valuable preliminary data on feasibility and efficacy of prehabilitation in older adults with frailty awaiting joint replacement with a clear positive effect on patients undergoing total knee replacement at 6-months postoperatively. While retention, data completion, adherence to some intervention components were optimal with respect to prespecified criteria, some aspects of the study design require modifications for better outcomes. We recommend increasing study recruitment sites, adapting protein supplements to participants needs and preferences, exploring reasons for low adherence to the implementation of medication review recommendation, utilising FITT principle for exercise prescription and reporting as well as increasing exercise accountability for better adherence. Larger trials powered to detect clinically significant differences are required for definitive guidance on effectiveness of prehabilitation in this patient population.

Abbreviations

RCT, Randomized controlled trial; SD, Standard deviation, CI, Confidence interval; OA, osteoarthritis; CONSORT, Consolidated Standards of Reporting Trials; MSK CIAC,

Musculoskeletal Central Intake and Assessment Centre; RJAP, Regional Joint Assessment Program; APP, Advanced Practice Physiotherapists; YMCA, Young Men Christian Association; RA, Research assistant, TiDier, Template for Intervention Description and Replication; SPPB, Short Physical Performance Battery; EQ5D3L, European Quality of Life 5-dimension 3-level REDCap, Research Data Capture; FITT, Frequency, Intensity, Type and Time.

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Authors' Contribution

Study conception and design: AM, MW, JDB, VA, BD, JDA, GI, CK, AL, SM, DA, SA, BL, AP, DW and AP. Data analysis and interpretation: CO, GI, LT and AP. Data acquisition and study implementation: AP, AM, MW, JDB, VA, BD, JDA, DP, GI, CK, AL, SM, DA, SA, GH BL, and AP. Manuscript drafting: CO. Manuscript revision for important intellectual content: AM, MW, JDB, VA, BD, JDA, DP, LT, GI, CK, AL, SM, DA, SA, GH, BL, AP, DW and AP. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Hamilton Integrated Research Ethics Board (file #2017-1565). All participants provided written informed consent prior to randomization.

Competing interests

David Armstrong: Research funding: Weston Foundation and Nestlé Health Sciences; Consulting: Cinclus Pharma and Phathom Pharma; Speaker honorarium: Fresenius Kabi and Takeda Canada, Amgen; Industry: Co-founder A.I. VALI; Not-for-profit: Board member, Canadian Digestive Health Foundation, Treasurer and Board member, International Working Group for the Classification of Oesophagitis. All other authors declare that they have no competing interests.

Data availability

The data are held by a third party and includes potentially identifying patient information so cannot be shared publicly. However, the dataset is available upon request from the principal investigator Dr Alexandra Papaioannou: papaioannou@hhsc.ca, GERAS Centre for Aging Research, Hamilton, Health Sciences, Hamilton, ON, Canada.

