Mechanisms of Ageing and Development 180 (2019) 29–41

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

The impact of physical activity and sedentary behaviors on frailty levels

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ARTICLE INFO

Keywords:
Frail elderly
Exercise
Sedentary lifestyle
Physical activity

ABSTRACT

Heterogeneity in aging can be explained by frailty. Lifestyle behaviors such as physical activity can help manage frailty levels. Conversely, sedentary behaviours are associated with frailty independently of physical activity. Here, we summarize epidemiological and clinical trial evidence concerning the impact of physical activity and sedentary behaviors on frailty levels. We also analysed the National Health and Nutrition Examination Survey (NHANES) data to describe physical activity and sedentary behavior accumulation patterns across frailty levels and their impact on mortality risk. The few prospective and intervention studies demonstrate that higher physical activity levels are associated with a lower incidence of frailty. There are no interventions published which limit sedentary behaviors to manage frailty. Using the NHANES data we demonstrate that individuals are less likely to meet physical activity guidelines and are more likely to accumulate sedentary time in prolonged bouts. Prolonged sedentary bouts and total sedentary time were associated with a higher mortality risk in frail individuals but not in the fit group. Non-bouted sedentary time was not associated with mortality risk. Our review and novel data suggest that there is a need for more intervention studies which focus on increasing physical activity or minimizing sedentary time to manage frailty levels.

1. Introduction

As the population ages, there are a greater number of people living with more health problems which can negatively impact their quality of life and ability to live independently. However, people accumulate health problems at different rates. The concept of frailty is intended to define this heterogeneity in aging. Frailty captures increased vulnerability and susceptibility to poor health outcomes as a result of declining redundancy across multiple physiologic systems (Abellan van Kan et al., 2008). There are multiple ways to capture frailty levels (Buta et al., 2016). The two most popular ways to measure frailty are with the accumulation of deficits model and the frailty phenotype (Fried et al., 2001; Mitnitski et al., 2001). The former views frailty as a state of vulnerability in relation to the accumulation of health deficits quantified by a frailty index (FI). The frailty phenotype views frailty as a syndrome characterized by the loss of strength, walking speed, weight, energy, and physical activity. Despite which frailty tool is used, evidence consistently demonstrates that frailty has a detrimental impact on the health of older adults, including a greater risk of falls, hospitalizations, institutionalization and premature mortality (Clegg et al., 2013; Shamliyan et al., 2013). As such, the identification of frailty and its severity could play an important role in developing and tailoring treatment and prevention strategies to manage frailty.

Regular physical activity participation reduces the risk of developing a number of chronic conditions such as cardiovascular disease, diabetes and some cancers, and also reduces the risk of falls (Aune et al., 2015; Moore et al., 2016; Sattelmair et al., 2011; Sherrington et al., 2017). However, physical activity levels decline with old age and older people tend to sit more and move less in their leisure time (Colley et al., 2011; Troiano et al., 2008). There is burgeoning evidence that spending too much time in sedentary behaviors such as sitting have a negative impact on adverse outcomes independently of physical inactivity. These outcomes include mortality and the development of and death from cardiovascular disease, cancer, and type 2 diabetes (Biswas et al., 2015). In fact, high volumes of physical activity are needed to offset the detrimental impact of excessive sedentary time on mortality risk (Ekelund et al., 2016). Despite the rapid growth of sedentary behavior research, there are relatively few investigations measuring the impact of sedentary behaviors and regular participation in physical activity on frailty levels.

Here, we review epidemiological and interventional studies which examine the relationship between physical activity and sedentary

Abbreviations: LIFE, Lifestyle Interventions and Independence for the Elderly; NHANES, National Health and Nutrition Examination Survey; MVPA, moderate to vigorous intensity physical activity; OR, odds ratio; WHO, World Health Organization

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https://doi.org/10.1016/j.mad.2019.03.004
Received 30 November 2018; Received in revised form 12 March 2019; Accepted 25 March 2019
Available online 26 March 2019
0047-6374/

behaviors with frailty levels. We also present data from the National Health and Nutrition Examination Survey (NHANES) to describe the movement patterns by levels of frailty in a nationally representative sample of community-dwelling middle-aged to older adults living in the United States. We also examine the associations between sedentary time accumulation patterns with mortality risk. Lastly, we provide promising lines of inquiry for future investigation.

2. Physical activity

Physical activity is defined as bodily movement produced by skeletal muscle that significantly increases energy expenditure (World Health Organization, 2018). According to the World Health Organization (WHO), physical inactivity is defined as not meeting the public health recommendations of 150 min/wk of moderate to vigorous intensity physical activity (MVPA) in bouts of at least 10 uninterrupted min (World Health Organization, 2010). With older age, the prevalence of physical inactivity increases dramatically. It is estimated that only 2–5% of North Americans 60 years or older meet the physical activity recommendations (Colley et al., 2011; Troiano et al., 2008). On average, older adults accumulate only 2–12 min per day of MVPA, measured objectively by accelerometry in 10 min bouts or longer (Colley et al., 2011; Troiano et al., 2008). However, if total accumulated MVPA in bouts lasting at least one min is objectively measured, estimates of MVPA increase to 3–28 min/day (Berkemeyer et al., 2016; Evenson et al., 2012). Total accumulated physical activity may be more representative of typical physical activity behaviors in older adults who are less likely to engage in structured physical activity to improve or maintain fitness (i.e., exercise) as they age. Furthermore, recent public health recommendations in the United States recognize the importance of short bouts of physical activity for health benefits (Piercy et al., 2018).

Meeting WHO physical activity recommendations may be challenging with higher levels of frailty. However, few investigations are available which describe the physical activity and sedentary behaviors by levels of frailty (Blodgett et al., 2015; Higueras-Fresnillo et al., 2018). Here, we analyzed accelerometry data from the 2003–2004 and 2005–2006 cycles of the National Health and Nutrition Examination Survey (NHANES). We describe the physical activity and sedentary levels of 2,569 community-dwelling adults aged 50 years or older by frailty levels using a 46-item frailty index that was derived from previous literature (Figs. 1 and 2). Participants spent a minimal amount of their waking hours in MVPA with increasing levels of frailty. Similarly, light intensity physical activity was lower as frailty level increased. For example, individuals who were non-frail spent approximately 40% of their waking hours in light intensity physical activity, whereas the moderately to severely frail groups spent approximately 30% in light activity (Fig. 1).

The majority of participants across frailty levels did not meet the physical activity guidelines of 150 min/wk of MVPA in at least 10 min (Fig. 2). However, there was a dramatic drop in participants meeting the guidelines with higher frailty levels ($p < 0.05$ for all comparisons). A higher proportion of non-frail (35%) and vulnerable (24%) participants met the physical activity guidelines when MVPA was analyzed in total accumulated bouts of at least 1 min compared to 10-min bouted MVPA (15% and 8%, respectively) (Fig. 2). Similarly, while a higher proportion of the mild, moderate, and severely frail groups met the guidelines in total accumulated MVPA (10%, 9%, and 3%, respectively) compared to bouted MVPA (3%, 3% and 1%, respectively), the WHO physical activity guidelines remain largely unattainable in these individuals. Alternatively, accumulating light intensity physical activity may be more feasible for individuals with higher frailty levels, but there are no guideline recommendations provided based on frailty level.

