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Pathways from physical frailty to activity limitation in older people: identifying moderators and mediators in the English Longitudinal Study of Ageing

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Abstract

Physical frailty increases the risk of future activity limitation, which in turn, compromises independent living of older people and limits their healthspan. Thus, we seek to identify moderators and mediators of the effect of physical frailty on activity limitation change in older people, including gender- and age-specific effects. In a longitudinal study using data from waves 2, 4, and 6 of the English Longitudinal Study of Ageing, unique physical frailty factor scores of 4,638 respondents aged 65 to 89 years are obtained from confirmatory factor analysis of physical frailty, which is specified by three indicators, namely slowness, weakness, and exhaustion. Using a series of autoregressive cross-lagged models, we estimate the effect of physical frailty factor score on activity limitation change, including its moderation by social conditions, and indirect effects through physical and psychological conditions. We find that the effect of physical frailty on activity limitation change is significantly stronger with older age, while it has significant indirect effects through low physical activity, depressive symptoms, and cognitive impairment. In turn, indirect effects of physical frailty through low physical activity and cognitive impairment are stronger with older age. Sensitivity analyses suggest that these effects vary in their robustness to unmeasured confounding. We conclude that low physical activity, depressive symptoms, and cognitive impairment are potentially modifiable mediators on pathways from physical frailty to activity limitation in older people, including those who are very old. This evidence offers support for population-level interventions that target these conditions, to mitigate the effect of physical frailty on activity limitation, and thereby enhance healthspan.

Key words

Disability, pathways, physical activity, depression, cognition, cross-lagged

1. Introduction

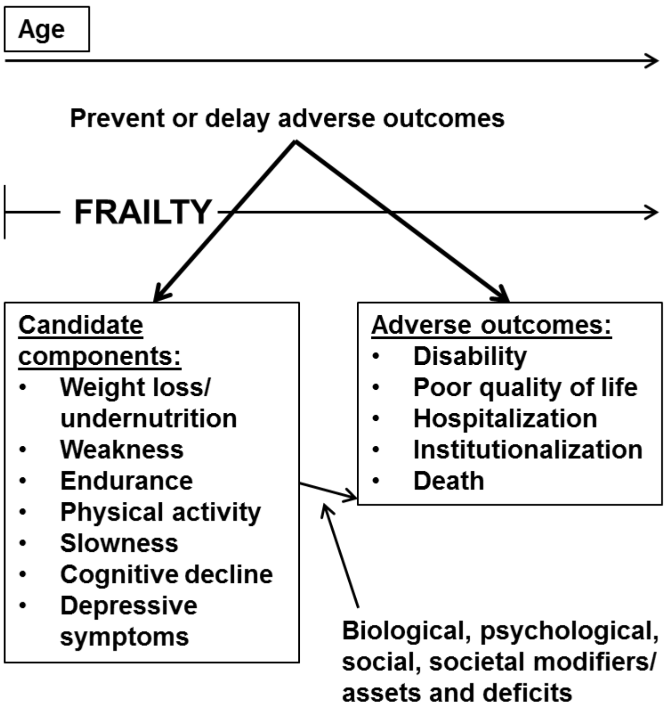
Frailty is widely regarded as the multidimensional loss of an individual's body system reserves which results in vulnerability to developing adverse health-related outcomes (Espinoza & Walston, 2005; Lally & Crome, 2007; Pel-Littel et al., 2009), such as death, disability, falls, hospitalization, and institutionalization (Daniels et al., 2012; Ensrud et al., 2009; Ensrud et al., 2008; Jones et al., 2005; Kiely et al., 2009; Pilotto et al., 2012; Woo et al., 2012). Across a spectrum of definitions applied, the prevalence of frailty is estimated to be about 10% among people aged 65 years or older (Collard et al., 2012). The potential adverse outcomes of frailty and its size of problem combine to create significant health and social impact for ageing populations. Consequently, frailty plays a central role in influencing the well-being of older people and holds major public health importance (Woo et al., 2006).

As an adverse outcome of frailty, functional disability reduces the quality of life in older people (Murphy et al., 2007 ; Walker & Lowenstein, 2009). The latest WHO classification of disability defined three levels of functioning. They are impairment, activity limitation, and participation restriction (ICF, 2002). Typically, activity limitation is measured in terms of needing assistance in basic and instrumental activities of daily living (BADL and IADL). BADL items include bathing, dressing, toileting, transferring, feeding and walking (Katz et al., 1963). Activity limitation exerts a negative impact on older people. Those with increasing levels of activity limitation have lower levels of well-being, which manifests as higher prevalence of depression, less life satisfaction, poorer quality of life, and more loneliness, even after stratifying for age (Demakakos et al., 2010). Moreover, activity limitation compromises healthspan, which is measured by length of healthy life (Crimmins, 2015), and is equally if not more important than lifespan for many older people.

Frailty and functional disability, represented by activity limitation, are considered distinct entities with some degree of overlap (Fried et al., 2004). More importantly, frailty indicators predict future activity limitation in terms of BADL and IADL dependence among community-dwelling older people (Avila-Funes et al., 2008; Gobbens et al., 2012b; Romero-Ortuno et al., 2011; Vermeulen et al., 2011). However, the precise mechanisms by which frailty exerts this effect are less clear. There is sparse knowledge on pathways from frailty to eventual activity limitation. Better understanding of these pathways including the identification of moderators and mediators on them can inform public health and social policy with respect to organizing effective population-level interventions that could potentially minimize the impact of frailty where it already occurs. This may in turn slow down or even delay the onset of activity limitation in older people.

To conceptualize pathways from frailty to activity limitation, a good starting point is the working framework proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) which is simplified and has its relevant portion shown in Figure 1. Biological, psychological, social, and societal assets and deficits are represented as moderators on pathways to adverse outcomes which include disability. These assets and deficits represent potential target conditions for intervention to reduce the negative impact of frailty. More recently, the integral concept of frailty (Gobbens et al., 2010b) incorporated a similar set of frailty pathways adapted from those of the Canadian working framework. Other frailty pathways have also been proposed, but are largely restricted to the biological sphere, and are therefore less suitable for a broader investigation of the effects of frailty. Thus, the Canadian working framework offers a useful foundation on which to build a conceptual model for pathways from frailty to activity limitation.

Figure 1. Working framework of the Canadian Initiative for Frailty and Aging: frailty to its adverse outcomes (adapted from Bergman, 2004 with modifications)