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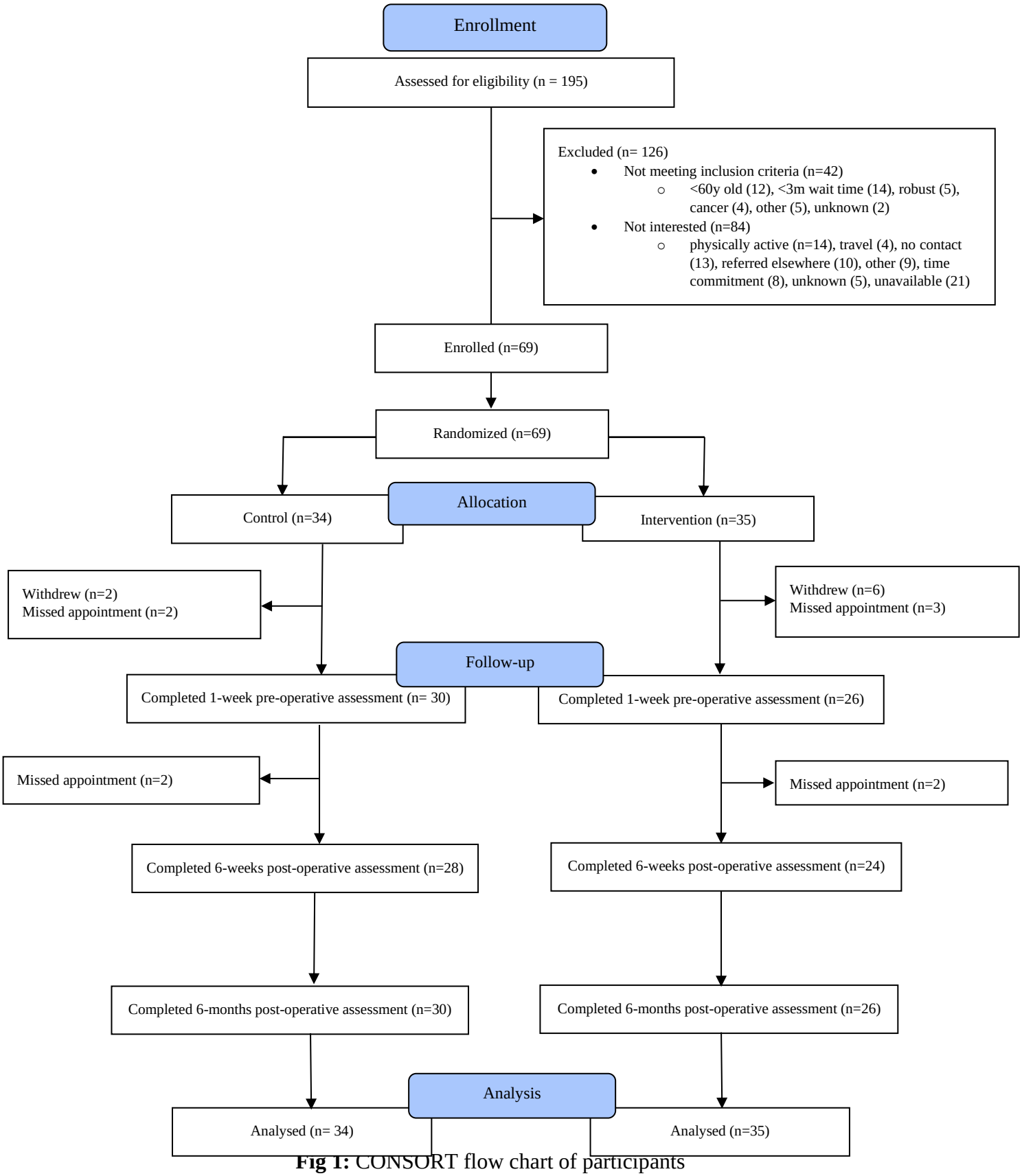