Our review of epidemiological studies suggest an association between physical activity and a lower risk of either developing or mitigating the severity of frailty (Table 1). However, most studies have relied on self-reported measures of activity levels which tend to be less accurate and overestimate true physical activity levels compared to objective measures such as accelerometry (Prince et al., 2008). Studies also demonstrate that there is a dose-response relationship between higher amounts of physical activity and lower frailty levels (Garcia-Esquinas et al., 2015; Graciani et al., 2016; Ribeiro et al., 2016; Savela et al., 2013; Wade et al., 2016a, b; Woo et al., 2010). For example, the odds of incident frailty measured by the phenotypic model was reduced by 6% for every additional 1 MET-h/wk increase in self-reported

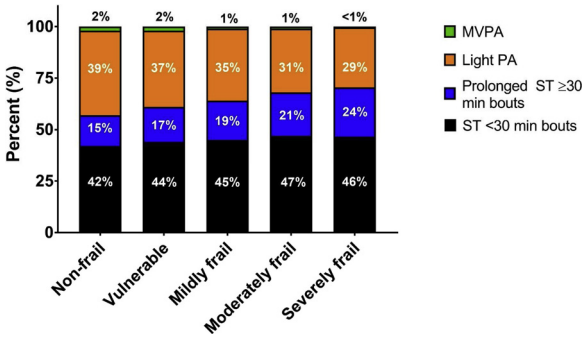

Fig. 1. Percent of waking hours spent in sedentary time, and light and moderate to vigorous intensity physical activity among community-dwelling older adults. Data were obtained from the 2003–2004 and 2005–2006 cycles of the National Health and Nutrition Examination Survey. The sample included community-dwelling adults aged 50 years or older. Accelerometer cut-points for sedentary time were 0–100 counts/min, 101–2019 counts/min for light intensity physical activity, and ≥2020 counts/min for moderate to vigorous physical activity based on previously established cut-points.(Troiano et al., 2008) Frailty index scores (range 0–1) were: Non-frail = 0-0.10 (n = 347); Vulnerable = 0.10-0.20 (n = 909); Mildly frail = 0.20-0.30 (n = 682); Moderately frail = 0.30-0.40 (n = 370); Severely frail = > 0.4 (n = 261). ST = Sedentary time. A one-way ANOVA was completed for each physical activity and sedentary behavior variable to measure differences across frailty levels. P-values were $p < 0.05$ for all comparisons across frailty groups.

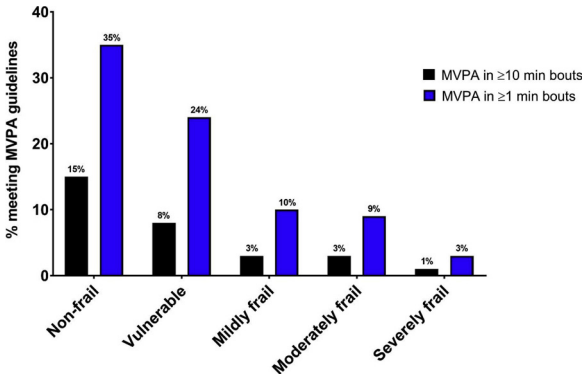

Fig. 2. Proportion of community-dwelling older adults meeting physical activity guidelines by frailty level.
Data were obtained from the 2003–2004 and 2005–2006 cycles of the National Health and Nutrition Examination Survey. Accelerometer cut-points for sedentary time were 0–100 counts/min, 101–2019 counts/min for light intensity physical activity, and ≥2020 counts/min for moderate to vigorous physical activity based on previously established cut-points.(Troiano et al., 2008) The sample included community-dwelling adults aged 50 years or older. Frailty index scores (range 0–1) were: Non-frail = 0-0.10 (n = 347); Vulnerable = 0.10-0.20 (n = 909); Mildly frail = 0.20-0.30 (n = 682); Moderately frail = 0.30-0.40 (n = 370); Severely frail = > 0.4 (n = 261). A Chi-Square Test was completed to compare differences in meeting the physical activity guidelines with bouted and total accumulated MVPA. P-values were < 0.0001 for trend across all frailty groups for bouted and total accumulated MVPA. There were no differences in meeting the guidelines through bouted or total accumulated MVPA in the mildly and moderately frail groups.

Table 1
Association between physical activity and frailty from prospective cohort studies.

Reference ID/sample size	Physical activity measure	Statistical Analysis/Adjustment variables	Frailty tool Frail at baseline/ follow-up	Effect estimates
Ahmad et al., 2018 (n = 1855)	Physical Activity Scale for the Elderly	Multivariable logistic regression Adjustment variables: Age, sex	Frailty phenotype Frailty at baseline/ follow-up: 9.4%/9.8% 1-year follow-up	OR (95% CI) for transitioning to a worse state (robust to pre-frail or frail; pre-frail to frail; active as reference): **3.0 (2.3-4.1)** OR (95% CI) for improving frailty state (frail to robust or pre-frail, or pre-frail to robust; active as reference): **0.3 (0.2-0.4)**
Bouillon et al., 2013 (n = 2707)	Modified Minnesota Leisure-time Physical Activity Questionnaire	Multivariable logistic regression Adjustment variables: Age, sex, parental/sibling history of diabetes, BMI, waist circumference, blood pressure, hypertension therapy, corticoid treatment, smoking status, fruit/vegetable consumption, fasting glucose, HDL cholesterol, Triglycerides	Frailty phenotype Frail at baseline/follow up: 2.8%/not reported Mean follow-up 10.5 years	OR (95% CI) for being frail (active as reference): **2.49 (2.08–2.98)**
Espinoza et al., 2012 (n = 597)	Minnesota Leisure Time Physical Activity Questionnaire	Generalized Estimating Equations Adjustment variables: Age, sex, ethnicity, income, education, comorbid disease, uncomplicated and complicated (macrovascular) diabetes	Frailty phenotype Frail at baseline/follow-up: 9.3%/12.7% Mean follow-up 6.4 years	OR (95% CI) for frailty worsening vs. remaining unchanged or improving at follow up (inactive group as reference): **0.36 (0.25–0.52)**
Garcia-Esquinas et al., 2015 (n = 1750)	Minnesota Leisure Time Physical Activity Questionnaire	Logistic regression Adjustment variables: Age, sex, education level	Frailty phenotype Frail at baseline/follow-up: 0%/6.6% Mean follow-up 3.5 years	OR (95% CI) for incident frailty for every additional 1 MET-h/week increase: **0.94 (0.92-0.96)**
Garcia-Esquinas et al., 2017 (n = 6381)	Not clear	Random effects meta-analysis from logistic regression results of both cohorts Adjustment variables: Age, sex, education, BMI, tobacco consumption, CVD, diabetes, chronic lung disease, osteomuscular disease, total energy intake (Seniors-ENCRICA only), MEDAS index (Seniors-ENCRICA only).	Frailty phenotype Frail at baseline/follow-up: 0%/7.3% in the Seniors-ENRICA cohort and 5.1% in the ELSA cohort Mean follow-up 3.6 years	OR (95% CI) for incident frailty stratified by tertiles of TV viewing time (lowest tertile as reference): **Seniors-ENRICA cohort** 2.1-3 h/day of TV viewing time: *Inactive:* 1.21 (0.71, 2.07) *Active:* 1.09 (0.28, 4.19) > 4 h/day of TV viewing time: *Inactive:* **1.62 (1.01, 2.58)** *Active:* 1.13 (0.29, 4.33) **ELSA cohort** 3.7-5.6 h/day sedentary(women); 3-5 h/day sedentary (men) < *10 MET-h/wk:* 0.84 (0.49, 1.45) *10-16 MET-h/wk:* 1.30 (0.67, 2.53) > *16 MET-h/wk:* 1.04 (0.23, 4.73) > 5.6 h/day sedentary (women); > 5 h/day sedentary (men): < *10 MET-h/wk:* 1.06 (0.63, 1.78) *10-16 MET-h/wk:* 1.41 (0.74, 2.68) > 16 MET-h/wk: **4.89 (1.46, 16.4)**
Graciani et al., 2016 (n = 1745)	Not clear. Responded to a single question of being active or inactive	Cox-regression Adjustment variables: Age, sex, education, alcohol consumption, cancer, obstructive lung disease, osteomuscular disease, depression requiring treatment, IADL limitation, smoking status, healthy diet score, total cholesterol, blood pressure, fasting glucose	Frailty phenotype Frail at baseline/follow-up: 0%/6.7% Mean follow-up 3.5 years	HR (95% CI) for time to mortality compared to being inactive: Intermediate active: **0.60 (0.37-0.97)** Ideal active: **0.49 (0.24-0.97)**
Peterson et al., 2009 (n = 2964)	Modified Minnesota Leisure Time Physical Activity Questionnaire	Generalized estimating equation logistic Regression models using an autoregressive covariance structure Adjustment variables: Age, sex, race, education, marital status, smoking status, drinking status, waist circumference, and count of diagnoses	Combined gait speed and chair stand Frail at baseline/follow-up: 0%/13.0% moderately frail; 3.0% severely frail Up to 5 years follow-up	ORs (95% CI) for incident moderate or severe frailty by activity category: Volume (recommended amount as reference): Low dose: 1.03 (0.83-1.28) Intensity (vigorous activity as reference): Sedentary: 1.10 (0.75-1.63) Light: 1.48 (0.88-1.59) Moderate: 0.91 (0.65-1.28) Activity type (exercise as reference): Sedentary: 1.45 (1.04-2.01) Lifestyle active: 1.08 (0.83-1.41) ORs (95% CI) for incident severe frailty in moderately frail at baseline (n = 410): Volume (recommended amount as reference): Low dose: 0.97 (0.55-1.70) Intensity (vigorous activity as reference): Sedentary: 1.47 (0.58–3.73)