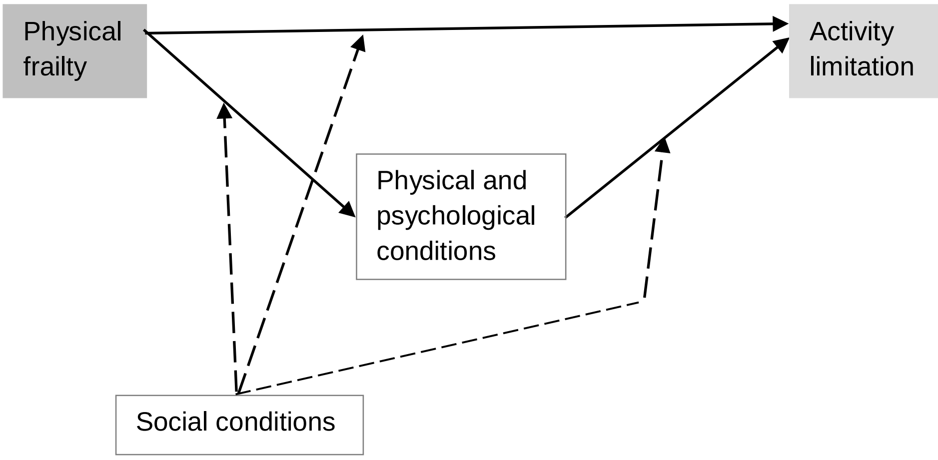


With the basis for a conceptual model of frailty pathways available, the challenge is then to identify a frailty specification which is suitable for investigation of these pathways. In his seminal work, Strawbridge recognized the multidimensional nature of frailty and conceptualized frailty as involving problems in at least two from among physical, nutritive, cognitive, and sensory domains (Strawbridge et al., 1998), More recently, the view of frailty being multidimensional has been expressed in part through the development of frailty identifiers that measure deficits across more than a single domain (Bielderman et al., 2013; Gobbens et al., 2010b; Rockwood, 2005). However, some of these multidimensional elements in these frailty specifications, including those components in the Canadian working framework in Figure 1, are also hypothesized to be key conditions on pathways from frailty to its adverse outcomes. Having these elements as part and parcel of the frailty specification complicates the task of teasing out the relationship between frailty and these key deficits. As an alternative, the integral concept of frailty explicitly specifies frailty as having three distinct domains namely physical, psychological, and social (Gobbens et al., 2010a). Being able to specify frailty on the basis of a single domain facilitates its disentanglement from conditions related to the other two domains. This in turn facilitates less constrained exploration of the relationship of frailty with multidimensional conditions which may turn out to be mediators or moderators on its effect.

Among these three frailty domains, physical frailty offers the most promising choice as a frailty specification for the investigation of related pathways. There are a number of reasons for this. Firstly, physical frailty is far better understood than psychological or social frailty. Secondly, physical frailty contributes most to prediction of disability among the three frailty domains (Gobbens et al., 2012a). Finally, there exists an excellent prototype for physical frailty in the CHS frailty phenotype (Fried et al., 2001). It conceptualizes physical frailty has having five indicators, which are slow walking speed, weak grip strength, self-reported exhaustion, unintentional weight loss, and low physical activity level. However, exercise as a counter of low physical activity, is a modifier of frailty's effect (Daniels et al., 2008). Thus, given that low physical activity is a lifestyle condition on pathways from frailty to its adverse outcomes, it may be argued that it should be excluded from the set of indicators for a physical frailty specification implemented for examining its relationship with activity limitation. On the other hand, the other four indicators are either symptoms or physical measurements that are not considered to be conditions on frailty pathways which need to be excluded from being a physical frailty indicator. Indeed, our previous work argues that specifying physical frailty with three of the five indicators, namely slow walking speed, weak grip strength, and exhaustion retains face and content validity. In addition, we demonstrate construct and concurrent validity for this physical frailty specification. Weight loss did not enhance these aspects of validity, and can therefore be omitted from the final set of indicators (Ding, 2016). In the light of these points, physical frailty specified by these three indicators holds promise for the investigation of pathways from frailty to activity limitation.

Our conceptual model for investigating the relationship of physical frailty with activity limitation is shown in Figure 2. In this model, indirect or mediated effects through physical and psychological conditions are included in addition to the direct effect. Furthermore, moderation of these effects by social conditions is also included (dotted lines). We base these hypothesized pathways in part on the Canadian working framework, while advancing beyond to also include indirect effects. These pathways are also consistent with current thinking that posits psychosocial resources as possible moderators and mediators of the effects of frailty (Dent & Hoogendijk, 2015).

Figure 2. Conceptual model for investigation of pathways from physical frailty to activity limitation



Thus, the overarching aim of our study is to identify and estimate the effects of multidimensional conditions which have roles as moderators and mediators of the relationship between physical frailty and future activity limitation in older people. Within this broad aim, we seek to answer three research questions, namely: 1) whether the effect of physical frailty on activity limitation varies across various levels of key social conditions; 2) whether physical frailty has an indirect effect on activity limitation through key lifestyle and psychological conditions; and 3) whether the effects of physical frailty on activity limitation vary across gender and age. To answer these questions, we use longitudinal data from the English Longitudinal Study of Ageing (ELSA).

2. Materials and Methods

2.1 Data

Our study population comprises a cohort of 4,638 older respondents who are aged 65 to 89 years at wave 2 (2004) of ELSA (Marmot et al., 2015). Those aged 90 years and older are excluded given that their age is uniformly coded as "90", and that their number is small. ELSA is a longitudinal survey of a representative sample of the English population aged 50 years and older living in their homes at baseline (Steptoe et al., 2013). It offers a broad range of reliable and multidimensional data across biennial waves beginning from 2002, and is still ongoing. All participants gave informed consent. Ethical approval for ELSA was granted by the Multicentre Research and Ethics Committee. Ethical oversight for this study is provided by procedures of the London School of Economics Ethics Policy.

This is a longitudinal study using data from waves 2, 3, 4, and 6 of ELSA. Data was collected at the respondents' homes using face-to-face interview, self-completion questionnaire, and a walking test. In addition, nurse visits were conducted to collect anthropometric and physical performance measurements including hand grip strength and lung function tests, as well as blood samples.

2.2 Variables

References are provided for variables implementing previously developed definitions. All others use categories or scores developed by ELSA (ELSA, 2006; Nunn et al., 2006). Physical frailty is specified by three indicators drawn from those of the CHS frailty phenotype (Fried et al., 2001), namely slowness, weakness, and exhaustion. *Slowness* is a continuous physical performance measure based on the average gait speed (in m/s) of two attempts at walking a distance of 2.4 m, but with values reversed through multiplication by -1. Neither gender nor height is accounted for, given the evidence of high agreement and correlation of cut-off values with and without taking these two characteristics into account (Saum et al., 2012). *Weakness* is also a continuous physical performance measure based on the dominant hand grip strength in kg which is multiplied by 1.5 for women. The differential handling of raw grip strength values in men and women is based on gender-specific and population-independent cut-off values for grip strength previously proposed for the CHS frailty phenotype criteria (Saum et al., 2012). After that, reversal of all values is achieved by multiplying them by -1. On the other hand, *exhaustion* is a binary self-report variable based on a positive response to at least one of two items in the revised 8-item CES-D scale on whether the respondent "felt everything they did during the past week was an effort" and "could not get going much of the time in the past week" (Turvey et al., 1999). We have previously argued and demonstrated that the combination of these three indicators is preferred to represent the physical frailty construct from among other permutations of the five components of the CHS frailty phenotype (Ding, 2016). Given that measures for these indicators are only available at waves 2, 4, and 6, we measured physical frailty at these time points. Confirmatory factor analysis (CFA) with these three indicators across waves 2, 4, and 6 is performed, while assuming and thereby imposing scalar (strong) invariance, where all loadings and intercepts are held constant across time. From CFA, unique physical frailty factor scores for waves 2, 4, and 6 are obtained for each respondent, and then used for the subsequent regression analyses. This factor score is a continuous measure where higher values reflect higher levels of frailty, and where there is no defined cut-off value that discriminates between frail and non-frail respondents.