Fig 1: CONSORT flow chart of participants

Table 1: Baseline Characteristics of Participants

Characteristic	All	Control	Intervention
Age mean, (SD)	73.9 (7.5)	72.3 (7.6)	75.9 (7.1)
Age, n (%)			
<75	38 (55.1)	23 (67.7)	15 (42.9)
75 – 84	25 (36.2)	9 (26.5)	16 (45.7)
≥85	6 (8.7)	2 (5.9)	4 (11.4)
Sex, n (%)			
Male	22 (31.9)	12 (35.3)	10 (28.6)
Female	47 (68.1)	22 (64.7)	25 (71.4)
Living arrangement n (%)			
Lives with others	49 (71.0)	25 (73.5)	24 (68.6)
Lives alone	20 (29.0)	9 (26.5)	11 (31.4)
Education n (%)			
≤High school	42 (60.9)	17 (50.0)	25 (71.4)
>High school	27 (39.1)	17 (50.0)	10 (39.1)
Smoking n (%)			
Former	31 (44.9)	11 (32.4)	20 (57.1)
Current	4 (5.8)	3 (8.8)	1 (2.9)
Never	34 (49.3)	20 (58.8)	14 (40.0)
Falls in the past year n (%)			
No	40 (58.0)	18 (52.9)	22 (62.9)
Yes	29 (42.0)	16 (47.1)	13 (37.1)
Walking aid use n (%)			
No	21 (30.4)	13 (38.2)	8 (22.9)
Yes	48 (69.6)	21 (61.8)	27 (77.1)
Previous fractures n (%)			
No	32 (46.4)	14 (41.2)	18 (51.4)
Yes	37 (53.6)	20 (58.8)	17 (48.6)
Comorbidity			
0	8 (11.6)	4 (11.8)	4 (11.4)
1	33 (47.8)	16 (47.0)	17 (48.6)
2 – 3	28 (40.6)	14 (41.2)	14 (40.0)
Oxford hip score, mean (SD)	19.5 (7.3)	20.0 (8.5)	19.1 (6.0)
Oxford knee score, mean (SD)	20.5 (7.7)	20.5 (8.6)	20.6 (7.3)
Frailty index, mean (SD)	0.30 (0.11)	0.30 (0.12)	0.29 (0.10)
Fried frailty phenotype			
Non-frail	6 (8.7)	4 (11.7)	2 (5.7)
Prefrail	35 (51.0)	17 (50.0)	18 (51.4)
Frail	28 (40.3)	13 (38.2)	15 (42.9)
EQ5D3L, mean (SD)	0.68 (0.11)	0.68 (0.12)	0.69 (0.11)
SARC-F, mean (SD)	4.1 (2.31)	4.1 (2.43)	4.2 (2.22)
SPPB, mean (SD)	6.77 (2.31)	6.88 (2.45)	6.66 (2.19)
No of medications			
<5	17 (24.6)	9 (26.5)	8 (22.9)
≥5	52 (75.4)	25 (73.5)	27 (77.1)

SD, standard deviation; n, number; %, percentage; EQ5D3L, European Quality of Life, 5 Dimension 3 Levels; SARC-F, Strength, Assistance with walking, Rising from a chair, and falls; SPPB, Short Performance Physical Battery

Table 2: Feasibility outcomes

Outcome	Evaluation metric	Estimate	Criteria for success
Recruitment	% patients assessed out of all referred surgical patients	n (%) 195 (19)	≥80%
	% patients enrolled out of all patients assessed for eligibility	69 (35)	≥80%
Retention	% participants who completed intervention phase and the study	n (%) 56 (81)	≥80%
Data completion	% participants with complete data for the following outcomes:	% (95% CI)	≥80%
	SPPB	81 (70 – 89)	≥80%
	Oxford hip score	85 (73 – 93)	
	Fit frailty index	80 (68 – 88)	
Participants adherence	Intervention components		
	Exercise Strength: average number of days/week	Mean (95% CI) 4.0 (3.2 – 4.7)	 ≥2 days
	Aerobic: average number of mins/week	92.1 (63.5 – 120.7)	≥150 mins/week
	Balance: average number of days/week	2.9 (2.2 – 3.7)	≥2 days
	Flexibility: average number of days/week	3.4 (2.8 – 4.0)	≥2 days
	Protein supplement % daily protein supplements consumed per month	% (95% CI) 66.5 (54.6 – 78.4)	 ≥80%
	Vitamin D % daily Vitamin D consumed per month	% (95% CI) 82.3 (73.4 – 91.5)	 ≥80%
	Medication review % participants who received medication review % participants who implemented recommendations	% (95% CI) 86.2 (67.5 – 95.0) 41.4 (24.6 – 60.4)	 ≥80%

n, number; %, percentage; CI, confidence interval; SPPB, Short Performance Physical Battery

