



# Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project)

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## ABSTRACT

### OBJECTIVE

To determine whether a multicomponent intervention based on physical activity with technological support and nutritional counselling prevents mobility disability in older adults with physical frailty and sarcopenia.

### DESIGN

Evaluator blinded, randomised controlled trial.

### SETTING

16 clinical sites across 11 European countries, January 2016 to 31 October 2019.

### PARTICIPANTS

1519 community dwelling men and women aged 70 years or older with physical frailty and sarcopenia, operationalised as the co-occurrence of low functional status, defined as a short physical performance battery (SPPB) score of 3 to 9, low appendicular lean mass, and ability to independently walk 400 m. 760 participants were randomised to a multicomponent intervention and 759 received education on healthy ageing (controls).

### INTERVENTIONS

The multicomponent intervention comprised moderate intensity physical activity twice weekly at a centre

and up to four times weekly at home. Actimetry data were used to tailor the intervention. Participants also received personalised nutritional counselling. Control participants received education on healthy ageing once a month. Interventions and follow-up lasted for up to 36 months.

### MAIN OUTCOME MEASURES

The primary outcome was mobility disability (inability to independently walk 400 m in <15 minutes). Persistent mobility disability (inability to walk 400 m on two consecutive occasions) and changes from baseline to 24 and 36 months in physical performance, muscle strength, and appendicular lean mass were analysed as pre-planned secondary outcomes. Primary comparisons were conducted in participants with baseline SPPB scores of 3-7 (n=1205). Those with SPPB scores of 8 or 9 (n=314) were analysed separately for exploratory purposes.

### RESULTS

Mean age of the 1519 participants (1088 women) was 78.9 (standard deviation 5.8) years. The average follow-up was 26.4 (SD 9.5) months. Among participants with SPPB scores of 3-7, mobility disability occurred in 283/605 (46.8%) assigned to the multicomponent intervention and 316/600 (52.7%) controls (hazard ratio 0.78, 95% confidence interval 0.67 to 0.92; P=0.005). Persistent mobility disability occurred in 127/605 (21.0%) participants assigned to the multicomponent intervention and 150/600 (25.0%) controls (0.79, 0.62 to 1.01; P=0.06). The between group difference in SPPB score was 0.8 points (95% confidence interval 0.5 to 1.1 points; P<0.001) and 1.0 point (95% confidence interval 0.5 to 1.6 points; P<0.001) in favour of the multicomponent intervention at 24 and 36 months, respectively. The decline in handgrip strength at 24 months was smaller in women assigned to the multicomponent intervention than to control (0.9 kg, 95% confidence interval 0.1 to 1.6 kg; P=0.028). Women in the multicomponent intervention arm lost 0.24 kg and 0.49 kg less appendicular lean mass than controls at 24 months (95% confidence interval 0.10 to 0.39 kg; P<0.001) and 36 months (0.26 to 0.73 kg; P<0.001), respectively. Serious adverse events occurred in 237/605 (39.2%) participants assigned

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Mobility is a primary target to maintain function and foster active ageing Lifestyle interventions (eg, physical activity alone or with nutritional counselling/supplementation) are feasible, safe, and effective for improving physical function in older adults at risk of mobility disability

The identification of a condition encompassing reduced physical function and target organ damage (ie, muscle failure) might stimulate the development of preventive interventions against disability in older people who are at risk

## WHAT THIS STUDY ADDS

Physical frailty and sarcopenia is a novel, objectively measurable condition that identifies a subset of the older population at risk of adverse health related events, including mobility disability, whose medical needs are currently unmet

A multicomponent intervention based on moderate intensity physical activity with technological support and nutritional counselling was associated with a reduction in the incidence of mobility disability over 36 months of follow-up in older adults with physical frailty and sarcopenia

to the multicomponent intervention and 216/600 (36.0%) controls (risk ratio 1.09, 95% confidence interval 0.94 to 1.26). In participants with SPPB scores of 8 or 9, mobility disability occurred in 46/155 (29.7%) in the multicomponent intervention and 38/159 (23.9%) controls (hazard ratio 1.25, 95% confidence interval 0.79 to 1.95;  $P=0.34$ ).

### CONCLUSIONS

A multicomponent intervention was associated with a reduction in the incidence of mobility disability in older adults with physical frailty and sarcopenia and SPPB scores of 3-7. Physical frailty and sarcopenia may be targeted to preserve mobility in vulnerable older people.

### TRIAL REGISTRATION

ClinicalTrials.gov NCT02582138.

### Introduction

In advanced age, impaired mobility is associated with higher risk of disability, poor quality of life, admission to hospital, admission to residential care, and death,<sup>1 2</sup> as well as greater healthcare costs.<sup>3</sup> The disabling trajectory of mobility limited older adults might be deflected by lifestyle interventions.<sup>4</sup> In 2013, the Innovative Medicines Initiative Joint Undertaking, a public-private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations, proposed to focus on “physical frailty and sarcopenia” as a prototypical geriatric condition to be targeted for advancing the care of older people at risk of disability.<sup>5</sup> The condition of interest was expected to encompass reduced physical function and target organ damage (ie, low muscle mass), both of which should be objectively measurable. The design and validation of physical frailty and sarcopenia are pivotal in providing regulatory authorities with the framework of a novel nosological condition with clinical relevance and a well defined pathophysiology, that could be adopted to develop specific therapeutics following the standards of drug research.<sup>6</sup> The Sarcopenia and Physical Frailty in older people: multi-component Treatment strategies (SPRINTT) project was therefore designed to elaborate a new, objective definition of physical frailty and sarcopenia—conceptualised as a pre-disability condition with muscle failure as its biological substratum,<sup>7</sup> identify and characterise a population with physical frailty and sarcopenia at risk of adverse outcomes, and test interventions in this population. We defined physical frailty and sarcopenia as the combination of low physical function and low appendicular lean mass in the absence of actual mobility disability.<sup>7</sup>

We designed a multicentre, evaluator blinded, randomised controlled trial to determine whether a multicomponent intervention based on physical activity with technological support and nutritional counselling would reduce the risk of mobility disability in older adults with physical frailty and sarcopenia compared with a healthy ageing lifestyle educational programme.

### Methods

#### Study design

The SPRINTT trial was a multicentre randomised controlled trial conducted from January 2016 to 31 October 2019 at 16 sites across 11 European countries.<sup>8</sup> The European Medicines Agency accepted the trial methodology and analytical strategy during an ad hoc scientific advice procedure that was completed in early 2015. A summary description of the protocol is available on ClinicalTrials.gov (NCT02582138). Details were provided in a dedicated publication<sup>9</sup> and are included in the supplementary appendix. The Università Cattolica del Sacro Cuore in Rome, Italy, coordinated trial activities. Trial sites are listed in the supplementary appendix. As part of the Innovative Medicines Initiative Joint Undertaking of the EU ([www.imi.europa.eu](http://www.imi.europa.eu)), member companies of the European Federation of Pharmaceutical Industries and Associations gave in-kind support. The academic members provided an independent interpretation of results. An independent statistician replicated and verified the analyses.

#### Participants

Participants were men and women aged 70 years or older with physical frailty and sarcopenia, defined as having a short physical performance battery (SPPB)<sup>10</sup> score of 3 to 9 points (scores range from 0 to 12, with lower scores indicating poorer physical function), low appendicular lean mass according to sex specific cut-points recommended by the Foundation for the National Institutes of Health sarcopenia project,<sup>11</sup> and the absence of mobility disability, operationalised as being able to complete a 400 m walk test in less than 15 minutes without sitting, stopping for more than one minute, receiving help, or using a walker.<sup>12</sup> This operational definition of physical frailty and sarcopenia was discussed and agreed with EMA. Main exclusion criteria were self-reported walking disability, cognitive impairment (defined as a minimal state examination<sup>13</sup> score <24/30), terminal illness, participation in a structured physical activity programme, contraindications to safely engage in trial activities as judged by local study doctors, and plans to relocate out of the study area within at least two years.