Activity limitation is the outcome of interest and is defined by the number out of six BADL items performed with difficulty (score of 0 to 6) at waves 2, 4,and 6. As we focus on physical function, IADL is not used because its performance requires additional cognitive competency. Other predictors of activity limitation are drawn from the multidimensional categories listed in the Canadian working framework (Bergman et al., 2004). Beyond *age* and *gender*, physical predictors, namely *obesity* (binary: body mass index (BMI) of 30 kg/m^2 or more with reference to normal, defined by BMI less than 30 kg/m^2 but more than 20 kg/m^2) (WHO, 2000), being *underweight* (binary: BMI of 20 kg/m^2 or less with reference to normal, defined by BMI less than 30 kg/m^2 but more than 20 kg/m^2) (Sergi et al., 2005), *low physical activity* (four levels of decreasing intensity activity related to occupation and exercise), *chronic disease* (count of conditions from 0 to 14), *allostatic load* (score of 0 to 8) (Gruenewald et al., 2009), *smoking* (binary: whether ever smoked), and *high alcohol intake* (binary: whether had alcohol drink almost every day in the past 12 months). Allostatic load is a measure of physiological dysregulation in multiple body systems (Gruenewald et al., 2009), and is specified by eight biomarkers including blood pressure readings, anthropometric measurements, and blood tests for cholesterol levels, glucose control, and inflammatory markers. For each biomarker, a score of one is awarded for values beyond a cut-off level reflecting high risk, with a score of zero given if otherwise. The total score defines allostatic load.

Psychological predictors include *depressive symptoms* which are measured by a count of six out of eight items (score of 0 to 6) of the revised Center for Epidemiologic Studies Depression Scale (Turvey et al., 1999). The two omitted items are those already used to specify exhaustion as a physical frailty indicator. *Cognitive impairment* is measured by reversing a cognitive index based on the combined memory and executive function test performance (score of 0 to 49).

Social predictors include *low education* (binary: no qualifications compared with any qualification), and *low wealth* (binary: lowest 2 deciles compared with highest 8 deciles of non-pension wealth). Additionally, *low social integration*, reflecting social isolation, is based on a combined score on five items (score of 0 to 15) concerning whether participants have no spouse and partner living with them, had little contact with children, had little contact with other family members, had little contact with friends, and were not a member of any organization, club or society. Little contact was defined as less than monthly contact by meeting, phoning, or writing or email. Its composite scoring procedure is adapted from that of a previous study (Banks et al., 2010). Finally, *poor social support*, in terms of deficient emotional support, and reflecting negative social interaction with family and friends is measured by the combined scores on whether there is lack positive support, and the occurrence of negative support (score of 0 to 54). Lack of positive support is measured by negative answers to questions on “understand the way you feel”, “can rely on if you had a serious problem”, and “can open up to them if you need to talk” with respect to children, other family members, and friends. Negative support is measured by positive answers to questions on whether children, other family members, and friends "criticizes the respondent", "lets the respondent down", and "gets on the nerves of respondent". Its composite scoring procedure is again based on that of the aforementioned study (Banks et al., 2010).

2.3 Statistical analyses

A series of autoregressive cross-lagged models over waves 2, 4, and 6 of ELSA data are created to examine the effect of physical frailty on activity limitation change, and include moderated and mediated effects. Details of model and their equations are provided in the Supplementary Materials.

Model 1 predicts activity limitation by physical frailty controlling for other predictors, namely gender, age, obesity, underweight state, chronic disease, allostatic load, smoking history, high alcohol intake, low educational level, low wealth, poor social integration, and poor social support at wave 2. Physical frailty and activity limitation at waves 2, 4, and 6 are included in the model, with auto-regressive effects for activity limitation (waves 2 and 4 predicting waves 4 and 6 respectively) and physical frailty (wave 2 predicting wave 4). Cross-lagged effects of physical frailty at waves 2 and 4 predicting activity limitation change at waves 4 and 6 respectively are the focus of estimation. Equivalent effects are constrained to be equal across time. Since prediction of activity limitation is controlled for (or holding constant) its previous value, this model predicts activity limitation *change* across waves. Thus, positive values of change indicate activity limitation worsening, while negative values indicate its recovery. In addition, stratified analyses according to gender and age group (at least 75 years and less than 75 years) are performed to obtain gender- and age group-specific estimates of the effect of physical frailty. Model 2 extends Model 1 by examining moderation of the effect of physical frailty by poor social support, and poor social integration through stratified analyses according to values below the mean and those at least the mean.

Model 3 extends Model 1 by including mediation of the indirect effects of physical frailty on activity limitation *change* by low physical activity, depressive symptoms, and cognitive impairment. For the indirect effect of physical frailty (wave 2) on activity limitation change (wave 4), the mediators are either at wave 3 (cognitive impairment) or wave 4 (low physical activity and depressive symptoms). Correspondingly, for the indirect effect of physical frailty (wave 4) on activity limitation change (wave 6), the mediators are either at wave 4 (cognitive impairment) or wave 6 (low physical activity and depressive symptoms). Cognitive impairment at waves 3 and 4 are used because the full cognitive index is not available at waves 5 and 6. Mediation effects are inferred from the product of coefficients for the physical frailty-mediator and mediator-activity limitation effects, using Sobel's test to test significance (Sobel, 1982). Absence of physical frailty-mediator interaction is assumed. Stratified analyses according to gender and age group are also performed. Finally, Model 4 is an extension of Model 3 with the addition of analyses for moderation of mediated effects (moderated mediation or conditional indirect effects) (Preacher et al., 2007) by poor social support, and poor social integration through stratified analyses as for Model 2. Full details of the model specifications are provided by the Appendix in the Supplementary Materials.

Sensitivity analyses are performed to relax three important assumptions in our analyses and then to observe whether there are important changes in the results. Firstly, physical frailty-mediator interaction is also included in Model 3, relaxing the assumption of its absence. Secondly, we relax the assumption that there is no unmeasured confounding when estimating the physical frailty-mediator, mediator-activity limitation, and physical frailty-activity limitation effects. This is accomplished by including continuous latent variables ("phantom" variables) with varying magnitude of effect on physical frailty, activity limitation, and any mediators in the model. This is to simulate the presence of unmeasured confounders and estimate the magnitude of their effects that would sufficient to cause the effects of physical frailty and mediators to be non-significant (VanderWeele, 2016). Thirdly, we relax the assumption that the activity limitation has an approximately normal distribution, given that this variable is measured by number of BADL items performed with difficulty, which can be considered as count data. In anticipation that this distribution is right skewed with a large proportion of zero values, negative binomial regression will be also performed for its prediction to check if there are any important differences in the results in doing so (Zaninotto & Falaschetti, 2011). In addition, we restrict our analyses to respondents who have available values for activity limitation at wave 6, thereby excluding those contributing to attrition across time. The purpose is to provide alternative analyses to those implementing maximum likelihood for the whole study population, which in turn assumes that missing values are MAR.

Missing values are handled under the assumption of missing at random (MAR) by full information maximum likelihood (FIML), which a procedure that is analogous to multiple imputation but without actual creation of imputation datasets. Rather, the missing data is handled within the analysis model using maximum likelihood estimation which identifies population parameters having the highest probability of producing the sample data. It uses all available data to generate their estimates and assumes multivariate normality. It is also implemented for predictor variables by treating them as dependent variables through estimating their sample means. Mplus version 7.4 (Muthén & Muthén, 1998-2012) is used to perform the autoregressive cross-lagged analyses, while STATA version 14.1 is used for all other analyses. Statistical significance is assessed at the 5% level, except for examination of moderated effects by the two social predictors, where it is assessed at the 2.5% level on account of Bonferroni's correction for multiple comparisons.