Table 3: Clinical Outcomes

Outcome	Mean (SD)		Mean difference (95% CI)
	Control	Intervention	
Oxford hip score			
1 week preoperative	17.73 (7.14)	16.50 (7.30)	-1.17 (-5.22 – 2.87)
6 weeks postoperative	36.73 (7.80)	37.33 (7.99)	1.44 (-3.40 – 6.28)
6 months postoperative	41.39 (7.11)	42.96 (4.74)	1.58 (-1.84 – 5.01)
Oxford knee score			
1 week preoperative	18.28 (8.56)	21.25 (14.97)	4.90 (-6.94 – 16.75)
6 weeks postoperative	30.00 (9.38)	39.33 (8.14)	9.11 (-2.66 – 20.87)
6 months postoperative	37.85 (6.67)	42.00 (2.65)	8.78 (0.40 – 17.16)*
SPPB			
1 week preoperative	6.87 (2.67)	6.73 (2.79)	-0.06 (-1.44 – 1.32)
6 weeks postoperative	7.46 (2.50)	7.25 (3.01)	-0.03 (-1.47 – 1.42)
6 months postoperative	9.00 (2.302)	8.61 (2.45)	-0.38 (-1.57 – 0.82)
Frailty index			
1 week preoperative	0.33 (0.12)	0.33 (0.08)	0.02 (-0.04 – 0.07)
6 weeks postoperative	0.22 (0.09)	0.22 (0.09)	-0.01 (-0.06 – 0.04)
6 months postoperative	0.23 (0.11)	0.18 (0.10)	-0.04 (-0.10 – 0.01)
EQ5D3L			
1 week preoperative	0.62 (0.16)	0.57 (0.19)	-0.04 (-0.13 – 0.05)
6 weeks postoperative	0.82 (0.16)	0.86 (0.13)	0.04 (-0.04 – 0.12)
6 months postoperative	0.82 (0.16)	0.85 (0.17)	0.02 (-0.06 – 0.11)

*p-value = 0.04; SD, standard deviation; CI, confidence interval; EQ5D3L, European Quality of Life, 5 Dimension 3 Levels; SPPB, Short Performance Physical Battery

Supplementary Table 1: Clinical Outcomes (complete case analyses)

Outcome	Mean (SD)		Mean difference (95% CI)
	Control	Intervention	
Oxford hip score			
1 week preoperative	19.05 (6.65)	16.11(7.72)	-2.94 (-7.46 – 1.57)
6 weeks postoperative	36.35 (7.82)	36.63 (8.09)	0.28 (-4.71 – 5.28)
6 months postoperative	42.70 (4.86)	43.05 (5.10)	0.35 (-2.77 – 3.48)
Oxford knee score			
1 week preoperative	17.20 (8.53)	14.33 (7.02)	-2.87 (-14.40 – 8.67)
6 weeks postoperative	27.80 (8.58)	39.33 (8.14)	11.53 (-0.55 – 23.61)
6 months postoperative	35.60 (6.58)	42.00 (2.65)	6.4 (-1.59 – 14.40)
SPPB			
1 week preoperative	7.20 (2.66)	6.91 (2.81)	-0.29 (-1.86 – 1.27)
6 weeks postoperative	7.48 (2.63)	7.45 (2.81)	-0.03 (-1.58 – 1.53)
6 months postoperative	9.32 (2.29)	8.73 (2.47)	-0.59 (-1.95 – 0.77)
Frailty index			
1 week preoperative	0.30 (0.11)	0.33 (0.09)	0.02 (-0.04 – 0.08)
6 weeks postoperative	0.22 (0.09)	0.22 (0.09)	-0.003 (-0.06 – 0.05)
6 months postoperative	0.21 (0.08)	0.18 (0.10)	-0.03 (-0.09 – 0.02)
EQ5D3L			
1 week preoperative	0.63 (0.16)	0.58 (0.20)	-0.05 (-0.15 – 0.05)
6 weeks postoperative	0.83 (0.15)	0.87 (0.13)	0.04 (-0.04 – 0.12)
6 months postoperative	0.83 (0.16)	0.87 (0.14)	0.04 (-0.05 – 0.13)

SD, standard deviation; CI, confidence interval; EQ5D3L, European Quality of Life, 5 Dimension 3 Levels; SPPB, Short Performance Physical Battery

CHAPTER 6

DISCUSSION AND CONCLUSION

This doctoral thesis examined methodological and interventional issues in research with older adults including attrition, missing data handling and reporting, feasibility trials in patients with frailty. This chapter brings together a summary of the key findings, implications for practice, limitations, and conclusion on the studies included in the thesis.