#### Interventions

The multicomponent intervention and the healthy ageing lifestyle educational programme are extensively described elsewhere.<sup>9</sup> Both interventions were administered for up to 36 months, depending on when participants were recruited during the trial. The multicomponent intervention comprised a combination of moderate intensity physical activity with technological support and nutritional counselling. Physical activity included aerobic, strength, flexibility, and balance exercises.<sup>14</sup> The intervention was divided into an adoption phase (weeks 1-52) and maintenance phase (week 53 to end of the trial). During the adoption phase, two centre based physical activity sessions were conducted weekly. These sessions were

used to initiate the aerobic programme and safely introduce participants to the strength, stretching, and balance components. Centre based sessions were progressively supplemented by home based physical activity sessions: once weekly during weeks 1-4, twice weekly during weeks 4-8, and up to four times weekly during weeks 9-52. The maintenance phase involved two centre based physical activity sessions and up to four home based sessions weekly. Training intensity was adapted through assessment of perceived exertion by the Borg scale (ratings range from 6 to 20, with 6 representing no exertion at all and 20 representing maximal exertion).<sup>15</sup> Participants were asked to walk at an intensity of 13 (somewhat hard). Lower extremity strengthening exercises were performed at an intensity of 15 or 16 (hard). Adherence was ascertained by registering centre attendance and participant completed diaries on frequency of home based sessions. The total amount of physical activity was monitored for seven consecutive days at baseline and every six months using the activPAL3 actimeter (PAL Technologies, Glasgow, UK) worn on the thigh. Instructors could request additional seven day actimetry recordings anytime if indications suggested participants were not complying with physical activity prescriptions. Instructors used the information to provide participants with personalised feedbacks on their performance goals to be reached as part of behavioural strategies to maximise adherence and remove possible disincentives. The nutritional component was designed to support the effects of the physical activity programme. The intervention involved individualised nutritional assessments and prescription of personalised dietary plans with two main targets: a daily energy intake of 25-30 kcal/kg bodyweight and a daily protein intake of at least 1.0-1.2 g/kg bodyweight.<sup>16</sup> A three day dietary record was collected at least once a year, followed by an individualised dietary interview. Adherence to nutritional prescriptions was ascertained through regular contacts with study staff during which participant feedback was collected and dietary plans reviewed. Additional dietary assessments could be performed at the discretion of the interventionist to maximise adherence.

The healthy ageing lifestyle educational programme consisted of seminars and workshops on topics relevant to older adults (eg, vaccinations, chronic pain management, gastrointestinal and urological problems, technological devices, personal safety). Meetings were offered in groups of 10-20 participants once or twice a month, with required participation of at least once a month. A short instructor led programme (5-10 minutes) of upper extremity stretching exercises or some relaxation techniques was offered at the end of each meeting.

### Outcomes

The primary outcome was mobility disability, operationalised as the inability to complete the 400 m walk test in less than 15 minutes without sitting,

stopping for more than one minute, requiring help, or using a walker.<sup>12-14</sup> For the test, participants were asked to complete 10 laps around a 20 m course at their usual pace without overexerting themselves. The 400 m walk test was administered after three months of randomisation and every six months from baseline.

If the 400 m walk test was not performed, a stepwise procedure was devised for outcome adjudication. A predefined algorithm was applied to automatically adjudicate mobility disability based on a 4 m gait speed  $\leq 0.4$  m/s or  $>0.4$  m/s if participants needed a walking aid other than a single straight cane, medical records, or self-reported or proxy reported walking disability. Those participants who did not perform the 400 m walk test and could not be automatically adjudicated were evaluated by an independent committee based on clinical variables, functional tests, and adverse events. Participants were censored at their last successful 400 m walk test if the mobility disability criterion was not met at the end of the trial, at their first consecutive visit when more than nine months had elapsed between two consecutive successful tests, or at the date of the randomisation visit when no post-baseline 400 m walk test was available. Mobility disability was considered to be present at the date participants failed the 400 m walk test, were unable to attempt the test, did not attempt the test and were classified as mobility disabled through the adjudication process, did not attempt the test and mobility disability could not be adjudicated, or died.

The SPRINTT trial includes several prespecified secondary outcomes (supplementary appendix). Here we report the secondary outcomes of persistent mobility disability, operationalised as failure to complete the 400 m walk test on two consecutive occasions or inability to complete the test followed by death,<sup>17</sup> and changes from baseline to 24 and 36 months in measures of physical performance, muscle strength, and appendicular lean mass.

### Sample size calculation

The size of the study population was determined to address the main requirements of the Innovative Medicines Initiative Joint Undertaking to evaluate whether a multicomponent intervention would reduce the risk of incident mobility disability in older adults with physical frailty and sarcopenia, and to characterise the physical frailty and sarcopenia condition and obtain information on intervention effects across its whole SPPB range (scores 3-9). To meet the first requirement, we performed a sample size estimation based on information retrieved from the Lifestyle Interventions and Independence for Elders (LIFE) study database<sup>17</sup> by running survival analyses for mobility disability according to different baseline SPPB score categories ( $<8$  v  $8$  or  $9$ ). In LIFE, the hazard of incident mobility disability was observed to be significantly reduced by physical activity only in participants with SPPB scores  $<8$  (hazard ratio 0.75, 95% confidence interval 0.59 to 0.94;  $P=0.012$ ). We therefore estimated that a sample of 1200 older

people with an SPPB score of 3 to 7, enrolled over 12 months, would provide 85% power (434 mobility disability events) to detect a 25% reduction in the hazard of mobility disability over a maximum follow-up of 36 months, considering a dropout rate of 25% over two years and a log-rank test with a 5% two sided  $\alpha$  level.<sup>9</sup> To address the second objective, we chose to enrol an exploratory sample of 300 participants with low appendicular lean mass and an SPPB score of 8 or 9.<sup>9</sup> The size of this subsample was determined based on feasibility and resource availability. A hierarchical testing procedure was devised to control type I error rate by testing the primary endpoint in the whole study population only in case of a significant result ( $P < 0.05$ ) in participants with SPPB scores of 3 to 7.<sup>9</sup>

Based on a blinded interim sample size reassessment at 11 months, we prolonged the accrual period by six months. A second blinded power reassessment at 29 months revealed a number of mobility disability events that were lower than expected. We extended the follow-up by seven months to maximise the probability of reaching the required number of events and to allow participants recruited during the last phase of accrual to receive intervention and be followed-up for 24 months. The maximum length of interventions and follow-up was kept at 36 months.

#### Randomisation and blinding

Eligible participants were invited to the study sites for an in-person meeting, during which trial procedures and requirements were mentioned again. Participants were then randomised 1:1 to the multicomponent intervention or lifestyle education using a web based randomisation system with permuted block algorithm, stratified by study site, sex, and SPPB score category (3-7 and 8 or 9). An evaluator blinded approach was used to preserve the trial integrity. Accordingly, outcome assessors were unaware of group assignment, clinic and laboratory measurements, and intervention adherence.

#### Safety

All study staff monitored participant safety and reported three categories of adverse events: serious adverse events, unexpected adverse events (those potentially related to study procedures or activities and not listed in the informed consent form or study protocol), and adverse events that occurred while the participant was under the supervision or guidance of study staff either onsite or offsite. Some adverse events were further flagged as of special interest if falling into prespecified categories (ie, abnormal test results requiring medical attention, emergency department visits, fractures, outpatient surgery, and restricted activity possibly due to study procedures). An independent committee reviewed safety data once a year.

#### Statistical analysis

All analyses were performed according to a predefined statistical analysis plan (supplementary appendix).

Baseline characteristics of participants allocated in the two intervention arms are described as means (standard deviations) for continuous variables and absolute numbers (percentages) for categorical variables. Analyses of intervention effects were based on the intention-to-treat principle. For the analysis of the primary efficacy endpoint (time to the first occurrence of mobility disability or death from any cause) we compared intervention arms using a two sided 5%  $\alpha$  level log-rank test procedure stratified by randomisation factors of site and sex. The primary comparison was conducted in randomised participants with baseline SPPB scores of 3 to 7. We used a Cox proportional hazard model stratified by randomisation factors of site and sex to estimate the hazard ratio of mobility disability between intervention groups and the corresponding 95% confidence interval. The Kaplan-Meier method was used to summarise cumulative incidence functions. If the findings of this primary analysis were statistically significant ( $P < 0.05$ ), we would perform an additional analysis to include the exploratory group of participants with SPPB scores of 8 or 9 only if no interaction was observed between SPPB category and intervention arm. We used the Kaplan-Meier method to compare the cumulative incidence functions for the two intervention arms between the two SPPB categories. Prespecified subgroup analyses based on Cox proportional hazard models were conducted to determine whether intervention effects were influenced by baseline personal, clinical, or functional characteristics.

We analysed secondary efficacy endpoints in the two SPPB categories separately. A Cox proportional hazard model stratified by randomisation factors of site and sex was used to estimate the hazard ratio of persistent mobility disability between intervention groups and the corresponding 95% confidence interval. Changes from baseline to 24 and 36 months in SPPB score, handgrip strength, and appendicular lean mass were analysed by mixed effect models with repeated measures. Models included the fixed categorical effects of intervention arm, the planned time point, the randomisation factors of site and sex, the intervention $\times$ time point interaction, and the continuous fixed covariates of baseline value and baseline value $\times$ time point interaction. For all analyses, a two sided  $P < 0.05$  was considered to be statistically significant.

We analysed safety data by intervention group in the two SPPB categories separately. Risk ratio with 95% confidence interval was used to estimate the probability of experiencing an adverse event.

All analyses were run using SAS version 9.4 (Cary, NC).

#### Patient and public involvement

A dialogue and knowledge platform was established at the beginning of the project through the mapping of stakeholders (older adults' representatives, healthcare professionals, and experts in bioethics, data security, privacy, storage and use, and bioinformatics), and



their invitation to conference calls and in-person meetings focused on the operational definition of physical frailty and sarcopenia, treatment protocols, strategies for participant recruitment and engagement, health literacy plans, and dissemination activities. The platform was subsequently extended to include regulatory experts from the EU to reach a consensus on the definition of the target population and trial methodology. After trial commencement, quarterly teleconferences were held with EMA to discuss progress of the project, emerging problems, safety aspects, and other relevant events in the trial.