3. Results

Table 1 describes the characteristics of the study population including physical frailty indicators, factor scores, frailty status, and activity limitation across waves 2, 4, and 6. In addition, predictors at wave 2 are also shown. Additional information on mediators at waves 2, 4, and 6 is also provided in the Supplementary Materials (Table A.1). The mean age is 74 years and women comprise approximately 55 percent. Activity limitation increases on over time with 27% needing assistance in one or more basic activities of living (BADL) item at wave 2 to 30% at wave 6. Correspondingly, the mean number of BADL items requiring assistance also increases from 0.51 to 0.70 from waves 2 to 6. There is more difficulty with BADL among women and those aged at least 75 years. Physical frailty increases over time as measured by factor scores (-0.02 to 0.02) and proportion categorized as having frailty (20% to 25%). Thus, increasing levels of activity limitation parallels increasing physical frailty over time in the study population.

Table 1. Characteristics of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included in analyses

Variables	**All**	**By gender**		**By Age group**	
		Male	**Female**	**< 75 years**	**>= 75 years**
General					
Mean age, years (SD)	74.0 (6.3)	73.5 (6.2)	74.3 (6.4)	69.3 (2.8)	80.2 (3.9)
Female, n/N (%)	2,568/4,638 (55.4)	-	-	1,399/2,643 (52.9)	1,169/1,995 (58.6)
Physical frailty					
Mean average walking speed, m/sec (SD)	0.8 (0.3)[1]	0.9 (0.3)[2]	0.8 (0.3)[3]	0.9 (0.3)[4]	0.7 (0.3)[5]
Hand grip strength, kg (SD)	25.9 (10.2)[6]	33.4 (8.9)[7]	19.6 (6.1)[8]	28.4 (10.2)[9]	22.2 (8.2)[10]
Exhaustion, n/N (%)	1,490/4,510 (33.0)	568/1,997 (28.4)	922/2,513 (36.7)	728/2,596 (28.0)	762/1,914 (39.8)
Frailty by Frailty Index, n/N (%):					
Wave 2	717/3,647 (19.7)	236/1,639 (14.4)	481/2,008 (24.0)	322/2,207 (14.6)	395/1,440 (27.4)
Wave 4	507/2,371 (21.4)	158/1,051 (15.0)	349/1,320 (26.4)	279/1,571 (17.8)	228/800 (28.5)
Wave 6	438/1,774 (24.7)	145/768 (18.9)	293/1,006 (29.1)	285/1,325 (21.5)	153/449 (34.1)
Mean physical frailty factor score (SD):					
Wave 2	-0.02 (0.81)[11]	-0.21 (0.76)[12]	0.12 (0.80)[13]	-0.28 (0.78)[14]	0.32 (0.71)[15]
Wave 4	0.01 (0.80)[11]	-0.18 (0.78)[12]	0.15 (0.78)[13]	-0.25 (0.78)[14]	0.35 (0.68)[15]
Wave 6	0.02 (0.76)[11]	-0.15 (0.74)[12]	0.16 (0.74)[13]	-0.22 (0.75)[14]	0.35 (0.64)[15]

Physical					
Obesity, n/N (%)	1,018/3,976 (25.6)	400/1,783 (22.4)	618/2,193 (28.2)	662/2,328 (28.4)	356/1,648 (21.6)
Underweight, n/N (%)	117/3,689 (3.2)	42/1,661 (2.5)	75/2,028 (3.7)	59/2,226 (2.7)	58/1,463 (4.0)
Mean chronic disease count [0 to 14] (SD)	1.9 (1.4)[16]	1.8 (1.4)[17]	2.0 (1.4)[18]	1.8 (1.4)[19]	2.1 (1.5)[20]
Mean allostatic load score [0 to 8] (SD)	2.0 (1.5)[21]	1.9 (1.5)[22]	2.1 (1.5)[23]	1.9 (1.5)[24]	2.1 (1.5)[25]
Mean low physical activity level [0 to 3] (SD)	1.2 (0.9)[26]	1.1 (0.9)[27]	1.3 (0.9)[28]	1.0 (0.9)[29]	1.4 (0.9)[30]
Smoking history, n/N (%)	2,963/4,634 (63.9)	1,567/2,069 (75.7)	1,396/2,565 (54.5)	1,649/2,639 (62.5)	681/1,995 (65.9)
Heavy alcohol intake, n (%)	1,249/3,871 (32.3)	720/1,742 (41.3)	529/2,129 (24.9)	792/2,344 (33.8)	457/1,527 (29.9)
Psychological					
Mean CESD-8 score [0 to 8] (SD)	1.7 (2.0)[31]	1.3 (1.7)[32]	1.9 (2.1)[33]	1.5 (1.9)[34]	1.9 (2.0)[35]
Mean cognitive impairment score [0 to 49] (SD)	27.5 (6.3)[36]	26.3 (6.4)[37]	25.5 (6.5)[38]	24.1 (6.0)[39]	28.4 (6.3)[40]
Social					
Low education, n (%)	2,256/4,618 (48.9)	885/2,061 (41.5)	1,401/2,557 (54.8)	1,158/2,630 (44.0)	1,098/1,998 (55.2)
Low wealth, n (%)	980/4,557 (21.5)	365/2,022 (18.1)	615/2,535 (24.3)	454/2,584 (17.6)	526/1,973 (26.7)
Mean poor social support score [0 to 54] (SD)	13.7 (7.0)[41]	14.7 (7.0)[42]	12.9 (6.8)[43]	13.9 (7.0)[44]	13.3 (6.8)[45]
Mean poor social integration score [0 to 15] (SD)	6.6 (2.5)[46]	6.7 (2.6)[47]	6.5 (2.5)[48]	6.4 (2.5)[49]	7.0 (2.6)[50]
Activity limitation					
Mean number of BADL items performed with difficulty [0 to 6] (SD):					
Wave 2 (2004)	0.51 (1.08)[51]	0.47 (1.03)[52]	0.55 (1.11)[53]	0.40 (0.96)[54]	0.66 (1.19)[55]
Wave 4 (2008)	0.58 (1.17)[56]	0.52 (1.13)[57]	0.63 (1.20)[58]	0.45 (1.04)[59]	0.79 (1.33)[60]
Wave 6 (2012)	0.70 (1.37)[61]	0.63 (1.32)[62]	0.75 (1.40)[63]	0.53 (1.18)[64]	1.07 (1.65)[65]
At least one BADL item performed with difficulty, n (%):					
Wave 2 (2004)	1,246/4,635 (26.9)	510/2,070 (24.6)	736/2,565 (28.7)	563/2,641 (21.3)	683/1.994 (34.3)
Wave 4 (2008)	917/3,127 (29.3)	336/1,356 (27.0)	551/1,771 (31.1)	457/1,916 (23.8)	460/1,211 (38.0)
Wave 6 (2012)	730/2,402 (30.4)	280/1,023 (27.4)	450/1,379 (32.6)	408/1,642 (24.9)	322/760 (42.4)