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Table 1 (*continued*)

Reference ID/sample size	Physical activity measure	Statistical Analysis/Adjustment variables	Frailty tool Frail at baseline/ follow-up	Effect estimates
				Light: 1.31 (0.58–2.95) Moderate: 0.66 (0.22–1.98) Activity type (exercise as reference): Sedentary: 2.80 (0.98–8.02) Lifestyle active: **2.81 (1.22–6.43)**
Ribeiro et al., 2016 (n = 432)	Yale Physical Activity Survey	Residual change score linear regression Adjustment variables: Age, sex, frailty scores at baseline, fruit and vegetable intake, all physical activity variables	FRAIL Scale Frail at baseline/follow-up: Not reported/Not reported Up to 6 years follow-up	β-coefficients (SE) for FRAIL scale residual change scores: Leisure walking: **−0.04 (0.01)**
Rogers et al., 2017 (n = 8649)	Not clear. Responded to a single question regarding level/intensity of activity.	Multilevel growth curve models Adjustment variables: Main effects for survey wave, age, cohort (divided into 5 year age groups), baseline PA; two way interaction terms (wave x age cohort; wave x PA; age cohort x PA); and three-way interactions (age cohort x wave x PA). Quadratic term added for time and age	56-item frailty index Frail at baseline/follow-up: 0%/Not reported Mean follow-up 10 years	β-coefficient (95% CI) for trajectories of frailty using the two-way interaction term for survey wave and PA for each 5-year age group (sedentary group as reference): 50-54 years: *Mild:* -0.006 (-0.017, 0.016) *Moderate:* **-0.021 (-0.036, -0.007)** *Vigorous:* **-0.031 (-0.046, -0.016)** 55-59 years: *Mild:* 0.009 (-0.007, 0.026) *Moderate:* **-0.009 (-0.024, 0.005)** *Vigorous:* **-0.025 (-0.040, -0.011)** 60-64 years: *Mild:* 0.013 (-0.004, 0.030) *Moderate:* -0.007 (-0.021, 0.008) *Vigorous:* **-0.019 (-0.035, -0.004)** 65-69 years: *Mild:* -0.008 (-0.024, 0.008) *Moderate:* **-0.034 (-0.047, -0.021)** *Vigorous:* **-0.040 (-0.054, -0.027)** 70-74 years: *Mild:* **0.001 (-0.017, 0.018)** *Moderate:* **-0.028 (-0.044, -0.012)** *Vigorous:* **-0.036 (-0.053, -0.019)** 75-79 years: *Mild:* **-0.005 (-0.015, 0.023)** *Moderate:* **-0.024 (-0.042, -0.007)** *Vigorous:* **-0.044 (-0.062, -0.025)** 80 + years: *Mild:* **-0.014 (-0.031, 0.004)** *Moderate:* **-0.039 (-0.054, -0.023)** *Vigorous:* **-0.061 (-0.081, -0.042)**
Savela et al., 2013 (n = 514)	Not clear. Responded to a single question to categorize activity level.	Multinomial logistic regression Adjustment variables: Baseline age, BMI, smoking status, blood pressure, alcohol consumption, and comorbidity index at follow up	Frailty phenotype Frail at baseline/follow-up: Not reported/ 51.6% pre-frail; 9.3% frail Up to 26 years follow-up	OR (95% CI) for being pre-frail at follow-up (low activity as reference): Moderate activity: 1.00 (0.57–1.78) High activity: 0.57 (0.31–1.03) OR (95% CI) for being frail at follow-up (low activity as reference): Moderate activity: 0.75 (0.32–1.74) High activity: **0.23 (0.08–0.65)**
Song et al., 2015 (n = 1333)	Uniaxial accelerometer (Actigraph GT1M)	Discrete-time survival regression by applying a generalized linear model Adjustment variables: Age, gender, race, marital status, education, income, BMI, comorbidity, depressive symptoms, knee and hip osteoarthritis, knee and hip symptoms, general pain, smoking status, alcohol consumption	Combined gait speed and chair stand Frail at baseline/follow-up: 0%/20.7 per 1000 person years over 2- year follow-up	HR (95% CI) for every additional h/day increase in moderate intensity physical activity for onset of frailty: 0.18 (0.02-1.73)
Lanziotti Azevedo da Silva et al., 2015 (n = 200)	Minnesota Leisure Time Physical Activity Questionnaire	Unclear. Manuscript indicates a multinomial regression but data presented as though it is logistic regression Adjustment variables: Unclear. Models are at least adjusted for age and sex.	Frailty phenotype Frail at baseline/follow-up: 13.5%/14.0% Up to 13 months follow-up	OR (95% CI) for those who improved their frailty score at follow-up (frail to pre-frail, frail to non-frail, pre-frail to non-frail) based on having low activity at baseline (reference is active group): **0.34 (0.15-0.76)** OR (95% CI) for those who had a worse frailty score at follow up (non-frail to frail, non-frail to pre-frail, pre-frail to frail) based on low activity

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Table 1 (*continued*)