Educational contents were produced for older people and their caregivers. In particular, to promote health literacy on the topics of frailty and sarcopenia, we developed leaflets that were freely downloadable from the project website.

Participants were actively involved in recruitment by advertising the trial among their peers. In addition, the dialogue and knowledge platform provided recommendations on strategies to reach out to the target population and maximise participant engagement in the trial activities. Participants were regularly asked to provide feedback on the intervention burden and other issues that might affect their motivation to participate in the trial. Local study staff evaluated the information collected and forwarded it to the coordinating centre in Rome for further evaluation with assistance of the dialogue and knowledge platform. No corrective actions were required.

## Results

### Participants

Participants were recruited from January 2016 to November 2017. Randomisation began on 3 February 2016 and enrolment finished on 15 November 2017. The final follow-up visit was on 31 October 2019. Details on screening, recruitment strategies, and characteristics of eligible participants are reported elsewhere.<sup>8</sup> Of 12 358 screened candidates, 1519 were eligible and agreed to be randomised: 760 to the multicomponent intervention and 759 to the lifestyle education group. Overall, 1205 (79.3%) participants had an SPPB score of 3 to 7 and 314 (20.7%) had an SPPB score of 8 or 9 (fig 1).

Baseline characteristics were comparable between intervention groups within SPPB categories (table 1). The mean age of the study population was 78.9 (standard deviation 5.8) years, 1088/1519 (71.6%) were women, and the average body mass index (BMI) was 28.6 (SD 5.7). The average SPPB score was 6.7 (SD 1.0). The mean appendicular lean mass was 21.0 (SD 3.6) kg in men and 14.6 (SD 2.1) kg in women; mean BMI adjusted appendicular lean mass was 0.72 (SD 0.07) and 0.53 (SD 0.07), respectively. Osteoarthritis was reported by 76.9% (1168/1519) of participants, hypertension by 65.9% (1001/1519), and diabetes by 21.5% (326/1519). Overall, 44.6% (678/1519) reported a fall in the previous year. The average length of follow-up from randomisation was 26.4 (SD 9.5) months.

### Intervention adherence

After excluding medical leave and other circumstances that prevented participants from exercising (eg, travel, personal problems, transportation issues, national holidays), those assigned to the multicomponent intervention on average attended 67.0% (SD 22.8%) and 73.5% (SD 36.5%) of centre based and home based physical activity sessions, respectively. The mean number of excluded centre based and home based sessions was 47.8 and 63.9, respectively. Walking activity, sitting and lying time, and standing activity time, captured through a wearable actimeter, showed participants in the multicomponent intervention had a more active lifestyle than those in the control group, especially those with SPPB scores of 3 to 7, during the first two years of the trial (supplementary appendix, fig S1). Differences in actimetry data between intervention groups were no longer evident 24 months after randomisation, when the number of observations was substantially lower. Overall, 78.6% of participants completed full nutritional assessments, including dietary records over three days. Relative to baseline daily energy intake (23.3 (SD 7.4) kcal/kg/day), values increased by 6.8% at 24 months (24.1 (SD 7.1) kcal/kg/day) and 10.7% at 36 months (26.1 (SD 7.5) kcal/kg/day). A similar pattern was observed for daily protein intake, the values of which increased from baseline (0.98 (SD 0.32) g/kg/day) by 10.9% at 24 months (1.10 (SD 0.32) g/kg/day) and by 14.8% at 36 months (1.15 (SD 0.32) g/kg/day).

Participants in the lifestyle education group attended on average 65.9% (SD 26.4%) of scheduled meetings, after medical leave and other circumstances that prevented participation had been excluded. A mean of 7.9 meetings were excluded.

### Primary outcome

Post-baseline 400 m walk tests were unavailable for 36/760 (4.7%) participants in the multicomponent intervention group and 39/759 (5.1%) in the lifestyle education group. In participants with an SPPB score of 3 to 7, mobility disability occurred in 283/605 (46.8%) in the multicomponent intervention group (six deaths, 1.0%) and 316/600 (52.7%) in the lifestyle education group (seven deaths, 1.2%) (hazard ratio 0.78, 95% confidence interval 0.67 to 0.92;  $P=0.005$ ) (fig 2). Results were consistent when death was removed from the primary outcome (0.79, 0.67 to 0.93;  $P=0.006$ ).

As a qualitative interaction between SPPB category and intervention arm was found when the cumulative event curves for participants with SPPB scores of 3-7 and a score of 8 or 9 were compared, we analysed those with an SPPB score of 8 or 9 separately. In this subset, mobility disability occurred in 46/155 (29.7%) participants in the multicomponent intervention group (three deaths, 1.9%) and 38/159 (23.9%) in the lifestyle education group (two deaths, 1.3%) (hazard ratio 1.25, 95% confidence interval 0.79 to 1.95;  $P=0.34$ ) (supplementary appendix, fig S2). Subgroup analyses in participants with an SPPB score of 3 to 7 showed that the effects of interventions on incident mobility disability were comparable across sexes,

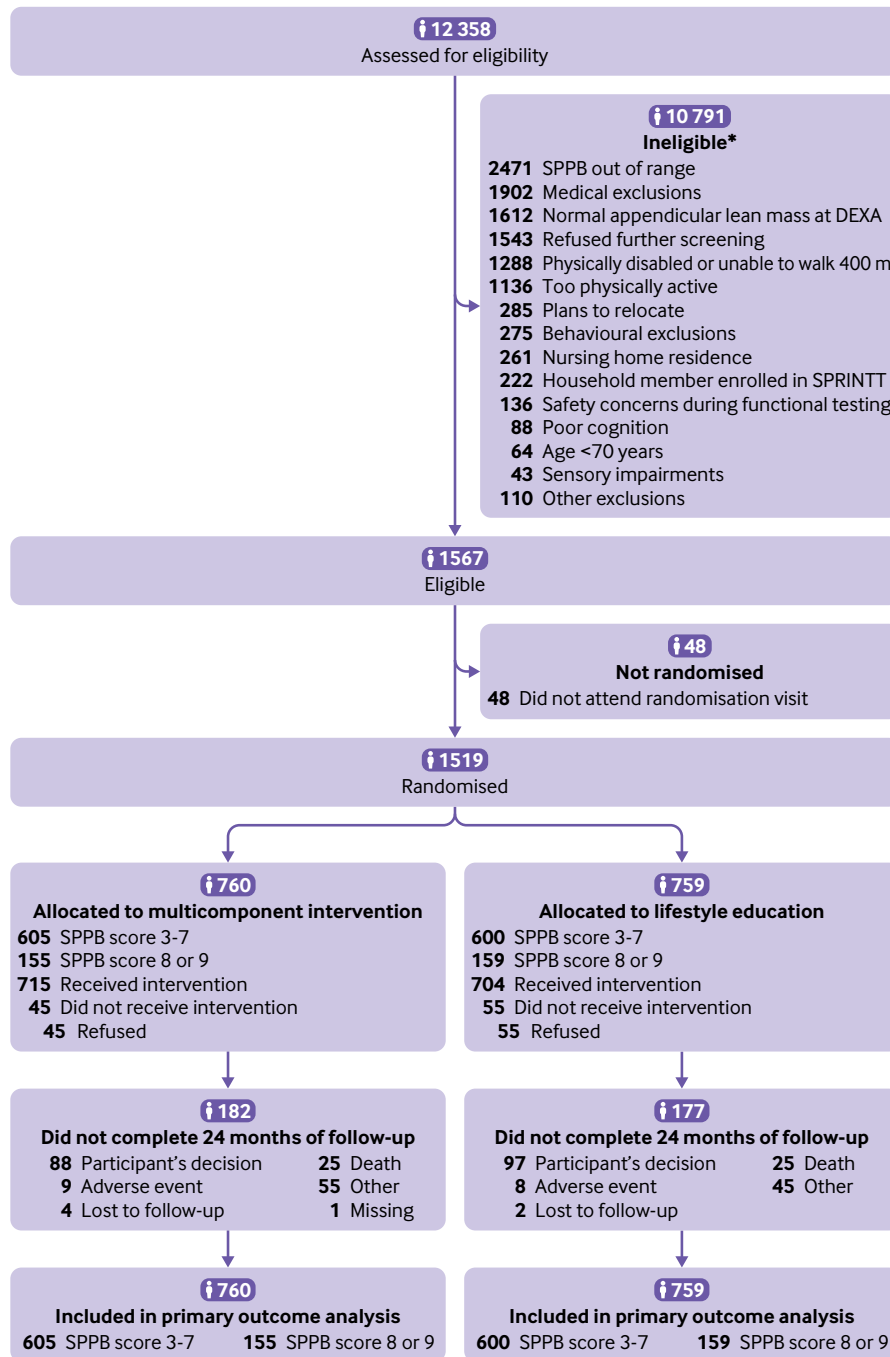


Fig 1 | Flow of participants through study. \*Sum of individual items is higher than number of ineligible participants because screening was not always stopped at the first unmet eligibility criterion. Some entries are different from those previously published<sup>8</sup> because of data updates after database cleaning. DEXA=dual energy x ray absorptiometry; SPPB=short physical performance battery; SPRINTT=Sarcopenia and Physical fRailty IN older people: multi-component Treatment strategies

rates, age groups, history of cardiovascular disease, history of diabetes, and 4 m gait speed <0.8 m/s or ≥0.8 m/s (fig 3). The gait speed cut-point was chosen based on previous findings, which showed that a walking speed at usual pace slower than 0.8 m/s identifies older adults at risk of adverse outcomes.<sup>2 18</sup>