Frail status by Frailty Index (FI): FI >=0.25
CESD-8: Center for Epidemiologic Studies Depression Scale (8 items)
BADL: basic activities of daily living
Unless indicated otherwise, N = 4,638 (all), 2,070 (male), 2,568 (female), 2,643 (less than 75 years old), and 1,995 (at least 75 years old).
N = [1]4,096 [2]1,826 [3]2,266 [4]2,400 [5]1,692 [6]3,869 [7]1,760 [8]2,109 [9]2,276 [10]1,593 [11]4,560 [12]2,025 [13]2,535 [14]2,616 [15]2,025 [16]4,608 [17]2,052 [18]2,556 [19]2,617 [20]1,991 [21]2,319 [22]1,064 [23]1,255 [24]1,436 [25]883 [26]4,567 [27]2,032 [28]2,535 [29]2,611 [30]1,956 [31]4,479 [32]1,987 [33]2,492 [34]2,586 [35]1,893 [36]4,349 [37]1,946 [38]2,403 [39]2,546 [40]1,803 [41]3,339 [42]1,529 [43]1,810 [44]2,068 [45]1,271 [46]3,267 [47]1,506 [48]1,761 [49]2,035 [50]1,232 [51]4,635 [52]2,070 [53]2,565 [54]2,641 [55]1,994 [56]3,127 [57]1,356 [58]1,771 [59]1,916 [60]1,211 [61]2,402 [62]1,023 [63]1,379 [64]1,642 [65]760

Moreover, physical frailty levels and proportions of respondents who are frail are higher among women and in the older group. Among multidimensional conditions at wave 2, there are minor gender-specific and age-specific differences with a few exceptions. Obesity is more common among women and in the younger group. Both history of smoking and high alcohol intake are more common among men. On the other hand, women and those in the older group have more depressive symptoms, while the latter also have more cognitive impairment.

Table 2 provides linear regression coefficients where physical frailty factor scores are standardized. Model 1 indicates that physical frailty significantly predicts activity limitation *change* two years later controlling for other key predictors. More precisely, one standard deviation increase in physical frailty predicts increase in activity limitation change of almost 0.25 BADL items performed with difficulty (first panel of coefficients) over this time interval.

Table 2. Main and moderated effects of physical frailty on activity limitation change controlling for other predictors using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: standardized regression coefficients for physical frailty for main and stratified analyses

Outcome: activity limitation change		**Coefficient estimate**
Physical frailty	All	0.234*
Physical frailty according to:		
Gender:	Men	0.254*
	Women	0.219*
Age**:	<75 years	0.190*
	>=75 years	0.312*
Poor social support:	Low level	0.230***
	High level	0.244***
Poor social integration:	Low level	0.207***
	High level	0.257***

Physical frailty: factor scores standardized according to standard deviation of wave 2 values
Low level: one standard deviation below the mean value
High level: one standard deviation above the mean value
All effects are controlled for lagged activity limitation, gender, age, chronic disease, allostatic load, body mass index (BMI) category, smoking history, alcohol intake level, educational level, wealth level, social support level, and social integration level.
* p-value <0.05
** p-value <0.05 for difference between two groups
*** p-value <0.025 (Bonferroni's correction for multiple comparisons for 2 separate moderation models)
Missing values are handled by full information maximum likelihood (FIML).
N = 4,638

Although this effect appears small in absolute terms, it is notable that physical frailty has by far the largest magnitude of effect on activity limitation change compared with other predictors when their standardized coefficients are compared in the Supplementary Materials (Table A.2). In fact, the magnitude of effect for physical frailty is almost 2.5 times that of older age which has the next largest significant effect. Viewed alternatively, one standard deviation increase in physical frailty predicts increase in activity limitation change that is equivalent to over two-fold that of the average increase observed in the study population, which is in the order of 0.1 BADL items performed with difficulty over two years (see Table 1). Results from Model 1 with stratification according to gender and age group are also shown in Table 2. The effect of physical frailty is stronger for men compared with women (first variable in second panel), but not significantly so. However, this effect is significantly stronger among those in the older group compared with those younger (second variable in second panel). Furthermore, Model 2 demonstrates that the effect of physical frailty on activity limitation change has mild and non-significant differences across different levels of poor social support and poor social integration (third and fourth variables in second panel).

Model 3 which includes mediation effects of physical frailty on activity limitation *change* yields interesting results that are shown in Table 3. Low physical activity, depressive symptoms, and cognitive impairment are all significant mediators (first panel), with their respective indirect effects being equivalent in magnitude to approximately 30%, 8%, and 4% that of the total effect indicated in Table 2. There are no differences in these indirect effects across gender (first variable in second panel). On the other hand, Model 4 indicates that indirect effects of physical frailty through low physical activity and cognitive impairment are significantly stronger with older age, whereas that through depressive symptoms is not (second variable in second panel). In addition, indirect effects are not significantly different across strata defined by poor social support and poor social integration levels (third and fourth variable in second panel), indicating that there is no significant moderation of the indirect effects by these two conditions. However, a trend in the indirect effect through depressive symptoms being more than 1.5 times stronger with higher compared with lower levels of poor social support is noted.

Sensitivity analyses yields informative results. Firstly, repeat analyses that include physical frailty-mediator interactions in the model obtain estimates of 0.075, 0.017, and 0.009 for the indirect effects mediated through low physical activity, depressive symptoms, and cognitive impairment respectively. These estimates are very similar to those obtained in models excluding these interactions, indicating that including the latter only has trivial impact. Secondly, additional analyses which simulate the presence of an unmeasured confounder indicate that the magnitude of its effect on activity limitation change needs to be equivalent to three-fold that of the strongest among other predictors for the effect of physical frailty on activity limitation change at a moderate level (0.5) of correlation between the unmeasured confounder and physical frailty to be rendered non-significant as shown in Supplementary Materials (Table A.3). This suggests that the estimated effect of physical frailty on activity limitation change is relatively robust to any unmeasured confounding. On the other hand, for indirect effects through low physical activity, depressive symptoms, and cognitive impairment, correlation of an unmeasured confounder with mediators only needs to be 0.3 for them to be rendered non-significant and in the opposite direction, even at correlation with physical frailty of only 0.1 and effect on activity limitation just equivalent to that of the strongest among other predictors. These results are shown in the Supplementary Materials (Table A.4), and suggest that estimated indirect effects may be relatively sensitive to any unmeasured confounder having low correlation with the mediator. Thirdly, given the large proportion of zero values and right skewed distribution for activity limitation, negative binomial regression is also performed as an alternative to linear regression for Model 1. The results are approximately equivalent to those of linear regression (results not shown). Thus, the results of linear regression for Models 1 to 4 represent our final findings. Lastly, repeat analyses for 2,402 respondents who have complete values for activity limitation at wave 6 obtain similar and significant estimates of the main and indirect effects of physical frailty, albeit with slightly lower magnitudes compared those for the analysis of the whole study population which assume MAR for missing values (results not shown).