Attrition

In **Chapter 2**, our exploration of attrition showed a considerably high rate of attrition at 30% for a relatively healthy cohort of postmenopausal women followed for 6 years. In the study, a substantial amount of the participant loss occurred during a gap year in data collection due to funding challenges. The pattern of attrition in the cohort was largely terminal, such that participants who missed a wave of data collection did not return for subsequent waves, despite efforts to reach and retain them. Those who did not complete the study were more likely to be older, current smoker, prefrail or frail, previously hospitalized, white, have lower education and lower quality of life depending on the type of attrition examined. However, older age, frailty and smoking were the only factors consistently associated with higher risks of participant loss for all types of attrition including all-cause, non-death, death, preventable and non-preventable attrition.

***Implications for practice*:** The significance of a longitudinal cohort study heavily relies on the ability to retain a substantial proportion of participants who are representative of the target population[1]. High rates of attrition as observed in our study could jeopardize its validity and generalizability, especially given its selectiveness to certain groups of participants. The use of multiple retention strategies as shown in previous reviews could potentially enhance participant retention[2,3], as opposed to using one approach as was done in this study. Oversampling, inclusion of proxy respondents, logistics support, flexible data collection, and periodic update on study progress are some measures that can mitigate attrition[4-7]. These strategies could

be optimized by tailoring them to the participants with the highest risk of loss such as those who are frail, older, and current smokers as well as continuously reviewing them to identify the most effective approach. In addition, the success of longitudinal cohort studies partly depends on sustained funding to maintain planned data collection flow, as our study showed how much impact unplanned breaks could have on participant retention.

Overall, this study reinforces the importance of examining attrition rates and patterns, as well as comparing the characteristics of completers and non-completers as part of exploratory data analysis. Exploring different types of attrition as we did, provides insights into how risk factors may differ for different reasons for participant loss and the varying level of bias each type of attrition may present; all of which may require different strategies to address in the design of future studies and analysis of the current study. This information is essential for strengthening the quality of evidence in future aging cohort studies.

Missing data handling and reporting

In **Chapter 3**, our survey of the reporting and handling of missing data in 165 longitudinal observational studies of older adults showed that the current practice is inadequate. There is still evidence of incomplete and unclear reporting, arbitrary exclusion of missing observations and failure to assess the stability of results to different assumptions of missingness. Approximately half of the studies included in the review had either no mention or unclear reporting about missing data. Among studies where missing data were reported, the average amount of missing data was nearly 15%. While the methods for handling missing data were described in most of the studies, the most common was complete case analysis, where missing observations were removed from the analysis. Although this method is valid in its own merit, only few studies examined the robustness of the results obtained to other methods for handling missing data.

***Implications for practice*:** Given that older adults have high propensity for drop-out and losses during follow-up[8,9], the issue of missing data should be an important consideration in the statistical analysis of

studies in this population. The current practice as evident in this review falls short of standards per existing guidelines[10,11]. The prevalent use of complete case only to address missing data is insufficient because the analysis relies on the assumption that the missing observations occur randomly and are not related to any specific pattern in the data[12,13]. Further, there is potential for bias where the analytical sample differs meaningfully from the initial sample, an issue that is common in aging studies[9,14]. As such, it is essential to include other methods of missing data handling, especially where the proportion of missing observations is high and there is an indication of non-random missingness[10,12]. While no method can adequately address the bias that could be introduced by missing data, the use of multiple methods could potentially strengthen the validity of the evidence, particularly, where the results remain robust to the methods and underlying assumptions of missingness[12]. Clear reporting of these results and how the missing data were addressed is equally important for transparency, interpretability, and replicability.

Randomized feasibility trial of a multimodal intervention in older adults living with frailty during the COVID-19 pandemic

In **Chapter 4**, we reported the evaluation of the feasibility of a virtually delivered multimodal intervention comprising exercise sessions, nutrition counselling and protein supplementation, medication optimization and social calls compared to social calls only in older adults with frailty during the COVID-19 pandemic. Based on the predefined criteria for the REAIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework used in the evaluation, the results were favorable for reach of participants, adoption across different sources of recruitment, adherence to implementation by study staff, participants adherence to virtual exercise session, and intention to maintain the intervention assessed by a satisfaction survey. The evaluation of clinical outcomes did not show any statistically significant difference between the study arms.