Reference ID/sample size	Physical activity measure	Statistical Analysis/Adjustment variables	Frailty tool Frail at baseline/ follow-up	Effect estimates
				at baseline (reference is active group): 0.96 (0.38-2.43)
Strawbridge et al., 1998 (n = 574)	Not clear. Responded to a single question to categorize activity levels.	Multivariable logistic regression Adjustment variables: Age, sex, race, education, chronic conditions	Frailty measured by 16 items assessing physical, nutritive, cognitive, and sensory function Frail at baseline/follow-up: Not reported/26.1% Up to 29 years follow-up	OR (no 95% CI reported) for being frail at follow-up (reference group includes those who were always active at each time point) Inactive for one follow up time point: **2.18** Inactive at two or three follow up time points: **1.95**
Wade et al., 2016a (n = 2736)	Physical Activity Scale for the Elderly	Logistic regression and negative binomial regression Adjustment variables: Age, centre, BMI, smoking status, depression, pain status	39-item frailty index Frail at baseline/follow-up: 4.7%/8.0% Mean 4.3 years follow-up	OR (95% CI) for being frail at follow-up for each score of the continuous PASE: **0.99 (0.98-0.99)** Incident rate ratios (95% CI) for being frail at follow-up for each score of the continuous PASE: 0.99 (0.99-1.00)
Wade et al., 2016b (n = 5316)	Allied Dunbar Survey of Fitness	Logistic regression analysis: Age, sex, BMI, smoking status, depressive symptoms, occupation, income, pain status Negative binomial regression analysis: Age, sex, BMI, smoking status, depressive symptoms, occupation, income, pain status, frailty index at baseline	51-item frailty index Frail at baseline/follow-up: 2.9%/6.2% Up to 8 years follow-up	OR (95% CI) for being frail at follow-up (high activity as reference, n = 4601): *Moderate*: **1.71 (1.06-2.76)** *Low*: **3.31 (2.01-5.43)** *Sedentary:* **9.54 (4.94-18.42)** Incident rate ratios (95% CI) for being frail at follow-up (high activity as reference, n = 4733): *Moderate*: **1.13 (1.08-1.17)** *Low*: **1.17 (1.12-1.23)** *Sedentary*: **1.15 (1.04-1.27)**
Woo et al., 2010 (n = 3378)	Physical Activity Scale for the Elderly	Path analysis Adjustment variables: Age, sex, socioeconomic status and living district	47-item frailty index Frail at baseline/follow-up: Not reported/Not reported; frailty measured as a continuous variable Up to 4 years follow-up	Standardized β-regression coefficient (no SE or 95% CI reported) for the log FI and the continuous PASE: **−0.1070**
Xue et al., 2008 (n = 420)	Not reported. Likely based on Minnesota Leisure Time Physical Activity Questionnaire	Discrete-time proportional hazard models Adjustment variables: Age, Race, Education, Comorbidity	Frailty phenotype Frail at baseline/follow-up: 0%/14.0% Up to 7.5 years follow-up	HR (95% CI) for being frail at follow up in those who were inactive at baseline compared to those who were non-frail at baseline: 2.48 (0.93-6.60)
Yuki et al., 2019	Uniaxial accelerometer (Lifecorder; Suzuken, Aichi, Japan)	Generalized estimating equation Adjustment variables: Follow-up year, age, sex, body fat, education, smoking status, energy intake, comorbidity, baseline frailty status	Frailty phenotype Frail at baseline/follow-up: 0%/not reported Mean follow-up 4.2 years over a mean 3.5 visits	OR (95% CI) for light intensity physical activity (< 40.0 min/day vs. ≥ 40.3 min/day): 1.35 (0.82-2.25) OR (95% CI) for MVPA (< 7.5 min/day vs. ≥ 7.5 min/day): **1.80 (1.05-3.09)**

Bolded values are statistically significant ($p < 0.05$).
BMI; body mass index. CI; confidence interval. CVD; cardiovascular disease. ELSA; English Longitudinal Study on Aging. FRAIL scale. Fatigue, Resistance, Ambulation, Illnesses, & Loss of weight Scale. HR; hazard ratio. HDL; high density lipoprotein. IADL; instrumental activities of daily living. MEDAS; Mediterranean diet adherence screener. MET; metabolic equivalent. NS; not significant. OR; odds ratio. PA; physical activity. PASE; physical activity scale for the elderly. RR; relative risk. Seniors-ENRICA; Social Inequalities in Cardiovascular Risk Factors Among Older Adults in Spain. SE; standard error. TV; television.

physical activity after adjusting for age, sex, and education (Garcia-Esquinas et al., 2015). However, the intensity rather than the volume of physical activity may be more protective of frailty (Peterson et al., 2009; Rogers et al., 2017). In fact, regular participation in low intensity activities such as vacuuming and laundry were not associated with frailty at any age (Rogers et al., 2017). Whereas, moderate and vigorous intensity physical activities such as brisk walking, dancing, cycling, or swimming, significantly reduced the rate of frailty progression over a mean 10 year period from middle to older age (Table 1) (Rogers et al., 2017). Another study showed that meeting half of the recommended physical activity guidelines (75–149 min/wk in ≥10 min bouts) was associated with lower frailty levels, providing that the intensity of activity was at least of moderate intensity (β-coefficient: -3.25 (SE: 0.80)) (Kehler et al., 2018a). Also short bouts of objectively measured MVPA lasting less than 10 min were associated with lower frailty levels, independent of meeting the WHO physical activity recommendations with bouted MVPA (accumulating at least 150 min/wk ≥100% β-coefficient: -3.43 (SE: 1.65); accumulating 75–149 min/wk β-coefficient: -4.01 (SE: 1.26)) (Kehler et al., 2018a).

Previous systematic reviews suggest that exercise training interventions improve the health outcomes of frail patients (Apostolo et al., 2018; Chin et al., 2008; Daniels et al., 2008; de Labra et al., 2015; de Vries et al., 2012; Giné-Garriga et al., 2014; Silva et al., 2017; Theou et al., 2011). However, the majority of these systematic reviews do not focus on studies that measure frailty changes with a validated measure. A recent scoping review concluded that exercise training in isolation or as part of a multicomponent intervention provided the most consistent evidence for the treatment or reversal of frailty levels (Puts et al., 2017). The included studies focused on single frailty markers and lacked sufficient sample sizes with adequate power to detect clinically meaningful frailty changes (Puts et al., 2017). This has led other investigators to suggest that frailty is not ready to be used as an outcome measure in clinical trials (Brown and Covinsky, 2018). We searched PubMed to identify studies that used a physical activity intervention to

Table 2
Intervention studies using exercise as a single-component or part of a multicomponent intervention to prevent/reverse frailty.