#### Secondary outcomes

Table 2 and table 3 show the results for secondary outcomes. In participants with an SPPB score of 3 to

7, persistent mobility disability occurred in 127/605 (21.0%) in the multicomponent intervention group (seven deaths, 1.2%) and 150/600 (25.0%) in the lifestyle education group (four deaths, 0.7%) (hazard ratio 0.79, 95% confidence interval 0.62 to 1.01; P=0.06). The SPPB score increased more in the multicomponent intervention group than lifestyle education group at both 24 months (least squares mean difference 0.8 points, 95% confidence interval 0.5 to 1.1 points; P<0.001) and 36 months (1.0 point, 0.5 to

**Table 1 | Baseline characteristics of study participants according to short physical performance battery (SPPB) score category and group allocation. Values are number (percentages) unless stated otherwise**

Characteristics	SPPB score 3-7			SPPB score 8 or 9		
	Multicomponent intervention (n=605)	Lifestyle education (n=600)	All (n=1205)	Multicomponent intervention (n=155)	Lifestyle education (n=159)	All (n=314)
<b>Personal characteristics</b>						
Mean (SD) age (years)	79.3 (5.9)	79.2 (5.8)	79.2 (5.8)	78.3 (5.7)	77.1 (5.4)	77.7 (5.6)
Women	434 (71.7)	425 (70.8)	859 (71.3)	113 (72.9)	116 (73.0)	229 (72.9)
<b>Ethnicity:</b>						
White	535 (88.4)	526 (87.7)	1061 (88.0)	136 (87.7)	138 (86.8)	274 (87.3)
Others	7 (1.2)	8 (1.3)	15 (1.2)	3 (1.9)	2 (1.3)	5 (1.6)
Not available	63 (10.4)	66 (11.0)	129 (10.7)	16 (10.3)	19 (11.9)	35 (11.1)
Mean (SD) BMI	28.7 (5.4)	28.7 (5.9)	28.7 (5.7)	28.2 (5.6)	28.3 (6.1)	28.2 (5.9)
<b>Physical frailty and sarcopenia defining criteria</b>						
Mean (SD) SPPB summary score	6.2 (1.1)	6.2 (1.1)	6.2 (1.1)	8.6 (0.5)	8.6 (0.5)	8.6 (0.5)
Mean (SD) appendicular lean mass (kg):						
Men	20.94 (3.55)	20.88 (3.52)	20.91 (3.53)	21.18 (3.17)	22.06 (3.99)	21.62 (3.61)
Women	14.61 (2.00)	14.74 (2.20)	14.68 (2.10)	14.54 (1.85)	14.47 (2.02)	14.50 (1.93)
Mean (SD) appendicular lean mass/BMI:						
Men	0.72 (0.08)	0.72 (0.07)	0.72 (0.07)	0.74 (0.09)	0.72 (0.07)	0.73 (0.08)
Women	0.52 (0.07)	0.52 (0.07)	0.52 (0.07)	0.54 (0.08)	0.54 (0.08)	0.54 (0.08)
<b>Cognition and physical performance</b>						
Mean (SD) MMSE score	27.9 (1.8)	27.8 (1.8)	27.9 (1.8)	28.1 (1.8)	28.4 (1.8)	28.2 (1.8)
Mean (SD) time to walk 400 m (min)	8.99 (2.51)	9.06 (2.50)	9.02 (2.51)	7.72 (2.11)	7.27 (1.59)	7.49 (1.87)
Mean (SD) 400 m walk speed (m/s)	0.80 (0.21)	0.79 (0.21)	0.79 (0.21)	0.92 (0.22)	0.95 (0.17)	0.94 (0.20)
Mean (SD) handgrip strength (kg):						
Men	28.3 (8.7)	28.7 (9.6)	28.5 (9.1)	29.3 (9.6)	29.9 (9.9)	29.6 (9.7)
Women	16.6 (5.5)	17.0 (5.9)	16.8 (5.7)	17.9 (4.9)	16.9 (5.0)	17.4 (4.9)
<b>Clinical characteristics</b>						
Osteoarthritis	466 (77.0)	463 (77.2)	929 (77.1)	122 (78.7)	117 (73.6)	239 (76.1)
Any cardiovascular medical history	443 (73.2)	423 (70.5)	866 (71.9)	114 (73.5)	100 (62.9)	214 (68.2)
Hypertension	413 (68.3)	392 (65.3)	805 (66.8)	105 (67.7)	91 (57.2)	196 (62.4)
Myocardial infarction	46 (7.6)	50 (8.3)	96 (8.0)	16 (10.3)	16 (10.1)	32 (10.2)
Congestive heart failure	42 (6.9)	45 (7.5)	87 (7.2)	4 (2.6)	9 (5.7)	13 (4.1)
Chronic lung disease	99 (16.4)	88 (14.7)	187 (15.5)	20 (12.9)	26 (16.4)	46 (14.6)
Stroke or brain haemorrhage	46 (7.6)	41 (6.8)	87 (7.2)	8 (5.2)	6 (3.8)	14 (4.5)
Diabetes mellitus	131 (21.7)	139 (23.2)	270 (22.4)	26 (16.8)	30 (18.9)	56 (17.8)
Cancer (excluding minor skin cancer)	79 (13.1)	82 (13.7)	161 (13.4)	25 (16.1)	25 (15.7)	50 (15.9)
Falls in past year	284 (46.9)	270 (45.0)	554 (46.0)	62 (40.0)	62 (39.0)	124 (39.5)
Injurious falls in past year	102 (35.9)	86 (31.9)	188 (33.9)	25 (41.0)	20 (32.3)	45 (36.6)
Previous hip fracture	35 (5.8)	34 (5.7)	69 (5.7)	12 (7.7)	10 (6.3)	22 (7.0)
Previous non-femoral fracture	198 (32.7)	191 (31.8)	389 (32.3)	48 (31.0)	53 (33.3)	101 (32.2)
Emotional, nervous, psychiatric problems	130 (21.5)	128 (21.3)	258 (21.4)	39 (25.2)	40 (25.2)	79 (25.2)
At least one drug at time of screening	578 (95.5)	578 (96.3)	1156 (95.9)	147 (94.8)	150 (94.3)	297 (94.6)
≥5 drugs at time of screening	358 (59.2)	340 (56.7)	698 (57.9)	76 (49.0)	80 (50.3)	156 (49.7)

BMI=body mass index; MMSE=mini-mental state examination.

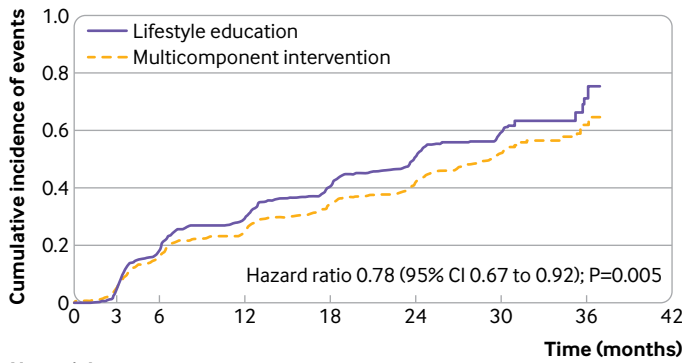
1.6 points;  $P<0.001$ ). The decline in handgrip strength at 24 months was smaller in women assigned to the multicomponent intervention than those assigned to lifestyle education (0.9 kg, 95% confidence interval 0.1 to 1.6 kg;  $P=0.028$ ). No significant between group differences were observed in men. Women in the multicomponent intervention group lost less appendicular lean mass than women in the lifestyle education group at both time points (24 months 0.24 kg, 0.10 to 0.39 kg;  $P<0.001$ ; 36 months 0.49 kg, 0.26 to 0.73 kg;  $P<0.001$ ). No significant between group differences were observed in men.

In participants with an SPPB score of 8 or 9, persistent mobility disability occurred in 16/155 (10.3%) in the multicomponent intervention group (one death, 0.6%) and 16/159 (10.1%) in the lifestyle education group (one death, 0.6%) (hazard ratio 1.14, 95% confidence interval 0.55 to 2.36;  $P=0.72$ ).