Table 3. Mediation and moderated mediation of physical frailty on activity limitation change controlling for other predictors using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: product of coefficients estimates for main and stratified analyses

Outcome: activity limitation change		**Mediator**		
		Low physical activity	**Depressive symptoms**	**Cognitive impairment**
Physical frailty	All	0.070*	0.019*	0.009*
Physical frailty according to:				
Gender:	Male	0.079*	0.019*	0.012*
	Female	0.062*	0.019*	0.009*
Age**:	<75 years	0.051*	0.011*	0.005*
	>=75 years	0.086*	0.030*	0.017*
Poor social support:	Low level	0.068****	0.015***	0.013****
	High level	0.073****	0.024****	0.006
Poor social integration:	Low level	0.067****	0.022****	0.010****
	High level	0.073****	0.017****	0.009****

All effects are controlled for lagged activity limitation, gender, age, chronic disease, allostatic load, body mass index (BMI) category, smoking history, alcohol intake level, educational level, wealth level, social support level, and social integration level
Low level: one standard deviation below mean value
High level: one standard deviation above mean value
Coefficients of physical frailty are standardized.
* p-value <0.05
** p-value <0.05 for difference between two groups (only where mediator is low physical activity or cognitive impairment, but not depressive symptoms)
*** p-value <0.05 but >=0.025
**** p-value <0.025 (Bonferroni's correction for multiple comparisons for 2 separate moderation models)
Missing values are handled by full information maximum likelihood (FIML).
N = 4,638

4. Discussion

For community-dwelling older people in England, increasing levels of physical frailty independently predict more activity limitation *change* two years later. This means that the significantly worse trajectory of activity limitation conferred by physical frailty remains even after taking into account the effects of a broad set of concurrent physical, psychological, and social predictors. This confirms previous work by others (Lang et al., 2007; Vermeulen et al., 2011). In terms of magnitude, one standard deviation increase in physical frailty level predicts increase in activity limitation change over two years that is more than two fold that of the population average. By any measure, this is a strong effect. However, our findings go beyond mere prediction. In particular, we find that this negative effect is mediated by low physical activity, depressive symptoms, and cognitive impairment. In addition, the effect of physical frailty is stronger with older age. Finally, the indirect effects of physical frailty on activity limitation through low physical activity and cognitive impairment are stronger with older age. In other words, the pathways from physical frailty to activity limitation appear to be more complex and involve mediation by physical and psychological conditions which is influenced by age. Notably, our findings add to the frailty pathways hypothesized in the Canadian working framework by identifying mediators on those pathways. To the best of our knowledge, this is the first report concerning indirect effects of physical frailty on activity limitation trajectory in older people.

The indirect effects we uncover provide insight on *how* physical frailty exerts its effect on activity limitation change. From our results, we infer that low physical activity mediates almost one third of the effect of physical frailty, whereas depressive symptoms and cognitive impairment do so much less. Low physical activity has previously been demonstrated to worsen activity limitation (Landi et al., 2007), with the exercise being shown to have the opposite desirable effect (Chou et al., 2012). Thus, the relatively large contribution of low physical activity to mediation is not surprising given that individuals who are physically frail are likely to have less physical activity, which in turn increases risk of activity limitation. However, the precise mechanism by which depressive symptoms and cognitive impairment mediate the effect of physical frailty on activity limitation change is less clear. Nevertheless, we know that physical frailty increases the risk of depression (Collard et al., 2015; Mezuk et al., 2012), which in turn increases the risk of activity limitation (Bruce et al., 1994). Furthermore, physical frailty predicts incident cognitive impairment (Canevelli et al., 2015). However, previous research yielded mixed results as to whether cognitive impairment had additional impact on disability for those who are already physically frail (Ament et al., 2014; Avila-Funes et al., 2009).

On the other hand, our findings go only to a limited extent to indicate *for whom* the effect of physical frailty on activity limitation change is stronger. It is quite expected that the effect of physical frailty, including its indirect effects, would be stronger among those who are older, given the additional physiological decline that occurs with older age that is not captured by physical frailty and other predictors and are therefore subsumed under it. Nevertheless, this finding suggests that the effect of physical frailty on activity limitation, including those mediated by low physical activity and cognitive impairment not only remains, but may even be more influential in very old people. Although previous research demonstrated that social support in the form of positive social interaction protects against functional decline in older people (Unger et al., 1997), we did not observe this moderating effect. However, there is some suggestion that the indirect effect through depressive symptoms may be stronger with poorer social support. It is plausible that better social support, particularly in terms of emotional support through positive social interaction, may to some extent protect against activity limitation on account of its psychological benefits, but we could not demonstrate a significant moderating effect. On the other hand, psychosocial resources may not protect against functional decline in physically frail older people to the degree as may be expected (Hoogendijk et al., 2014). That said, the relationship between these two conditions could be more complex, given that negative social exchanges have been shown to predict depression in ELSA respondents (Stafford et al., 2011). Nonetheless, alternative definitions of social support could be considered in further work investigating its influence on the effect of physical frailty on activity limitation.

The described mediators on pathways from physical frailty to activity limitation may lend themselves to modification by population-level interventions, which hold promise for addressing the larger public health implications of frailty on the healthspan of older people. Specifically, low physical activity, depressive symptoms, and cognitive impairment represent potential interventional opportunities for health and social programs which typically comprise behavioural and therapeutic components. At the very least, the evidence assembled here should go some distance in justifying the conduct of experimental or quasi-experimental trials testing interventions that encourage and facilitate physical activity, prevent depressive symptoms, delay the onset or slow down the progression of cognitive impairment, with the expressed objective of mitigating activity limitation resulting from physical frailty among older people. While it is possible that poor social support may have a moderating effect, addressing it is a more challenging task. Since social interactions are largely conducted at the personal level, it is hard to see how formal programs and policies can directly influence them. Instead, public education that raises awareness that positive interactions with frail older people may reduce the risk of activity limitation could be explored.

From a broader perspective, addressing low physical activity, depressive symptoms, and cognitive impairment may already be recognized as sensible objectives of health and social policies. However, ongoing initiatives with these objectives may benefit from the additional frailty-specific evidence assembled here, in terms of bolstering support for their continuation or even expansion.

We acknowledge two major limitations of our study. Firstly, dependence on observational data imposes limits on causal inference. Having said that, use of longitudinal data permits specification of cause preceding effect in our models. Moreover, inclusion of a broad range of multidimensional deficits in these models allows us to argue that the effects of any omitted variables are unlikely to be large and influential in changing the major conclusions of this study. In addition, our sensitivity analyses provide some degree of reassurance that our results on the main effect are relatively robust to model misspecification due to any unmeasured confounders. On the other hand, our results on indirect effects appear to be less robust to unmeasured confounding, particularly with respect to correlation with mediators. Notwithstanding this, our findings may offer the best available evidence on the possible mechanisms underlying the effect of physical frailty on activity limitation, in the absence of confirmation from experiments utilizing randomized or geographically-based treatment assignment. Secondly, the use of secondary data restricts the way key variables are specified, particularly those concerning lifestyle habits or social conditions. Fortunately, the availability of rich and credible data available in ELSA affords the opportunity to create these variables, or adopt the definitions used by others.

In conclusion, the evidence from ELSA suggests that low physical activity, depressive symptoms, and cognitive impairment have roles as mediators, while poor social support may be a moderator on pathways from physical frailty to activity limitation. In terms of minimizing activity limitation resulting from physical frailty in older people, population health and social measures addressing these four conditions merit consideration for further investigation, or even implementation. These measures can augment health promotion efforts directed at reducing physical frailty in the first place, thereby contributing to the wider effort of improving the healthspan of older people.