Reference	Participants	Intervention	Control group(s)	Main outcomes
Cameron et al., 2013	Older adults (≥70 years old; 64.7% females) who were treated by a clinician at a rehabilitation center 100% frail by frailty phenotype	Frequency: 10 home-based physiotherapy sessions over 12 months; prescription of a program to improve mobility and balance and prevent falls 3-5x/wk Intensity: Not reported Time: Not reported Type: Exercises to improve mobility and balance Additional components: the following were provided as needed if meeting individual frailty criteria: dietary assessment and supplementation; referral to psychiatrist; additional intervention based on comprehensive geriatric evaluation Sample size: 120	Usual care provided to patients receiving rehabilitation services. Sample size: 121	-% difference in frailty prevalence between groups **−14.7% (95% CI: -27.0% to -2.4%)** at 12-month follow-up -Mean difference (95% CI) in frailty score between groups **-0.41 (-0.68 to -0.14)** at 12-month follow-up -No specific improvement in any individual frailty criteria
Chan et al., 2012	Community-dwelling older adults (65-70 years; 59.0% female) 13.0% frail by frailty phenotype	Frequency: 3x/wk center-based exercise for 3 months; Intensity: Moderate intensity Time: 60 min/session at center Type: Brisk walking and resistance-band exercises Additional components: Dietary compliance; 6 sessions of problem-solving therapy Sample size: 55	Education booklet on frailty, healthy diets, exercise, and self-coping strategies. Sample size: 56	-Improvement in changing from pre-frail to robust or from frail to pre-frail or robust was 45% in the intervention versus 27% in control group at 3-month follow up (p = 0.008) -No differences at 6 and 12-month follow up -No specific improvement in any individual frailty criteria
Cesari et al., 2015 (LIFE-P study)	Community-dwelling adults 70-89 years old (68.9% female) with low physical activity and increased risk of mobility disability About 23% frail by frailty phenotype (Mean frailty score 1.67 ± 1.1)	Frequency: 3x/week for first 8 wk (centre-based); 2x/wk for wk 9-24 (centre-based); 1-2x/wk (optional) for wk 25-52 (home-based) Intensity: 60-80% max effort (progression) Time: 40-60 min for wk 1-24; wk 25-52 optional time Type: Aerobic (mainly walking), strength (focus on lower extremity w/ ankle weights, flexibility, balance Additional components: None Sample size: 213	Successful aging group: education meetings 1x/wk in small groups for wk 1-26. Education focused on nutrition, medications, foot care, and recommended preventive services Sample size: 211	-Frailty prevalence at 12-month follow up was 19.1% frail in the successful aging group and 10.0% frail in the intervention group (p = 0.01) -Mean difference in frailty criteria **(-0.48 (95% CI: -0.62 to -0.33)** -Only the prevalence of physical inactivity was significantly decreased among frailty criteria
de Souto Barreto et al., 2018	Community-dwelling adults ≥70 years old (64.7% female) with one of the following: memory complaints, limitation in at least 1 IADL, gait speed < 0.8 m/sec 21.2% frail at baseline by frailty index (Mean frailty index score 0.19 ± 0.08)	Frequency: 12 group/centre-based sessions in the first 2 months; 1 h session monthly for up to 3 years Intensity: Not reported Time: 45 min for first 2 months; not reported for remainder of study Type: Seminars on physical activity advice; goal to encourage participants to be active to meet guidelines Additional components: Cognitive training and nutrition counseling Sample size: 816	Omega-3 supplementation plus a placebo Sample size: 821	-No mean differences were observed at any time point up to 3 years. -Mean difference (95% CI) in frailty index for participants attending ≥75% of sessions: **-0.01 (-0.02 to -0.00**) -Frailty incidence risk was lower at 3 year follow up in intervention vs. control group **(HR 0.72 (95% CI: 0.55-0.93)** -Persistent frailty incidence risk at 2 or more time points was lower at 3 year follow up in intervention vs. control group **(HR 0.53 (95% CI: 0.33-.85))**
Jang et al., 2018	Community-dwelling adults ≥65 years old (75% women) 35% frail by frailty phenotype	Frequency: Group-based 2x/wk for 6 months Intensity: Progressively increased (specific intensity not reported) Time: 60 min/session Type: Resistance exercise (20 min/session); balance (20 min/session); aerobic/endurance (20 min/session) Additional components: Nutrition supplementation, supportive psychotherapy if needed, reduction in polyhpharmacy, home hazard reduction Sample size: 187	None. This was a designed-delay study	-OR for reducing frailty at 6 months was **0.08 (95% CI: 0.03-0.18)** -OR for reducing frailty at 12 months was **0.06 (95% CI: 0.02-0.16)**
Kim et al., 2015	Community-dwelling adults ≥75 years old (100% women) 100% frail by frailty phenotype	Frequency: Group-based 2x/wk for 3 months Intensity: Moderate intensity (12-14 on Borg scale) Time: 60 min/session	Placebo only (n = 33) or Milk Fat Globule Membrane only (n = 32)	-OR (95% CI) of reversing frailty at 3 months compared to placebo: 0.90 (0.31-2.62) Milk Fat Globule

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Table 2 (*continued*)

Reference	Participants	Intervention	Control group(s)	Main outcomes
		Type: Resistance-band exercises, additional lower extremity strength exercises, balance and gait training Additional components: One group received a placebo (Exercise + placebo) (n = 33) or Milk Fat Globule Membrane (Exercise + Milk Fat Globule Membrane) (n = 33)		Membrane only; 2.44 (0.89-6.70) Exercise + placebo; **3.12 (1.13-8.60)** Exercise + Milk Fat Globule Membrane -ORs (95% CI) of reversing frailty at 7-month follow up compared to placebo: 1.87 (0.54-6.47) Milk Fat Globule Membrane only; **3.64 (1.12-11.85)** Exercise + placebo; **4.67 (1.45-15.08)** Exercise + Milk Fat Globule Membrane
Maddocks et al., 2016	Outpatients with COPD (mean age 70(10) years; 41% women) attending pulmonary rehabilitation 26% frail by frailty phenotype	Frequency: Centre-based 2x/wk and at least 1x/wk home-based for 8wk Intensity: Up to 80% peak oxygen consumption for aerobic exercise; 60% 1RM for resistance exercise Time: 60 min for supervised sessions Type: Aerobic exercise; lower limb resistance training Additional components: Multidisciplinary education for disease management Sample size: 574	No control group	-Frail patients at baseline had a **2.20 (95% CI: 1.40-3.50)** odds of non-completion compared to non-frail patients −71/115 (61%) of previously frail patients no longer met the phenotype frail criteria
Nagai et al., 2018a	Community-dwelling adults (mean age 81.5; 90% women) 12% frail by frailty phenotype	Frequency: Center-based 2x/wk for 24 weeks Intensity: 50-80% of 1 repetition maximum Time: Not reported Type: Lower extremity resistance exercises Additional components: Accelerometer feedback to increase activity and to reduce sedentary time 10% every 2 wk; motivation/advice from physical trainers Sample size: 20	Resistance exercise training only Sample size: 21	-Greater reduction in frailty phenotype scores in the resistance exercise plus feedback/motivation group versus resistance exercise only (specific data not reported) -Involuntary weight loss and grip strength improved in the resistance exercise plus feedback/motivation group only (specific data not reported)
Ng et al., 2015	Community-dwelling adults 65 years or older (61.4% female) 28% frail by frailty phenotype	Frequency: Group-based 2x/wk for 12 weeks; 12 weeks of home-based exercises Intensity: 60-80% 10 repetition maximum Time: 90 min/session for group-based sessions; not reported for home-based sessions Type: Resistance exercise using functional tasks and major muscle groups; balance training Additional components: Exercise only (n = 48) or combination training with nutritional supplementation and cognitive training (n = 49) for 12 weeks	Placebo (n = 50); Nutrition supplementation only (n = 49); or cognitive training only (n = 50)	-Mean frailty change scores (95% CI) were decreased in all groups except the placebo group: -0.14 (-0.43 to 0.14) placebo group; **-0.63 (-0.92 to -0.34)** nutrition group; **-0.62 (-0.92 to -0.33)** cognitive group**; -0.83 (-1.12 to -0.54)** exercise group; **-0.92 (-1.21 to -0.64)** combination group -OR (95% CI) of reducing frailty criteria compared to placebo group: **2.98 (1.10-8.07)** nutrition group; 2**.89 (1.07-7.82)** cognitive group; **4.05 (1.50-10.8)** exercise group; **5.0 (1.88-13.3)** combination group
Serra-Prat et al., 2017	Community-dwelling phenotypic non-frail and pre-frail adults ≥70 years old (54% female) 0% frail by frailty phenotype	Frequency: 4-7x/wk for 12 months Intensity: Not reported Time: 30-45 min centre-aerobic; 20-25 min mixed exercises Type: Aerobic, resistance exercise, balance and coordination Additional components: Nutrition assessment and recommendations Sample size: 61	Usual care Sample size: 72	-RR (95% CI) of frailty at 12-month follow-up relative to the control group was 0.46 (0.20-1.04) -Age, sex, and lung-disease adjusted OR (95% CI) for frailty at 12-month follow up compared to control group was 0.28 (0.05-1.47)
Tarazona-Santabalbina et al., 2016	Community-dwelling adults ≥70 years old (54% female) who were frail at baseline 100% frail by frailty phenotype	Frequency: Group-based 5x/wk for 24 weeks Intensity: Up to 75% of one repetition maximum for resistance exercises and up to 65% of maximum heart rate for aerobic exercises Time: 65 min/session n Type: Resistance band and ball-based resistance exercise, walking and stepping aerobic exercise, and balance Additional components:	Usual care Sample size: 49	-Mean frailty criteria were significantly reduced to a greater extent in the intervention **(3.6 ± 0.8 pre vs. 1.6 ± 0.6 post)** vs. usual care group (3.8 ± 0.6 pre vs. 3.8 ± 0.3 post)