Implications for design of the main study: The study was conducted at the peak of the COVID-19 restrictions when there was a critical need for alternatives to in-person programs. The successful delivery of the purely remote intervention in a challenging time is valuable in the present day without the pandemic, given the large number of older adults living with frailty in Canada[15], and the long wait times for rehabilitation and home care services[16]. Virtual programs provide an option to support the rehabilitation needs of frail persons where access is challenging. There is also the benefit of accommodating more people in group sessions per time. However, some aspects of the intervention package require modification to optimize outcomes, including participants' adherence to recommended home-based exercise, protein supplement consumption, and implementation of the medication review recommendations. Larger trials are required to demonstrate intervention efficacy as our study was not sufficiently powered for statistical analysis. These trials should also consider longer duration to allow for a satisfactory evaluation of sustained behaviour change; recruitment from multiple sources using a variety of strategies for a wider reach of participants; strategies to enhance adherence to unsupervised home exercises and implementation of medication optimization recommendations. Further, the inclusion of an economic evaluation component would provide critical information for policymaking.

Randomized feasibility trial of multimodal prehabilitation in older patients living with frailty awaiting hip or knee replacement

In **Chapter 5**, our evaluation of the feasibility of a prehabilitation program for older adults with frailty scheduled for joint replacement showed success for retention, data completion, adherence to exercise, vitamin D supplements and medication review consultation. Participant recruitment, adherence to protein supplements, aerobic exercise and implementation of medication review recommendation did not meet the prespecified criteria for success. Only the oxford knee score at 6-months post surgery showed a clinically and statistically significant difference in effect between the two study arms. The intervention was safe with only few self-reported adverse events potentially linked to the intervention.

Implications for design of the main study: This study provides evidence that it is feasible to utilise the waiting times for surgery, which has now been prolonged by the recent COVID-19 pandemic[17], as a window of opportunity to prehabilitate older patients with frailty for better post surgical recovery. The few aspects of the study that failed to demonstrate feasibility are potentially modifiable items that could yield better outcomes in future larger trials. For the success of these studies, it is important to consider recruiting from multiple sources, improving exercise accountability strategies, reporting of all prescribed exercises based on the FITT (fitness, intensity, type, and time) principle, tailoring nutritional supplements to individual preferences and profile, as well as directly transmitting the recommendations of medication review consultation to participants family physician.

Strengths and limitations of this thesis

The major strength of this thesis is the utilization of different research methodologies to examine both methodological and interventional issues related to research in older adult populations. It includes a systematic survey of the literature (chapter 2), a secondary data analysis of a cohort study (chapter 3), and two randomized feasibility trials (chapters 4 and 5).

The limitations specific to each study are presented within their respective chapters. However, there were weaknesses that were common across the studies. First, the thesis was largely limited with respect to generalizability and representativeness. For example, studies included in the systematic survey were restricted by language and journal impact factor. Also, the cohort study lacked racial and gender diversity while the feasibility trials did not collect information on race to allow for broader assessment of representativeness and diversity. Second, the age cut-off to define older adults ranged from ≥55 to ≥ 65 years old across the studies in this thesis. These variations in definition could potentially have implications in the application of evidence. Third, varied instruments including frailty index, fried frailty, fit frailty index, clinical frailty scale were used to measure frailty in the studies. While these tools were employed based on

fit-for-purpose – ease of use for eligibility screening and sensitivity to change for analysis, this could introduce subtle differences in the identification and categorization of persons with frailty. Lastly, the studies on interventions in older adults with frailty lacked statistical power to provide definitive evidence on the effectiveness of the interventions.

Conclusion

In summary, this thesis examined some methodological and interventional gaps in research with older adults. It contributes to existing body of evidence by providing insights and considerations to improve the reporting and handling of missing data in longitudinal studies of older adults, retention in aging cohorts, and success of interventions in older adults living with frailty. More research is needed to strengthen the generalizability of the findings and demonstrate the effectiveness of the interventions evaluated.

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