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Supplementary Materials

Appendix

Mathematical equations for the statistical models with corresponding graphical representation

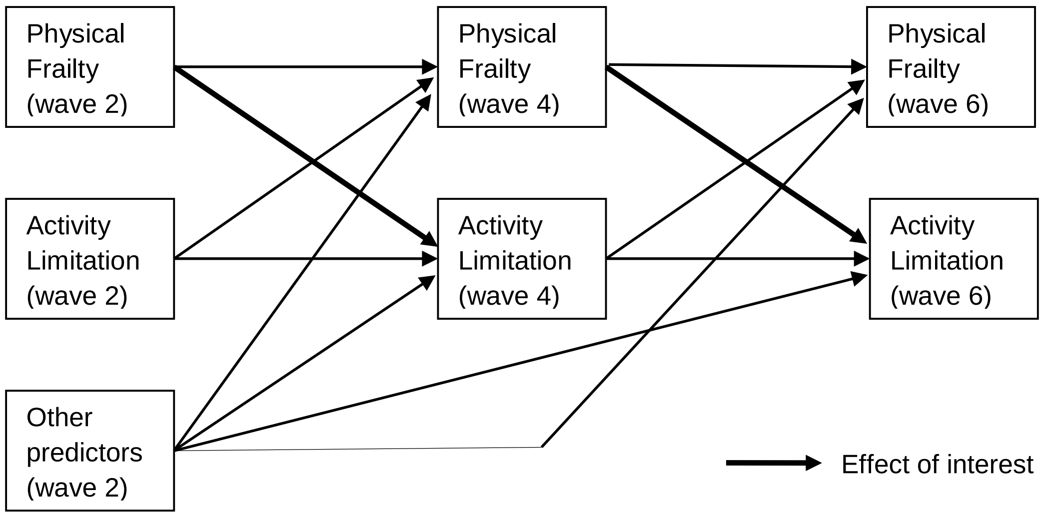
Model 1. Let y_{ti} denote activity limitation defined by number of items of basic activities of daily living performed with difficulty (score 0 to 6) across waves 2, 4, and 6, $y_{t\text{-}1i}$ be the lagged activity limitation, p_{ti} be the physical frailty factor score across waves 2, 4, and 6, and x_i represents a time-invariant predictor at t =1 (wave 2) for individuals i = 1..., n at t = 2 and 3 (waves 4 and 6).

The equation for the effect of interest in the autoregressive cross-lagged model is:

$$y_{ti} = \beta_0 + y_{t\text{-}1i} + \beta_1 p_{t\text{-}1i} + \beta_2 x_i + \varepsilon_{ti}$$

The coefficient β_1 describes the effect of lagged physical frailty factor score on activity limitation, while β_2 describes the effect of time-invariant predictors on activity limitation and β_0 is the intercept. The focus is on the estimated coefficient β_1 which is shown in Table 2. A graphical representation of this model is shown in Figure A.1.

Figure A.1. Autoregressive cross-lagged model for the effect of physical frailty on activity limitation (Model 1)



For gender- and age-specific effects, stratified analyses of two subgroups according to gender, age group use the same equation.

Model 2. The equation for Model 1 applies for stratified analyses of two subgroups according to moderating variables, namely poor social support and poor social integration.

Model 3. Suppose m_i is a mediator of the effect of $p_{t\text{-}1i}$ on y_{ti}, so that:

$$y_{ti} = \beta_0 + y_{t\text{-}1i} + \beta_1 p_{t\text{-}1i} + \beta_2 x_i + \beta_4 m_{ti} + \varepsilon_{ti}$$

Suppose further that

$$m_{ti} = \lambda_0 + \lambda_1 p_{t\text{-}1i} + \delta_{ti}$$

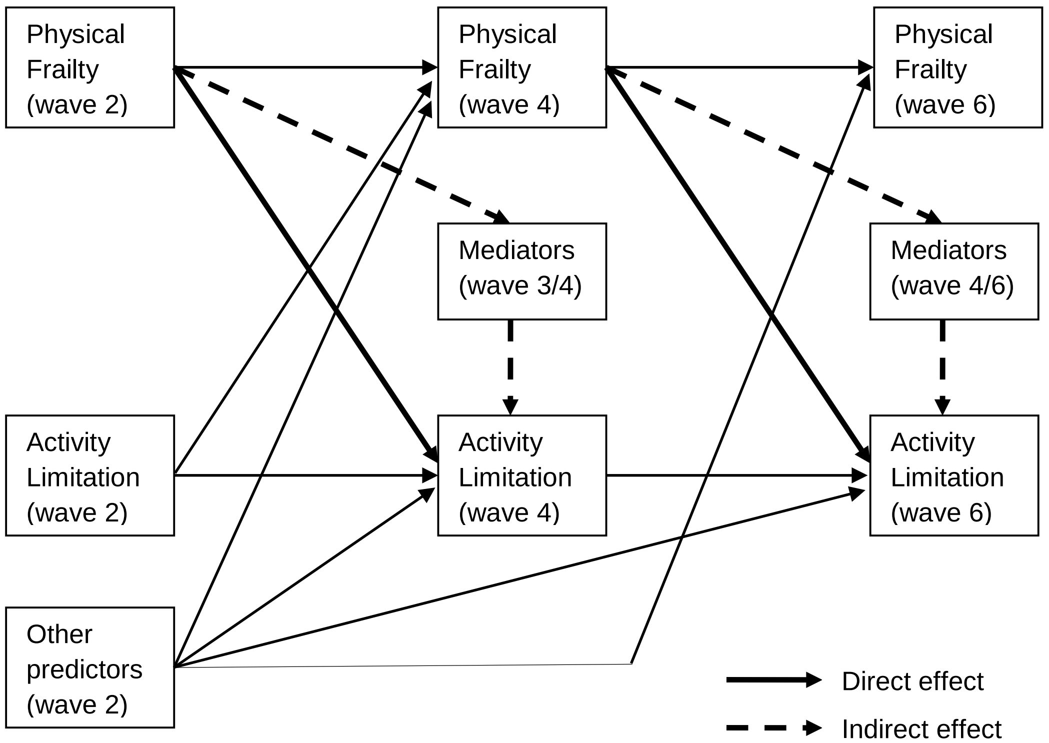
Then the model given $p_{t\text{-}2i}$ and x_i only, averaging over the distribution of m_{ti}, is

$$Y_{ti} = \beta_0 + y_{t\text{-}1i} + \beta_{*1} p_{t\text{-}1i} + \beta_2 x_i + \varepsilon_{*ti}$$

where $\varepsilon_{*ti} = (\varepsilon_{ti} + \beta_4 \delta_{ti})$ and $\beta_{*1} = \beta_1 + \beta_4 \lambda_1$

Here, β_{*1} is the total effect of $p_{t\text{-}1i}$ on activity limitation, β_1 is the direct effect of $p_{t\text{-}1i}$, and $\beta_4\lambda_1$ is the indirect effect of $p_{t\text{-}1i}$ mediated via m_{ti}.

Figure A.2. Autoregressive cross-lagged model for the effect of physical frailty on activity limitation with mediation (Model 3)



For gender- and age-specific effects, stratified analyses of two subgroups according to gender, age group use the same equation.

Model 4. The equation for Model 3 applies for stratified analyses of two subgroups according to moderating variables, namely poor social support and poor social integration.