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Table 2 (*continued*)

Reference	Participants	Intervention	Control group(s)	Main outcomes
Trombetti et al., 2018 (LIFE study)	Community-dwelling adults 70-89 years old (67.2% women) with low physical activity and increased risk of mobility disability 19.7% frail by Study of Osteoporotic Fractures index (mean 0.9 ± 0.8)	None Sample size: 51 Frequency: Centre/group-based 2x/wk for median of 3.5 years Intensity: 60-80% max effort Time: 40-60 min for wk 1-24; wk 25-52 optional time Type: Aerobic (mainly walking), strength (focus on lower extremity w/ ankle weights, flexibility, balance Additional components: None Sample size: 812	Successful aging group: education meetings 1x/wk in small groups for wk 1-26. Education focused on nutrition, medications, foot care, and recommended preventive services Sample size: 811	-Difference in prevalence (95% CI) of frailty was not different between groups at 24-month follow-up (-0.021 (-0.049 to 0.007) - Prevalence of inability to rise from a chair 5 times was lower in the intervention (prevalence difference **-0.05 (95% CI: -0.08 to -0.02)**

Bold values are statistically significant ($p < 0.05$).
CI; confidence interval. COPD; chronic obstructive pulmonary disease. HR; hazard ratio. OR; odds ratio. RR; relative risk.

change frailty scores based on highly cited and validated frailty measures (Table 2) (Buta et al., 2016; Cameron et al., 2013; Cesari et al., 2015; Chan et al., 2012; de Souto Barreto et al., 2018; Jang et al., 2018; Kim et al., 2015; Maddocks et al., 2016; Nagai et al., 2018a; Ng et al., 2015; Serra-Prat et al., 2017; Tarazona-Santabalbina et al., 2016; Trombetti et al., 2018). Studies that used frailty as a part of inclusion/exclusion criteria only were not summarized. The specific frailty tools used in our review were the frailty phenotype, a shortened version of the frailty phenotype using the Study of Osteoporotic Fractures frailty score, and the accumulation of deficits index.

This review showed that the majority (8/12) of the clinical trials have included exercise in combination with other treatments such as education, nutrition supplementation or cognitive training (Table 2) (Cameron et al., 2013; Chan et al., 2012; de Souto Barreto et al., 2018; Jang et al., 2018; Kim et al., 2015; Maddocks et al., 2016; Ng et al., 2015; Serra-Prat et al., 2017). The studies were generally conducted in community-dwelling older adults of at least 65 years of age, with the exception of one trial conducted with participants who were recently hospitalized (Cameron et al., 2013) and another study in patients with chronic obstructive pulmonary disease attending outpatient pulmonary rehabilitation (Maddocks et al., 2016). The prevalence of frailty at baseline ranged from 0% (Serra-Prat et al., 2017) to 100% (Cameron et al., 2013; Kim et al., 2015; Tarazona-Santabalbina et al., 2016). The frequency of the exercise-based interventions ranged from 12 weeks (Chan et al., 2012; Kim et al., 2015) to longer than three years (de Souto Barreto et al., 2018; Trombetti et al., 2018). The interventions were mainly centre-based and conducted in groups (Cesari et al., 2015; Chan et al., 2012; de Souto Barreto et al., 2018; Kim et al., 2015; Nagai et al., 2018a; Ng et al., 2015; Tarazona-Santabalbina et al., 2016; Trombetti et al., 2018). Some of the centre-based trials provided a home-based component to replace some or all of the center-based sessions (Cesari et al., 2015; Ng et al., 2015; Trombetti et al., 2018). The intensity of exercise (both aerobic and resistance-based exercise) was generally prescribed at a low to moderate intensity. Studies used either resistance training only (Nagai et al., 2018a; Ng et al., 2015) or combined aerobic training with resistance and/or balance training (Cameron et al., 2013; Cesari et al., 2015; Chan et al., 2012; Jang et al., 2018; Kim et al., 2015; Serra-Prat et al., 2017; Tarazona-Santabalbina et al., 2016; Trombetti et al., 2018) for the exercise components. One provided physical activity guidance to meet the physical activity guidelines (de Souto Barreto et al., 2018).

In general, these clinical trials demonstrate that the prevalence of frailty, or frailty levels, were reduced to a greater extent in the intervention versus control groups (10/12 trials demonstrated a benefit). Trials that used a combination of therapies showed that groups who received exercise therapy were more effective at managing frailty levels compared to groups not receiving a component of exercise.

Here, we summarize the larger randomized clinical trials to date. The pilot study of the Lifestyle Interventions and Independence for the Elderly intervention (LIFE-P) demonstrated that moderate intensity aerobic exercise training reduced the number of phenotypic frailty criteria to a greater extent in the intervention versus control group. Furthermore, the prevalence of frailty was lower in the intervention versus control group participants at 12-months of follow-up (Cesari et al., 2015). However, a secondary analysis of the larger LIFE study (n = 1,635) showed no differences in the prevalence of frailty between the intervention and control groups over 3.5-year follow up (Trombetti et al., 2018). It is possible that the shortened version of the frailty phenotype, the Study of Osteoporotic Fractures frailty tool, did not fully capture physical frailty. Even so, the prevalence of the inability to rise from a chair 5 times (a component of the frailty tool) was reduced to a greater extent in the intervention group compared to control group participants. The Multidomain Alzheimer's Preventive Trial, which used physical activity guidance in combination with cognitive training and nutrition counseling, found no differences in frailty levels measured with a frailty index between the intervention and control group (de

Souto Barreto et al., 2018). In contrast, those who attended at least 75% of the physical activity advice sessions had a significant reduction in frailty levels compared to the control group (de Souto Barreto et al., 2018). Frailty incidence, defined as a frailty index score of ≥0.25, was also significantly reduced in the intervention relative to the control group. Collectively, these studies suggest that frailty can be prevented or reversed with exercise training.

3. Sedentary behavior

As people age, they tend to spend more of their waking hours in sedentary pursuits. Sedentary behavior is defined as low energy expenditure (< 1.5 Metabolic Equivalents) activities during waking hours while in a seated, reclining, or lying position (Tremblay et al., 2017). In contrast to physical activity, self-reported measures of sedentary time tend to underestimate true sedentary time in older adults (Copeland et al., 2017). A study in the United States demonstrates that community-dwelling older adults 60 years or older spend between 60–70% (approximately 8–11 h/day) of their day sedentary (Evenson et al., 2012; Matthews et al., 2008). Most of this sedentary time is spent watching television or at a computer (Vallance et al., 2016). A systematic review identified that populations consisting primarily of community-dwelling older adults are sedentary for 9.4 h per day (Harvey et al., 2015). Sedentary time is even higher in nursing homes and in hospitalized patients; these patients spend about 85% (Marmeleira et al., 2017; Parry et al., 2018) and up to 95% (Baldwin et al., 2017) of their waking hours either seated, reclining, or in bed, respectively.