A 0.5 point difference in the SPPB score in favour of the multicomponent intervention was observed at 24 months (95% confidence interval 0.1 to 1.0 points;  $P=0.027$ ). No significant between group differences were observed for handgrip strength at any time point in either men or women. At 36 months, women in the multicomponent intervention lost less appendicular lean mass than women in the lifestyle education group (0.60 kg, 95% confidence interval 0.30 to 0.90;  $P<0.001$ ).

### Safety

Table 4 shows the results for safety. In participants with an SPPB score of 3 to 7, 337/605 (55.7%) in the multicomponent intervention group and 297/600 (49.5%) in the lifestyle education group experienced at least one adverse event during the trial (risk ratio 1.13, 95% confidence interval 1.01 to 1.25). Serious adverse



No at risk	
Multicomponent intervention	
605 547 474 413 346 259 106 18	
Lifestyle education	
600 537 452 378 299 196 98 13	
No of events	
Multicomponent intervention	
0 28 93 141 195 231 267 281	
Lifestyle education	
0 26 103 163 222 270 299 313	

Fig 2 | Kaplan-Meier curves for incident mobility disability in participants with baseline short physical performance battery (SPPB) score of 3-7. The graph is truncated at 36 months, after which two additional mobility disability events were recorded in the multicomponent intervention group and three in the lifestyle education group. CI=confidence interval

events occurred in 237/605 (39.2%) participants in the multicomponent intervention group and 216/600 (36.0%) in the lifestyle education group (1.09, 0.94 to 1.26). Falls were recorded in 80/605 (13.2%) participants in the multicomponent intervention group and 49/600 (8.2%) in the lifestyle education group

(1.62, 1.16 to 2.27). Deaths occurred in 31/605 (5.1%) participants in the multicomponent intervention group and 25/600 (4.2%) in the lifestyle education group (1.23, 0.74 to 2.06).

In participants with an SPPB score of 8 or 9, 79/155 (51.0%) in the multicomponent intervention group and 79/159 (49.7%) in the lifestyle education group experienced at least one adverse event during the trial (1.03, 0.82 to 1.28). Serious adverse events occurred in 45/155 (29.0%) participants in the multicomponent intervention group and 48/159 (30.2%) in the lifestyle education group (0.96, 0.68 to 1.35). Falls were recorded in 9/155 (5.8%) participants in the multicomponent intervention group and 16/159 (10.1%) in the lifestyle education group (0.58, 0.26 to 1.27). Deaths occurred in 5/155 (3.2%) participants in the multicomponent intervention group and 3/159 (1.9%) in the lifestyle education group (1.71, 0.42 to 7.03).

The proportion of participants who were admitted to hospital or to the emergency department was comparable between intervention groups within SPPB categories. Reasons for hospital admission and emergency department or urgent care visits were highly heterogeneous and were considered unrelated to study procedures.

Discussion

In the SPRINTT trial, an intervention based on physical activity with technological support and nutritional counselling in participants with physical frailty and sarcopenia and an SPPB score of 3 to 7 was associated with a reduction in the risk of incident mobility disability during 36 months of follow-up, compared with an intervention comprising lifestyle education. Participants with an SPPB score of 3 to 7 assigned to the multicomponent intervention showed greater improvements in physical performance than participants assigned to lifestyle education. Women with an SPPB score of 3 to 7 in the multicomponent intervention group lost less muscle strength and appendicular lean mass than women in the lifestyle education group. In participants with an SPPB score of 8 or 9, the multicomponent intervention did not affect the risk of developing mobility disability, had marginal effects on physical performance, and, in women, attenuated the loss of appendicular lean mass.

Comparison with previous studies

Several investigations have tested the impact of lifestyle interventions on frailty, disability, and other health outcomes in community dwelling older adults. In LIFE, a physical activity intervention was associated with a reduction in the risk of mobility disability over 2.6 years of follow-up compared with a health education programme in 1635 older adults with an SPPB score of  $\leq 9$ .<sup>17</sup> In participants with an SPPB score of  $< 8$  (731, 44.7%), mobility disability developed in 38.2% of those in the physical activity intervention group and 46.8% in the control group. In participants with an SPPB score of 8 or 9, mobility disability occurred in

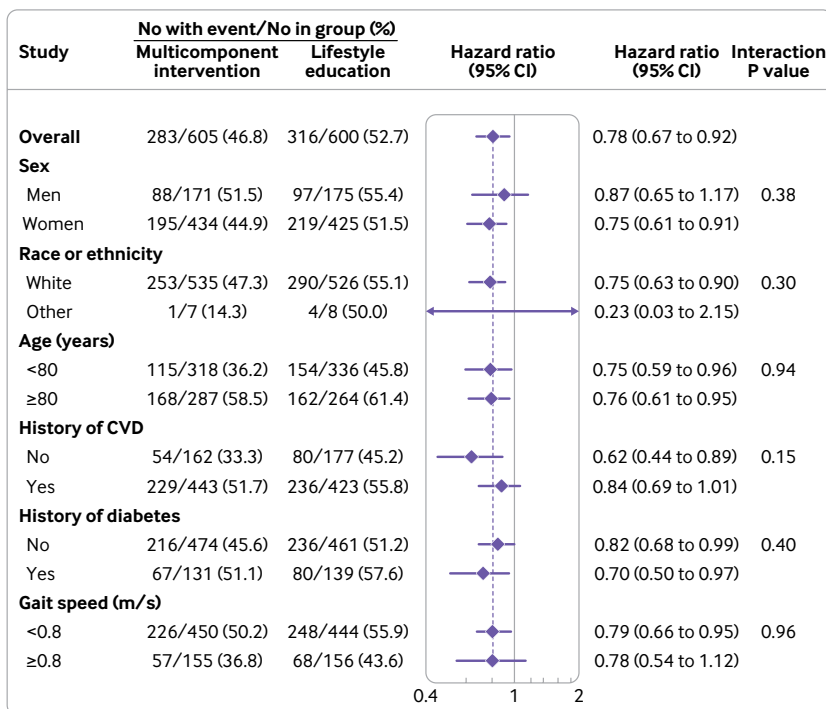


Fig 3 | Prespecified subgroup analyses in participants with baseline short physical performance battery (SPPB) score of 3-7. CVD=cardiovascular disease; CI=confidence interval



**Table 2 | Secondary outcomes in participants with baseline short physical performance battery (SPPB) score 3-7 according to group allocation**

Outcomes	Multicomponent intervention (n=605)	Lifestyle education (n=600)	Effect size (95% CI)	P value
No (%) of persistent mobility disability events	127 (21.0)	150 (25.0)	0.79 (0.62 to 1.01)*	0.06
<b>Changes from baseline in physical performance (SPPB summary score)</b>				
24 months	2.0 (0.1)	1.2 (0.1)	0.8 (0.5 to 1.1)	<0.001
36 months	2.0 (0.2)	1.0 (0.2)	1.0 (0.5 to 1.6)	<0.001
<b>Changes from baseline in handgrip (muscle) strength (kg)</b>				
Men:				
24 months	-1.6 (0.5)	-1.6 (0.5)	0.0 (-1.4 to 1.5)	0.97
36 months	-2.8 (1.4)	-4.4 (1.2)	1.6 (-2.2 to 5.4)	0.41
Women:				
24 months	-0.3 (0.3)	-1.1 (0.3)	0.9 (0.1 to 1.6)	0.028
36 months	-0.3 (0.4)	-1.3 (0.4)	0.9 (-0.2 to 2.1)	0.11
<b>Changes from baseline in appendicular lean mass</b>				
Men:				
24 months	-0.55 (0.12)	-0.83 (0.12)	0.28 (-0.06 to 0.62)	0.11
36 months	-0.55 (0.34)	-0.78 (0.33)	0.23 (-0.72 to 1.18)	0.65
Women:				
24 months	-0.13 (0.05)	-0.37 (0.05)	0.24 (0.10 to 0.39)	<0.001
36 months	-0.19 (0.09)	-0.68 (0.08)	0.49 (0.26 to 0.73)	<0.001
<b>Changes from baseline in appendicular lean mass/body mass index</b>				
Men:				
24 months	-0.01 (0.00)	-0.01 (0.00)	0.00 (-0.01 to 0.02)	0.48
36 months	-0.02 (0.02)	-0.01 (0.01)	-0.02 (-0.06 to 0.03)	0.53
Women:				
24 months	0.00 (0.00)	-0.01 (0.00)	0.01 (0.00 to 0.02)	0.002
36 months	0.00 (0.00)	-0.01 (0.00)	0.02 (0.01 to 0.03)	0.003

CI=confidence interval.

Values are least squared means (standard errors), except for persistent mobility disability.

\*Hazard ratio (95% CI). For all other secondary outcomes, effect size is shown as least squared mean difference (95% CI) between multicomponent intervention and lifestyle education.