Table A.1. Characteristics of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included in analyses: physical frailty-related and other time varying variables across different waves

Variables		All	By gender		By Age group	
			Male	Female	< 75 years	>= 75 years
Physical frailty-related:						
Mean average walking speed, m/sec (SD):	Wave 2	0.8 (0.3)[1]	0.9 (0.3)[2]	0.8 (0.3)[3]	0.9 (0.3)[4]	0.7 (0.3)[5]
	Wave 4	0.8 (0.3)[6]	0.8 (0.3)[7]	0.7 (0.3)[8]	0.8 (0.3)[9]	0.7 (0.2)[10]
	Wave 6	0.8 (0.3)[11]	0.8 (0.3)[12]	0.7 (0.3)[13]	0.8 (0.3)[14]	0.6 (0.2)[15]
Hand grip strength (dominant hand), kg (SD):	Wave 2	25.9 (10.2)[16]	33.4 (8.9)[17]	19.6 (6.1)[18]	28.4 (10.2)[19]	22.2 (9.0)[20]
	Wave 4	24.3 (10.2)[21]	32.0 (9.0)[22]	18.2 (6.2)[23]	26.6 (10.3)[24]	20.4 (8.6)[25]
	Wave 6	22.8 (9.5)[26]	29.6 (8.8)[27]	17.5 (5.9)[28]	24.4 (9.6)[29]	18.9 (7.9)[30]
Exhaustion, n/N (%):	Wave 2	1,490/4,510 (33.0)	568/1,997 (28.4)	922/2,513 (36.7)	728/2,596 (28.0)	762/1,914 (39.8)
	Wave 4	955/2,977 (32.1)	327/1,290 (25.4)	628/1,687 (37.2)	518/1,868 (27.7)	437/1,109 (39.4)
	Wave 6	632/1,962 (32.2)	218/848 (25.7)	414/1,114 (37.2)	401/1,402 (28.6)	231/560 (41.3)
Physical:						
Mean low physical activity level, n (%):	Wave 2	1.2 (0.9)[31]	1.1 (0.9)[32]	1.3 (0.9)[33]	1.0 (0.9)[34]	1.4 (0.9)[35]
	Wave 4	1.3 (1.0)[36]	1.2 (1.0)[37]	1.4 (0.9)[38]	1.1 (0.9)[39]	1.7 (1.0)[40]
	Wave 6	1.4 (1.0)[41]	1.3 (1.0)[42]	1.6 (0.9)[43]	1.2 (0.9)[44]	1.9 (0.9)[45]
Psychological:						
Mean CESD-8 score [0 to 8] (SD):	Wave 2	1.7 (2.0)[46]	1.3 (1.7)[47]	1.9 (2.1)[48]	1.5 (1.9)[49]	1.9 (2.0)[50]
	Wave 4	1.5 (1.9)[51]	1.1 (1.7)[52]	1.8 (2.0)[53]	1.3 (1.8)[54]	1.8 (2.0)[55]
	Wave 6	1.0 (1.4)[56]	0.8 (1.2)[57]	1.2 (1.5)[58]	0.9 (1.3)[59]	1.2 (1.5)[60]
Mean cognitive impairment score [0 to 49] (SD):						
	Wave 2	27.5 (6.3)[61]	26.3 (6.4)[62]	25.5 (6.5)[63]	24.1 (6.0)[64]	28.4 (6.3)[65]
	Wave 3	25.7 (6.6)[66]	26.0 (6.5)[67]	25.5 (6.8)[68]	24.0 (6.1)[69]	28.4 (6.5)[70]
	Wave 4	25.6 (6.8)[71]	25.8 (6.6)[72]	25.5 (6.9)[73]	24.0 (6.2)[74]	28.6 (6.7)[75]

Frail status: Frailty Index >=0.25
CESD-8: Center for Epidemiologic Studies Depression Scale (8 items)
N = [1]4,096 [2]1,826 [3]2,266 [4]2,400 [5]1,692 [6]2,649 [7]1,182 [8]1,467 [9]1,705 [10]944 [11]1,688 [12]754 [13]934 [14]1,254 [15]434 [16]3,869 [17]1,760 [18]2,109 [19]2,276 [20]1,593 [21]2,531 [22]1,115 [23]1,416 [24]1,621 [25]910 [26]1,868 [27]820 [28]1,048 [29]1,339 [30]529 [31]4,567 [32]2,032 [33]2,535 [34]2,611 [35]1,956 [36]3,125 [37]1,355 [38]1,770 [39]1,915 [40]1,210 [41]2,404 [42]1,023 [43]1,381 [44]1,643 [45]761 [46]4,479 [47]1,987 [48]2,492 [49]2,586 [50]1,893 [51]2,960 [52]1,285 [53]1,675 [54]1,859 [55]1,101 [56]2,215 [57]947 [58]1,268 [59]1,557 [60]658 [61]4,349 [62]1,946 [63]2,403 [64]2,546 [65]1,803 [66]2,605 [67]1,145 [68]1,460 [69]1,680 [70]925 [71]3,375 [72]1,492 [73]1,883 [74]2,041 [75]1,334

Table A.2. Effects of physical frailty on activity limitation controlling for other predictors using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: standardized regression coefficients for predictors at wave 2

Outcome: Activity Limitation	**Coefficient estimate**
Lagged activity limitation	0.572**
Physical frailty	0.234**
Female	-0.085**
Older age	0.097**
Chronic disease	0.079**
Allostatic load	-0.007
Obesity	0.043
Underweight state	0.195
Smoking history	-0.021
High alcoholic intake	<0.001
Low wealth	0.017
Low educational level	-0.004
Poor social support	0.052*
Poor social interaction	-0.022

Coefficients are standardized for continuous predictors. Thus, coefficients are interpreted as change in activity limitation score for a one standard deviation increase in continuous predictors, or from zero to one for binary predictors (female gender, obesity, underweight state, smoking, high alcohol intake, low wealth, and low educational level).
* p-value <0.05 but >=0.01
** p-value <0.01
Missing values are handled by full information maximum likelihood (FIML).
N = 4,638

Table A.3. Sensitivity analysis with simulation of unmeasured confounder of relationship between physical frailty and activity limitation using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: linear regression coefficients

Correlation between unmeasured confounder and physical frailty	Effect size of unmeasured confounder on activity limitation (comparison with that of strongest predictor of activity limitation)		
	1X	2X	3X
0.1 (very low)	0.430**	0.505**	0.575**
0.3 (low)	0.184**	0.450**	0.540**
0.5 (medium)	0.339**	0.429**	0.041

* p-value <0.05
Coefficients are interpreted as change in activity limitation score for a one standard deviation increase in physical frailty factor score.
Shaded areas indicate that the effect of physical frailty on activity limitation remains positive and significant.
Missing values are handled by full information maximum likelihood (FIML).
N = 4,638

Table A.4. Sensitivity analysis with simulation of unmeasured confounder of indirect effects of physical frailty on activity limitation using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: linear regression coefficients

Mediator	Correlation between unmeasured confounder and mediators	Correlation between unmeasured confounder and physical frailty	Effect size of unmeasured confounder on activity limitation (comparison with that of strongest predictor of activity limitation)	
			1X	3X
Low physical activity	0.1 (very low)	0.1 (very low)	0.104**	0.093**
		0.3 (low)	0.102**	0.100**
	0.3 (low)	0.1 (very low)	0.001	0.001
		0.3 (low)	-0.019**	-0.017**
Depressive symptoms	0.1 (very low)	0.1 (very low)	0.029**	0.025**
		0.3 (low)	0.027**	0.025**
	0.3 (low)	0.1 (very low)	-0.003	-0.002
		0.3 (low)	-0.008**	-0.007**
Cognitive impairment	0.1 (very low)	0.1 (very low)	0.019**	0.013**
		0.3 (low)	0.019**	0.019**
	0.3 (low)	0.1 (very low)	-0.007**	-0.001
		0.3 (low)	-0.014**	-0.010*

* p-value <0.05

Coefficients are interpreted as change in activity limitation score for a one standard deviation increase in physical frailty factor score.

Shaded areas indicate that the effect of physical frailty on activity limitation remains positive and significant.

Missing values are handled by full information maximum likelihood (FIML).

N = 4,638