The evidence is limited regarding sedentary behaviors in relation to frailty levels. A study of community-dwelling older adults demonstrates that the frailest community-dwellers spent 9.5 h per day sedentary compared to 8.2 h amongst those who were non-frail (Blodgett et al., 2015). Our analysis of the 2003–2004 and 2005–2006 NHANES cycles align with these previous findings (Fig. 1). Specifically, 57%, 61%, 64%, 68%, and 70% of waking hours were spent sedentary in the non-frail, vulnerable, mildly frail, moderately frail, and severely frail groups, respectively ($p < 0.05$ for all comparisons). With increasing frailty levels, individuals replaced non-bouted sedentary time with prolonged, uninterrupted sedentary bouts lasting at least 30 min during waking hours (non-frail: 15%; vulnerable: 17%; mildly frail: 19%; moderately frail: 21%; severely frail: 24% of awake time were in prolonged sedentary bouts; $p < 0.05$ for all comparisons). Prolonged sedentary bout accumulation may be more detrimental than non-bouted sedentary accumulation, as previous studies suggest that longer sedentary bouts are associated with higher frailty levels (discussed later).

To date, there are no clinical trials which have examined the impact of reducing sedentary time on frailty levels, which means that the impact of sedentary behaviors on frailty rely on epidemiological evidence. A recent systematic review of 16 observational studies demonstrated that high levels of sedentary time have an independent, deleterious association with frailty (Kehler et al., 2018b). Of the seven studies which adjusted for physical activity in their statistical models (Blodgett et al., 2015; Castaneda-Gameros et al., 2017; Eyigor et al., 2015; Garcia-Esquinas et al., 2017; Kehler et al., 2018a; Ribeiro et al., 2016; Song et al., 2015), six studies revealed an independent association between high levels of sedentary time and a higher frailty prevalence or greater frailty levels (Blodgett et al., 2015; Castaneda-Gameros et al., 2017; Garcia-Esquinas et al., 2017; Kehler et al., 2018a; Ribeiro et al., 2016; Song et al., 2015). These data suggest that physical activity levels may not fully attenuate the detrimental association between high amounts of sedentary behaviors and frailty.

Prolonged, uninterrupted sedentary bouts may have a more deleterious association with frailty than total sedentary time. A higher proportion of sedentary time spent in prolonged sedentary bouts lasting at least 10 min was associated with higher frailty levels independent of age, sex, and comorbidities in a cohort of community-dwelling and institutionalized older adults (β-coefficient: 0.16 (95% CI: 0.08-0.23); $p < 0.05$) (del Pozo-Cruz et al., 2017). The association with prolonged sedentary time was stronger than total sedentary time. A cross-sectional study demonstrated that prolonged sedentary bouts lasting at least 30 min are associated with higher frailty scores, measured with a 46-item frailty index (β-coefficient: 1.14 (SE: 0.30); $p < 0.001$) (Kehler et al., 2018b). This significant association was robust after controlling for age, sex, demographics, total sedentary time, and MVPA which suggests that breaking up prolonged bouts of sedentary time may be protective from higher frailty levels.

Replacing sedentary time with physical activity is associated with reducing frailty levels (Mañas et al., 2018; Nagai et al., 2018b). One study used an isotemporal substitution linear regression model to demonstrate that replacing 30 min per day of sedentary time with 30 min of light intensity physical activity was not associated with reducing frailty levels, as measured with the Frailty Trait Scale (Mañas et al., 2018). In contrast, replacing 30 min of sedentary time with 30 min of MVPA was significantly associated with a lower frailty score, independent of age, sex, demographics, physical function, and comorbidities (β-coefficient: -2.46 (95% CI: -3.78 to -1.14); $p < 0.01$). While light intensity physical activity was not associated with frailty levels in the entire cohort of the study, replacing 30 min of sedentary time with light intensity was independently associated with a lower frailty score (β-coefficient: -0.57 (95% CI: -1.05 to -0.09); $p < 0.05$) in patients with comorbidities (Mañas et al., 2018). Furthermore, another cross-sectional study showed that the odds of phenotypic frailty was lower when replacing 30 min of sedentary time with light intensity physical activity (OR: 0.85 (95% CI: 0.80-0.92); $p < 0.05$) (Nagai et al., 2018b). These data suggest that light intensity physical activity is a possible target to manage frailty in those with the highest levels of frailty.

The impact of sedentary time on adverse outcomes may be different across levels of frailty. High levels of sedentary time were not associated with mortality risk in the most fit group (least frail), measured by a frailty index (HR: 0.90 (95% CI: 0.70–1.14); p = NS) (Theou et al., 2017). This non-significant association remained irrespective of meeting the WHO physical activity guidelines. However, for participants who were vulnerable (HR: 1.14 (95% CI:1.01–1.28); $p < 0.05$), mildly frail (HR: 1.31 (95% CI: 1.14–1.50); $p < 0.05$) or moderately to severely frail (HR: 1.35 (95% CI: 1.21–1.50), there was a dose-response association between higher levels of sedentary time and all-cause mortality. The detrimental impact of sedentary time was attenuated amongst patients who met the physical activity guidelines. These data suggest that high amounts of physical activity are needed to offset the deleterious effects of sedentary behaviors for premature mortality risk.

In this paper, we extend these findings by comparing the associations between prolonged sedentary bouts, non-bouted sedentary time, and total accumulated sedentary time with all-cause mortality from NHANES 2003-04 and 2005-06 data (Fig. 3). Neither sedentary time accumulation pattern was associated with mortality in the non-frail group. The highest tertile of prolonged sedentary bouts for the vulnerable (218.0 (3.8) min/day), mild (248.1 (5.5) min/day), moderate (277.7 (7.2) min/day), and severe (321.0 (11.5) min/day) frailty groups had the lowest survival compared to the lower prolonged sedentary tertile group (Supplemental Table contains tertiles of sedentary patterns across frailty levels). Similarly, the highest tertile groups for total sedentary time had the highest risk of mortality in the vulnerable (678.4 (5.4) min/day) to severely frail (785.1 (10.4) min/day) groups. In contrast, non-bouted sedentary time was not associated with mortality risk in any frailty group. In a Cox-Proportional Hazards regression model, these findings were robust after controlling for age, sex, meeting the WHO physical activity guidelines, and accelerometer wear time (Table 3). The strength of the association with mortality risk was slightly higher for total sedentary time compared to prolonged sedentary time. These data suggest that prolonged sedentary bouts are a main driver of mortality risk with sedentary behaviors. Indeed, interventions