23.9% of those in the physical activity intervention group and 25.7% in the control group.<sup>17</sup> In SPRINTT, the proportion of participants with an SPPB score of 3 to 7 who experienced mobility disability was 46.8% (283/605) in the multicomponent intervention group (45.8% excluding deaths) and 52.7% (316/600) in the lifestyle education group (51.5% excluding deaths). In those with an SPPB score of 8 or 9, incident mobility disability occurred in 29.7% of participants (46/155) in the multicomponent intervention group and 23.9% (38/159) in the control group. These findings suggest that in older adults with an SPPB score of <8 the presence of reduced appendicular lean mass might identify a subset of mobility limited adults at especially high risk of disability. This observation might also explain why the effect size of the multicomponent intervention was lower than expected (22% v 25%). The estimation was based on the results of LIFE, in which only a portion of participants presumably had low appendicular lean mass.<sup>19</sup> In the exploratory sample of older adults with moderate reduction in physical function, the primary outcome was observed more frequently in those assigned to the multicomponent intervention than those assigned to lifestyle education. This finding is unexpected and in contrast with results from LIFE; owing to insufficient power and wide confidence intervals, however, no meaningful interpretations can be provided.

Participants with an SPPB score of 3 to 7 assigned to the multicomponent intervention had a 2 point higher score at 36 months relative to baseline. The SPPB score in those in the lifestyle education group had increased by 1 point at 36 months. A 0.5 point increase in SPPB score was observed at 36 months in participants with an SPPB score of 8 or 9, regardless of group allocation. The improvement experienced by participants with an SPPB score of 3 to 7 equals or exceeds clinically meaningful changes of the test (1.0-1.5 points).<sup>20 21</sup> The between group difference in SPPB score in favour of the multicomponent intervention (0.8 points at 24 months and 1.0 point at 36 months) is consistent with previous studies that tested lifestyle interventions in frail older people.<sup>22-25</sup>

The multicomponent intervention showed a positive effect on appendicular lean mass in women, irrespective of SPPB category. Studies have shown that sex influences body composition changes in response to exercise in old age, with women experiencing greater benefits than men.<sup>26 27</sup> In addition, sex specific associations between protein intake and longitudinal changes in appendicular lean mass have been described in older people.<sup>28</sup>

### Strengths and limitations of this study

The SPRINTT trial has several strengths. The physical frailty and sarcopenia construct, albeit original, relies on validated tests and assessments. SPPB is a comprehensive test that captures limitations in lower extremity function.<sup>10</sup> For its validity, sensitivity to changes, reproducibility, feasibility, and predictive value for disability and mortality across healthcare settings, the EMA indicated SPPB as the preferred option to characterise physical frailty for intervention trials in older adults.<sup>29</sup> Indeed, changes in SPPB scores are increasingly used as key efficacy endpoints in clinical trials on sarcopenia, physical frailty, and other age related conditions.<sup>22 24 25 30 31</sup> The presence of low appendicular lean mass was determined according to the cut-points recommended by the Foundation for the National Institutes of Health as the best predictors of mobility disability.<sup>11</sup> Study participants were followed for up to 36 months, confirming the feasibility of identifying, enrolling, and retaining frail older adults on a large scale.<sup>17 22 32</sup> The study sample included a geographically and culturally heterogeneous cohort of frail older people across Europe. The key efficacy endpoints are reliable, standardised, and well validated outcomes in older people.<sup>33 34</sup> Dietary plans were tailored to the nutritional needs of individual participants following expert recommendations for standard practice in geriatrics.<sup>16</sup> The physical activity routine, which can be performed at home after a supervised familiarisation phase, is included in international guidelines for the management of frailty in older people.<sup>35 36</sup> Retention and adherence to interventions were high and comparable with other major non-drug trials in frail older adults.<sup>17 22 32</sup> Finally, the multicomponent intervention proved to be feasible, safe, and effective in a highly vulnerable population. The risk of adverse events was, however,

**Table 3 | Secondary outcomes in participants with baseline short physical performance battery (SPPB) score 8 or 9 according to group allocation**

Outcomes	Multicomponent intervention (n=155)	Lifestyle education (n=159)	Effect size (95% CI)	P value
No (%) of persistent mobility disability events	16 (10.3)	16 (10.1)	1.14 (0.55 to 2.36)*	0.72
Changes from baseline in physical performance (SPPB summary score)				
24 months	1.0 (0.2)	0.5 (0.2)	0.5 (0.1 to 1.0)	0.027
36 months	0.5 (0.3)	0.5 (0.3)	-0.0 (-0.8 to 0.7)	0.94
Changes from baseline in handgrip (muscle) strength (kg)				
Men:				
24 months	-2.0 (1.2)	-0.4 (1.1)	-1.7 (-5.0 to 1.7)	0.33
36 months	-3.7 (1.9)	-2.4 (1.6)	-1.2 (-6.2 to 3.8)	0.65
Women:				
24 months	0.1 (0.4)	-0.2 (0.4)	0.2 (-0.8 to 1.2)	0.70
36 months	-1.2 (0.5)	0.0 (0.6)	-1.2 (-2.7 to 0.3)	0.12
Changes from baseline in appendicular lean mass				
Men:				
24 months	-0.63 (0.26)	-0.46 (0.22)	-0.17 (-0.86 to 0.52)	0.64
36 months	-1.34 (0.38)	-1.33 (0.32)	-0.01 (-1.05 to 1.04)	0.99
Women:				
24 months	-0.12 (0.08)	-0.35 (0.08)	0.22 (-0.01 to 0.46)	0.06
36 months	-0.18 (0.11)	-0.78 (0.11)	0.60 (0.30 to 0.90)	<0.001
Changes from baseline in appendicular lean mass/body mass index				
Men:				
24 months	-0.01 (0.01)	-0.02 (0.01)	0.01 (-0.01 to 0.03)	0.52
36 months	-0.02 (0.02)	-0.07 (0.01)	0.05 (-0.01 to 0.10)	0.08
Women:				
24 months	0.00 (0.00)	-0.01 (0.00)	0.01 (-0.01 to 0.02)	0.33
36 months	-0.01 (0.01)	-0.02 (0.01)	0.02 (0.00 to 0.03)	0.022

CI=confidence interval.

Values are least squared means (standard errors), except for persistent mobility disability.

\*Hazard ratio (95% CI). For all other secondary outcomes, effect size is shown as least squared mean difference (95% CI) between multicomponent intervention and lifestyle education.

greater among participants with a baseline SPPB score of 3 to 7 assigned to the multicomponent intervention than those assigned to lifestyle education (table 4). A similar finding was reported in LIFE<sup>17</sup> and in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial,<sup>32</sup> and is consistent with the results of a recent systematic review and meta-analysis of clinical trials on exercise interventions.<sup>37</sup> Participants in the multicomponent intervention had more frequent contacts with study staff, potentially resulting in a higher rate of adverse event recognition and reporting. The incidence of serious adverse events was, however, comparable between the intervention groups.

SPRINTT has limitations. Almost all participants were white, which impedes generalising findings to other ethnic groups. Older adults with important cognitive deficits were not included in the trial. Owing to the need for frequent in-person contacts, most participants resided within a short distance of the study sites. Therefore, they might not be fully representative of people from the community or those living in rural areas. Differences between intervention groups in the frequency of interactions with their peers and the study staff could have influenced outcomes. The composite nature of the multicomponent intervention does not allow the relative contribution of its individual components to the overall effect to be established. However, previous studies have shown that physical activity conveys most functional

benefits of multidomain interventions in frail older adults.<sup>38</sup> The confidence interval of the primary outcome analysis was wide, which is consistent with major trials on lifestyle interventions in frail older adults.<sup>17 22 24 25 32</sup> This might be explained—at least partly—by the heterogeneity of frail older people and might reflect various degrees of responsiveness to interventions.<sup>39</sup> Finally, although outcome assessors were blinded to group assignment, it was not possible to blind participants to their intervention allocation.

### Unanswered questions and future research

The multicomponent intervention showed no effect on mortality or other major outcomes, such as risk of severe illnesses and admission to hospital. The trial design does not allow inference about whether this was due to the duration of the intervention or its characteristics. Future, ad hoc designed studies are warranted to establish whether interventions involving physical activity and nutritional counselling improve survival and overall health in vulnerable older adults. Although regular physical activity might be beneficial for preventing falls and fall related fractures in older people,<sup>40</sup> rates of falls were greater in participants with SPPB scores of 3 to 7 in the multicomponent intervention group than in participants in the lifestyle education group (table 4). These findings are in line with those of LIFE<sup>17 41</sup> and suggest that the SPRINTT training programme may not be adequate for preventing falls in frail older adults. Physical activity routines mostly based on walking, such as those tested in SPRINTT and LIFE, may paradoxically expose participants to a greater risk of falling, possibly through increasing confidence in daily activities.<sup>42 43</sup> Studies are needed to identify the optimal characteristics of physical activity programmes (eg, duration, frequency, volume, type of exercises) that allow prevention of disability and falls in vulnerable older adults. The technological support part of the multicomponent intervention was based on the use of a research grade actimeter. Future studies are warranted to explore whether increasingly available, user friendly, and reliable activity monitoring systems and e-health platforms could enable frail older people to better adhere to physical activity recommendations and be regularly monitored for safety.