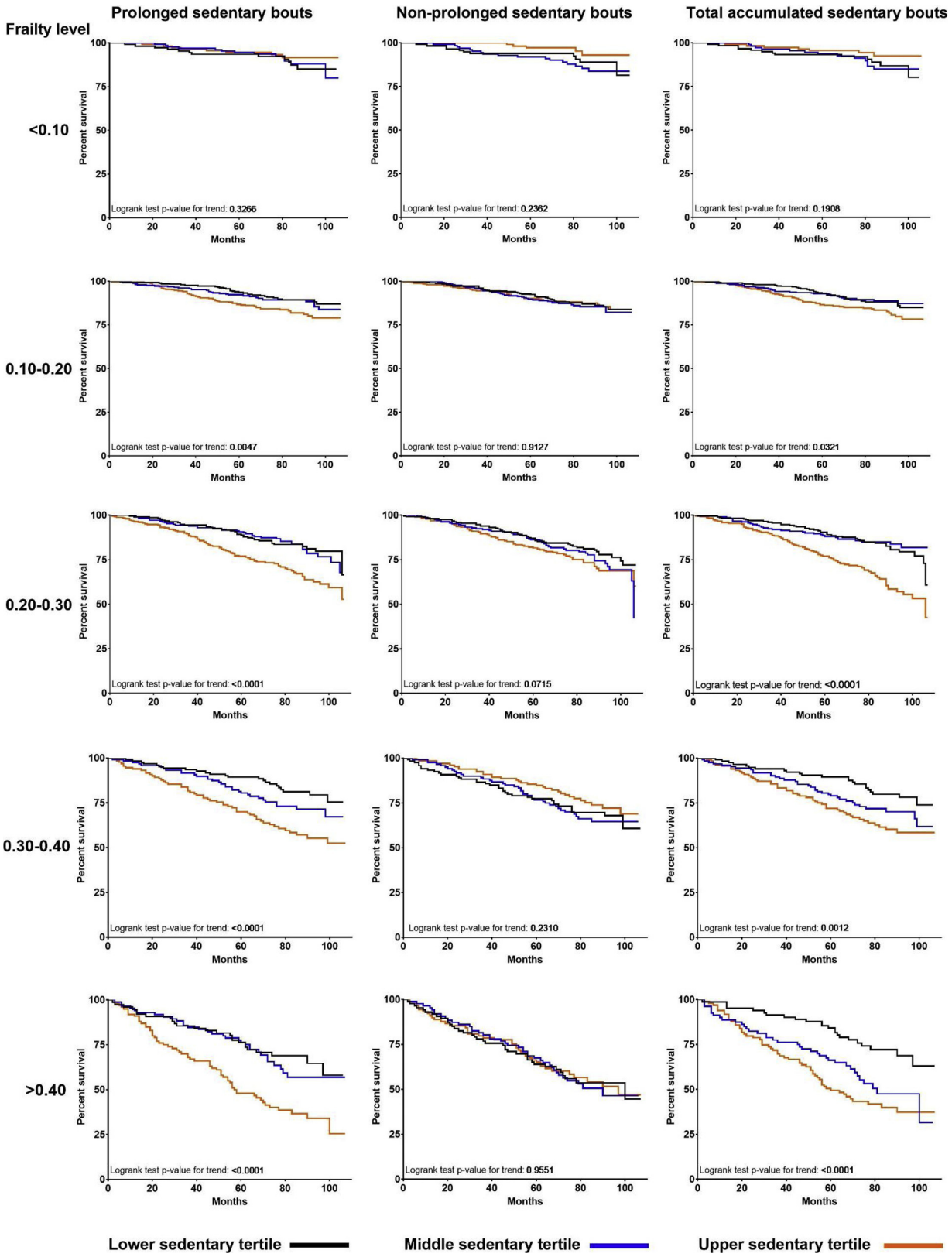

Fig. 3. Kaplan-Meier curves showing the association between sedentary behavior accumulation patterns and time to death in relation to frailty levels.

should target prolonged periods of sedentary behaviors (e.g., bed rest, prolonged sitting).

4. Future investigations

Despite the promising outcomes from the exercise trials, providing recommendations for exercise regimens that prevent or reverse frailty levels is a challenge. For example, there is significant variability in the

Table 3
Hazard ratios for the association between sedentary accumulation pattern variables with mortality by frailty levels.

	Frailty level				
Variable	< 0.10	0.10-0.20	0.20-0.30	0.30-0.40	> 0.40
Time spent in prolonged sedentary bouts (per 30 min/day)	1.00 (0.81-1.23)	1.06 (0.96-1.61)	1.14 (1.06-1.23)	1.08 (1.00-1.17)	1.12 (1.06-1.18)
Time spent in non-bouted sedentary time (per 30 min/day)	0.95 (0.75-1.21)	1.05 (0.90-1.22)	1.15 (0.91-1.29)	0.97 (0.85-1.11)	1.00 (0.90-1.11)
Total sedentary time (per 30 min/day)	0.98 (0.82-1.17)	1.06 (0.96-1.17)	1.23 (1.12-1.34)	1.08 (1.01-1.17)	1.19 (1.08-1.31)

Data are hazard ratios (95% CI). Cox proportional hazards models are adjusted for age, sex, meeting the physical activity guidelines, and accelerometer wear time.

frequency, intensity, time, and type of exercise used across the studies. It is also difficult to conclude whether physical activity was the main driver of reducing the prevalence or severity of frailty when interventions combined other forms of therapy. The intervention studies highlighted in Table 2 suggest that longer duration interventions of at least 6 months, performed 2-3x/wk for at 45–60 min/session are optimal for reducing or preventing frailty, but further investigation to establish these recommendations is needed. Furthermore, supervised group and centre-based training was a primary mode of delivery in the exercise studies; this type of training may help with adherence to the exercise training regimens and to support individuals to learn the skills needed to increase or maintain exercise levels. The efficacy and safety of high-intensity interval training, where a short period of vigorous or very vigorous exercise is interspersed with low to moderate intensity exercise (Weston et al., 2014), to improve frailty levels is also a worthwhile investigation. This mode of exercise training is shown to reduce phenotypic frailty in aged mice over a 16-week period (Seldeen et al., 2018), but its impact on humans in relation to frailty has yet to be realized.

Most of the exercise clinical trials to date have focused on changes in physical frailty using the phenotypic frailty model (Cameron et al., 2013; Cesari et al., 2015; Chan et al., 2012; de Souto Barreto et al., 2018; Nagai et al., 2018a; Ng et al., 2015; Tarazona-Santabalbina et al., 2016; Trombetti et al., 2018) (or a simpler version (Trombetti et al., 2018)). This frailty tool includes measures of slow walking, muscle weakness, fatigue, low physical activity, and unintentional weight loss (Fried et al., 2001). While this tool provides information on changes to physical frailty, it may not fully capture the complexity of frailty and aging. Measuring frailty across multiple physiologic systems with a frailty index may provide further insight into the impact of exercise on frailty levels.

There is a limited understanding of the biological mechanisms associated with exercise, sedentary behaviors, and frailty. In particular, it is unclear whether there are unique or independent effects of sedentary behaviors on frailty levels beyond those of physical inactivity. Frailty is associated with the activation of inflammatory pathways; inflammation can dysregulate nearly every organ system (Ferrucci and Fabbri, 2018; Walston et al., 2002). In contrast, exercise training, both aerobic and resistance exercise, may reduce levels of systemic inflammation (Monteiro-Junior et al., 2018; Sardeli et al., 2018). However, the impact of sedentary behavior on inflammatory cytokine profiles needs to be elucidated (Wirth et al., 2017). Sedentary behaviors negatively impair lipid and glucose metabolism and dysregulate lower extremity hemodynamics independent of physical inactivity (Hamilton et al., 2004; Tremblay et al., 2010). Undermining the normal function of these processes may lead to a low-grade inflammatory state and subsequent increase in frailty levels.

Many researchers have studied the association between individual biological markers with frailty. However, it is unclear if a single biomarker can be used to define frailty levels (Cardoso et al., 2018). A motivating line of inquiry is to investigate the impact of exercise and sedentary behavior levels on the accumulation of subcellular deficits, which address subclinical dysfunction in multiple aging pathways. A frailty index can be developed solely from laboratory tests and has been shown to predict adverse outcomes (Howlett et al., 2014; Mitnitski et al., 2015). Intriguingly, subclinical deficits are observable even before there are any clinically observable health problems (Blodgett et al., 2016). Discovering if increasing physical activity or reducing sedentary levels can be used as a countermeasure to the accumulation of biological markers associated with aging and frailty will improve our understanding of the role of these health behaviors in treating and preventing the onset of frailty.

5. Conclusion

There is an emerging literature that physical activity can significantly reduce the prevalence or severity of frailty. However, evidence from clinical trials is scant especially regarding frailty measures that capture dysregulation across multiple organ systems. Spending less time in sedentary pursuits confer a protective association with frailty, however there are no clinical trials to date to confirm the findings from epidemiological studies. Experimental evidence which examine the impact of exercise and/or sedentary time on the accumulation of subcellular deficits is needed to better understand how these interventions may prevent or delay the onset of clinically observable health problems.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mad.2019.03.004.

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