### Policy implications

US and EU data indicate that about 13% of community dwelling adults aged 70 years and older have mobility disability.<sup>1 44</sup> Almost half of participants in SPRINTT developed mobility disability over 36 months, indicating that the condition of interest is clinically relevant and identifies an important public health problem. This may support the recognition of physical frailty and sarcopenia as a new clinical entity by regulatory agencies. The multicomponent intervention was associated with a decrease in the risk of incident mobility disability in those with SPPB scores of 3 to 7, which may help overcome the therapeutic nihilism that has so far surrounded low physical function and muscle failure in old age. This, in turn, is expected to

**Table 4 | Adverse events experienced by study participants throughout the trial according to short physical performance battery (SPPB) score category and group allocation**

Type of event	SPPB score 3-7					SPPB score 8 or 9				
	Multicomponent intervention (n=605)		Lifestyle education (n=600)			Multicomponent intervention (n=155)		Lifestyle education (n=159)		
	No (%) of participants	No of events	No (%) of participants	No of events	Risk ratio (95% CI)	No (%) of participants	No of events	No (%) of participants	No of events	Risk ratio (95% CI)
Any adverse event	337 (55.7)	832 (0.66)	297 (49.5)	678 (0.53)	1.13 (1.01 to 1.25)	79 (51.0)	176 (0.49)	79 (49.7)	163 (0.43)	1.03 (0.82 to 1.28)
Serious adverse events	237 (39.2)	451 (0.36)	216 (36.0)	393 (0.31)	1.09 (0.94 to 1.26)	45 (29.0)	83 (0.23)	48 (30.2)	72 (0.19)	0.96 (0.68 to 1.35)
Death	31 (5.1)	31 (0.02)	25 (4.2)	25 (0.02)	1.23 (0.74 to 2.06)	5 (3.2)	5 (0.01)	3 (1.9)	3 (<0.01)	1.71 (0.42 to 7.03)
Life threatening illness	24 (4.0)	29 (0.02)	16 (2.7)	23 (0.02)	1.49 (0.80 to 2.78)	4 (2.6)	4 (0.01)	2 (1.3)	4 (0.01)	2.05 (0.38 to 11.04)
Hospital admission	204 (33.7)	378 (0.30)	196 (32.7)	352 (0.27)	1.03 (0.88 to 1.21)	40 (25.8)	65 (0.18)	43 (27.0)	63 (0.17)	0.95 (0.66 to 1.38)
Permanent disability	11 (1.8)	13 (0.01)	6 (1.0)	6 (<0.01)	1.82 (0.68 to 4.88)	2 (1.3)	2 (<0.01)	2 (1.3)	2 (<0.01)	1.03 (0.17 to 7.19)
Other serious illness	28 (4.6)	31 (0.02)	17 (2.8)	22 (0.02)	1.63 (0.90 to 2.95)	6 (3.9)	12 (0.03)	3 (1.9)	3 (<0.01)	2.05 (0.52 to 8.06)
Unexpected events possibly related to study procedures	33 (5.5)	60 (0.05)	38 (6.3)	65 (0.05)	0.86 (0.55 to 1.35)	7 (4.5)	13 (0.04)	14 (8.8)	29 (0.08)	0.51 (0.21 to 1.24)
Falls	80 (13.2)	108 (0.09)	49 (8.2)	61 (0.05)	1.62 (1.16 to 2.27)	9 (5.8)	13 (0.04)	16 (10.1)	19 (0.05)	0.58 (0.26 to 1.27)
Events under supervision or guidance of study staff	26 (4.3)	27 (0.02)	10 (1.7)	10 (<0.01)	2.58 (1.25 to 5.30)	7 (4.5)	8 (0.02)	2 (1.3)	2 (<0.01)	3.59 (0.76 to 17.01)
Adverse events of special interest	169 (27.9)	345 (0.27)	135 (22.5)	252 (0.20)	1.24 (1.02 to 1.51)	51 (32.9)	89 (0.25)	38 (23.9)	72 (0.19)	1.38 (0.96 to 1.97)
Abnormal test results requiring medical attention	28 (4.6)	30 (0.02)	18 (3.0)	21 (0.02)	1.54 (0.86 to 2.76)	7 (4.5)	10 (0.03)	2 (1.3)	2 (<0.01)	3.59 (0.76 to 17.01)
Emergency department visits	102 (16.9)	191 (0.15)	84 (14.0)	156 (0.12)	1.20 (0.92 to 1.57)	30 (19.4)	53 (0.15)	26 (16.4)	41 (0.11)	1.18 (0.74 to 1.91)
Fractures	33 (5.5)	43 (0.03)	30 (5.0)	37 (0.03)	1.09 (0.67 to 1.77)	9 (5.8)	10 (0.03)	9 (5.7)	10 (0.03)	1.03 (0.42 to 2.51)
Outpatient surgery	29 (4.8)	40 (0.03)	34 (5.7)	46 (0.04)	0.85 (0.52 to 1.37)	4 (2.6)	6 (0.02)	11 (6.9)	21 (0.06)	0.37 (0.12 to 1.15)
Restricted activity possibly due to study procedures	49 (8.1)	71 (0.06)	13 (2.2)	15 (0.01)	3.74 (2.05 to 6.82)	18 (11.6)	20 (0.06)	2 (1.3)	2 (<0.01)	9.23 (2.18 to 39.12)

CI=confidence interval.

Sum of individual items is higher than number of participants who experienced at least one adverse event because single events may fall into more than one category. Event rate was calculated as ratio between total number for whom an event was recorded and participant years. In the multicomponent intervention arm, participant years were 1265.96 for SPPB scores 3-7 and 361.85 for SPPB score 8 or 9. In the lifestyle education arm, participant years were 1282.88 for SPPB scores 3-7 and 378.05 for SPPB score 8 or 9.

instigate further research on therapeutic interventions targeting skeletal muscle decline to prevent adverse outcomes in people who do not respond, or are unable to adhere, to lifestyle modifications.

### Conclusions

Older adults with physical frailty and sarcopenia represent a subset of the older population at risk of adverse health related events and whose medical needs are currently unmet. A multicomponent intervention based on physical activity with technological support and nutritional counselling was associated with a reduction in the incidence of mobility disability over 36 months of follow-up in older adults with physical frailty and sarcopenia and SPPB scores of 3 to 7. Therefore, such an intervention may be proposed as a strategy to preserve mobility in older people at risk of disability.

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SPRINTT consortium partners are listed in the supplementary appendix.

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**Ethical approval:** The study protocol was approved by the ethics committee of the Università Cattolica del Sacro Cuore, Rome, Italy (protocol No 15611/15), and was subsequently ratified by the ethics committees of all participating institutions.

**Data sharing:** Anonymised raw trial data can be shared on request to Luca Mariotti ([luca.mariotti1@unicatt.it](mailto:luca.mariotti1@unicatt.it)). A data access agreement needs to be signed.

The lead authors (EM, FrL, RC, RR, and RoB) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

**Dissemination to participants and related patient and public communities:** The study results will be disseminated to the public through press release, broadcasts, newspapers, and the SPRINTT website (<http://www.mysprintt.eu/en/public>).

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- 1 Newman AB, Simonsick EM, Naydeck BL, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA* 2006;295:2018-26. doi:10.1001/jama.295.17.2018.
- 2 Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA* 2011;305:50-8. doi:10.1001/jama.2010.1923.
- 3 Hardy SE, Kang Y, Studenski SA, Degenholtz HB. Ability to walk 1/4 mile predicts subsequent disability, mortality, and health care costs. *J Gen Intern Med* 2011;26:130-5. doi:10.1007/s11606-010-1543-2.
- 4 Chen LK, Hwang AC, Lee WJ, et al. Taiwan Health Promotion Intervention Study for Elders research group. Efficacy of multidomain interventions to improve physical frailty, depression and cognition: data from cluster-randomized controlled trials. *J Cachexia Sarcopenia Muscle* 2020;11:650-62. doi:10.1002/jcsm.12534.
- 5 Innovative Medicines Initiative. 9th call for proposals 2013 – Innovative Medicines Initiative. July 2013. [https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi1/Call9\\_Text.pdf](https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi1/Call9_Text.pdf) (accessed 2 Mar 2022)



- 6 Landi F, Cherubini A, Cesari M, et al. Sarcopenia and frailty: From theoretical approach into clinical practice. *Eur Geriatr Med* 2016;7:197-200. doi:10.1016/j.eurger.2015.12.015.
- 7 Cesari M, Landi F, Calvani R, et al, SPRINTT Consortium. Rationale for a preliminary operational definition of physical frailty and sarcopenia in the SPRINTT trial. *Aging Clin Exp Res* 2017;29:81-8. doi:10.1007/s40520-016-0716-1.
- 8 Marzetti E, Cesari M, Calvani R, et al, SPRINTT Consortium. The "Sarcopenia and Physical Frailty IN older people: multi-component Treatment strategies" (SPRINTT) randomized controlled trial: Case finding, screening and characteristics of eligible participants. *Exp Gerontol* 2018;113:48-57. doi:10.1016/j.exger.2018.09.017.
- 9 Landi F, Cesari M, Calvani R, et al, SPRINTT Consortium. The "Sarcopenia and Physical Frailty IN older people: multi-component Treatment strategies" (SPRINTT) randomized controlled trial: design and methods. *Aging Clin Exp Res* 2017;29:89-100. doi:10.1007/s40520-016-0715-2.
- 10 Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;49:M85-94. doi:10.1093/geronj/49.2.M85.
- 11 McLean RR, Shardell MD, Alley DE, et al. Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the foundation for the National Institutes of Health (NIH) sarcopenia project. *J Gerontol A Biol Sci Med Sci* 2014;69:576-83. doi:10.1093/gerona/glu012.
- 12 Simonsick EM, Montgomery PS, Newman AB, Bauer DC, Harris T. Measuring fitness in healthy older adults: the Health ABC Long Distance Corridor Walk. *J Am Geriatr Soc* 2001;49:1544-8. doi:10.1046/j.1532-5415.2001.4911247.x.
- 13 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98. doi:10.1016/0022-3956(75)90026-6.
- 14 Fielding RA, Rejeski WJ, Blair S, et al, LIFE Research Group. The lifestyle interventions and independence for elders study: Design and methods. *J Gerontol A Biol Sci Med Sci* 2011;66:1226-37. doi:10.1093/gerona/66.12.1226.
- 15 Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;2:92-8.
- 16 Volkert D, Beck AM, Cederholm T, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. *Clin Nutr* 2019;38:10-47. doi:10.1016/j.clnu.2018.05.024.
- 17 Pahor M, Guralnik JM, Ambrosius WT, et al, LIFE study investigators. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA* 2014;311:2387-96. doi:10.1001/jama.2014.5616.
- 18 Abellan van Kan G, Rolland Y, Andrieu S, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people: an International Academy on Nutrition and Aging (IANA) Task Force. *J Nutr Health Aging* 2009;13:881-9. doi:10.1007/s12603-009-0246-z.
- 19 Liu CK, Leng X, Hsu FC, et al. The impact of sarcopenia on a physical activity intervention: the Lifestyle Interventions and Independence for Elders Pilot Study (LIFE-P). *J Nutr Health Aging* 2014;18:59-64. doi:10.1007/s12603-013-0369-0.
- 20 Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 2006;54:743-9. doi:10.1111/j.1532-5415.2006.00701.x.
- 21 Kwon S, Perera S, Pahor M, et al. What is a meaningful change in physical performance? Findings from a clinical trial in older adults (the LIFE-P study). *J Nutr Health Aging* 2009;13:538-44. doi:10.1007/s12603-009-0104-z.
- 22 Rodriguez-Mañas L, Laosa O, Vellas B, et al, European MID-Frail Consortium. Effectiveness of a multimodal intervention in functionally impaired older people with type 2 diabetes mellitus. *J Cachexia Sarcopenia Muscle* 2019;10:721-33. doi:10.1002/jcsm.12432.
- 23 Casas-Herrero Á, Sáez de Asteasu ML, Antón-Rodrigo I, et al. Effects of Vivifrail multicomponent intervention on functional capacity: a multicentre, randomized controlled trial. *J Cachexia Sarcopenia Muscle* 2022;13:884-93. doi:10.1002/jcsm.12925.
- 24 Jang IY, Jung HW, Park H, et al. A multicomponent frailty intervention for socioeconomically vulnerable older adults: a designed-delay study. *Clin Interv Aging* 2018;13:1799-814. doi:10.2147/CLIA.S177018.
- 25 Kitzman DW, Whellan DJ, Duncan P, et al. Physical rehabilitation for older patients hospitalized for heart failure. *N Engl J Med* 2012;365:203-16. doi:10.1056/NEJMoa2026141.
- 26 Zhang Y, Zou L, Chen ST, et al. Effects and moderators of exercise on sarcopenic components in sarcopenic elderly: A systematic review and meta-analysis. *Front Med (Lausanne)* 2021;8:649748. doi:10.3389/fmed.2021.649748.
- 27 Chen N, He X, Feng Y, Ainsworth BE, Liu Y. Effects of resistance training in healthy older people with sarcopenia: a systematic review and meta-analysis of randomized controlled trials. *Eur Rev Aging Phys Act* 2021;18:23. doi:10.1186/s11556-021-00277-7.
- 28 Elstgeest LEM, Schaap LA, Heymans MW, et al, Health ABC Study. Sex- and race-specific associations of protein intake with change in muscle mass and physical function in older adults: the Health, Aging, and Body Composition (Health ABC) Study. *Am J Clin Nutr* 2020;112:84-95. doi:10.1093/ajcn/nqaa099.
- 29 European Medicines Agency. Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials. January 2018. [www.ema.europa.eu/documents/scientific-guideline/reflection-paper-physical-frailty-instruments-baseline-characterisation-older-populations-clinical\\_en.pdf](http://www.ema.europa.eu/documents/scientific-guideline/reflection-paper-physical-frailty-instruments-baseline-characterisation-older-populations-clinical_en.pdf) (accessed 2 Mar 2022)
- 30 Arrieta H, Astrugue C, Regueme S, et al. Effects of a physical activity programme to prevent physical performance decline in onco-geriatric patients: a randomized multicentre trial. *J Cachexia Sarcopenia Muscle* 2019;10:287-97. doi:10.1002/jcsm.12382.
- 31 Rooks D, Swan T, Goswami B, et al. Bimagrumab vs optimized standard of care for treatment of sarcopenia in community-dwelling older adults: A randomized clinical trial. *JAMA Netw Open* 2020;3:e2020836. doi:10.1001/jamanetworkopen.2020.20836.
- 32 Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 2015;385:2255-63. doi:10.1016/S0140-6736(15)00461-5.
- 33 Patrizio E, Calvani R, Marzetti E, Cesari M. Physical functional assessment in older adults. *J Frailty Aging* 2021;10:141-9. doi:10.14283/jfa.2020.61.
- 34 Rolland YM, Cesari M, Miller ME, Penninx BW, Atkinson HH, Pahor M. Reliability of the 400-m usual-pace walk test as an assessment of mobility limitation in older adults. *J Am Geriatr Soc* 2004;52:972-6. doi:10.1111/j.1532-5415.2004.52267.x.
- 35 Dent E, Morley JE, Cruz-Jentoft AJ, et al. Physical frailty: ICFSR international clinical practice guidelines for identification and management. *J Nutr Health Aging* 2019;23:771-87. doi:10.1007/s12603-019-1273-z.
- 36 Izquierdo M, Merchant RA, Morley JE, et al. International exercise recommendations in older adults (ICFSR): Expert consensus guidelines. *J Nutr Health Aging* 2021;25:824-53. doi:10.1007/s12603-021-1665-8.
- 37 Niemeijer A, Lund H, Stafne SN, et al. Adverse events of exercise therapy in randomised controlled trials: a systematic review and meta-analysis. *Br J Sports Med* 2020;54:1073-80. doi:10.1136/bjsports-2018-100461.
- 38 Gielen E, Beckwée D, Delaere A, De Breucker S, Vandewoude M, Bautmans I, Sarcopenia Guidelines Development Group of the Belgian Society of Gerontology and Geriatrics (BSGG). Nutritional interventions to improve muscle mass, muscle strength, and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. *Nutr Rev* 2021;79:121-47. doi:10.1093/nutrit/nuaa011.
- 39 Ferrucci L, Kuchel GA. Heterogeneity of aging: Individual risk factors, mechanisms, patient priorities, and outcomes. *J Am Geriatr Soc* 2021;69:610-2. doi:10.1111/jgs.17011.
- 40 de Souto Barreto P, Rolland Y, Vellas B, Maltais M. Association of long-term exercise training with risk of falls, fractures, hospitalizations, and mortality in older adults: A systematic review and meta-analysis. *JAMA Intern Med* 2019;179:394-405. doi:10.1001/jamainternmed.2018.5406.
- 41 Gill TM, Pahor M, Guralnik JM, et al, LIFE Study Investigators. Effect of structured physical activity on prevention of serious fall injuries in adults aged 70-89: randomized clinical trial (LIFE Study). *BMJ* 2016;352:i245. doi:10.1136/bmj.i245.
- 42 Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: a systematic review and meta-analysis. *J Am Geriatr Soc* 2008;56:2234-43. doi:10.1111/j.1532-5415.2008.02014.x.
- 43 Pua YH, Ong PH, Clark RA, Matcher DB, Lim EC. Falls efficacy, postural balance, and risk for falls in older adults with falls-related emergency department visits: prospective cohort study. *BMC Geriatr* 2017;17:291. doi:10.1186/s12877-017-0682-2.
- 44 Stenholm S, Shardell M, Bandinelli S, Guralnik JM, Ferrucci L. Physiological factors contributing to mobility loss over 9 years of follow-up—results from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2015;70:591-7. doi:10.1093/gerona/glv004.

**Supplementary information:** Study protocol, statistical analysis plan, SPRINTT trial sites and consortium partners, and figs S1 and S2