**Cognitive abilities in later life and the onset of physical frailty:**

**the Lothian Birth Cohort 1936**

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Running head: Cognitive abilities and physical frailty

**STRUCTURED ABSTRACT**

**OBJECTIVES*:*** To investigate whether poorer cognitive ability is a risk factor for the development of physical frailty, and whether this risk varies by cognitive domain.

**DESIGN*:***  Prospective longitudinal study with six-year follow-up.

**SETTING*:***  Edinburgh, Scotland.

**PARTICIPANTS*:*** 594 members of the Lothian Birth Cohort 1936.

**MEASUREMENTS*:*** Frailty was assessed at ages 70 and 76 using the Fried criteria. Cognitive functions were assessed at ages 70, 73, and 76. Factor score estimates were derived for baseline level of and change in four cognitive domains: visuospatial ability, memory, processing speed, and crystallized cognitive ability.

**RESULTS*:***  Higher baseline levels of processing speed, memory, visuospatial ability and crystallized ability derived from ages 70, 73 and 76, and less decline in speed, memory and crystallized ability were associated with a reduced risk of becoming physically frail by age 76. When all cognitive domains were modelled together, processing speed was only domain associated with frailty risk: for a standard deviation increment in initial level of processing speed, the relative risk for frailty (RR) (95% confidence interval (CI)) was 0.53 (0.33, 0.85), after adjustment for age, sex, baseline frailty status, social class, depressive symptoms, number of chronic physical diseases, levels of inflammatory biomarkers, and other cognitive factor score estimates; for a SD increment in processing speed change (i.e. less decline) the RR (95% CI) was 0.26 (0.16, 0.42). When we conducted additional analyses using a single test of processing speed that did not require fast motor responses—Inspection Time—results were similar.

**CONCLUSIONS:**The speed with which older people process information and the rate at which this declines over time may be an important indicator of the risk of physical frailty.

**Keywords:**  Fried frailty phenotype; processing speed; memory; visuospatial ability; crystallized ability.

**INTRODUCTION**

Frailty is a clinical syndrome observed in older people, the core feature of which is increased vulnerability to stressors due to impairments in multiple systems, decreased physiological reserves, and a decline in the ability to maintain homeostasis.1 It increases the risk of adverse outcomes.1-3 The phenotype model—in which frailty is based on three or more components: poor grip strength, slow walking speed, low physical activity, exhaustion, and unintentional weight loss2—is one of the two principal models of frailty.1 The frailty index, or cumulative deficit model, defines frailty in terms of the accumulation of ‘deficits’ (symptoms, signs, diseases and disabilities), whereby an individual’s frailty index score reflects the proportion of potential deficits present.4 These models differ in the potential role that cognitive impairment plays in their definition of frailty. The Fried phenotype defines frailty in purely physical terms, whereas the cumulative deficit model permits cognitive impairment to be included as a deficit. A consensus conference agreed that this broader definition of frailty should be distinguished from the medical syndrome of physical frailty.5 Given the importance of cognitive function and physical robustness for quality of life and survival, it is crucial to understand the extent to which cognitive ability and physical frailty are associated and the reasons for this.

Physical frailty and poorer cognitive function often co-exist.6-8 The direction of this relationship and the underlying mechanisms are uncertain. Some longitudinal studies suggest that physical frailty increases risk of cognitive decline9, 10 or dementia.11-13 Poor cognitive function might be a risk factor for becoming physically frail, but evidence is sparse. Two longitudinal studies have found that lower MMSE scores increase the risk of incident physical frailty,14, 15 but it remains uncertain whether differences over the range of cognitive ability can predict the onset of physical frailty, or whether some domains of cognitive ability are more important as risk factors than others. Results from a longitudinal study found that lower level of executive function and greater decline in it was more strongly linked to physical frailty than level or decline in psychomotor speed or memory.16 Further longitudinal investigations are needed to understand the role of specific cognitive domains in the development of physical frailty.

The Lothian Birth Cohort 1936 was established to study cognitive ageing.17 We used three waves of data on processing speed, memory, visuospatial ability, and crystallized cognitive ability to examine how initial level of and change in cognitive function in these domains related to risk of developing physical frailty or pre-frailty.

**METHODS**

**Participants**

The Lothian Birth Cohort 1936 was established to study cognitive ageing in surviving members of the 1947 Scottish Mental Survey.17, 18 1,091 community-dwelling people were recruited aged around 70 years. Wave 2 took place when participants were aged about 73 years; 866 people participated. Wave 3 took place when participants were aged about 76 years; 697 people participated. Ethical approval was obtained from the Multi-Centre Ethics Committee for Scotland and Lothian Research Ethics Committee.

**Measures**

*Physical frailty*

Frailty status was assessed during Wave 1 and Wave 3 using the Fried phenotype.2 Frailty is defined as the presence of three or more of: unintentional weight loss, weakness, self-reported exhaustion, slow walking speed, and low physical activity. Pre-frailty is defined as the presence of one or two of these criteria. We operationalized these criteria using definitions similar to Fried’s2, 19 (Supplementary text S1).

*Cognitive abilities*

Participants took a variety of cognitive tests in an identical fashion at each wave. We used these as indicators of four domains of cognitive ability. *Visuospatial ability* was indicated by scores on tests of Matrix Reasoning and Block Design from the Wechsler Adult Intelligence Scale (WAIS-IIIUK)20 and Spatial Span Forwards and Backwards from the Wechsler Memory Scale (WMS-IIIUK).21 Verbal-declarative memory (henceforth *Memory*) was indicated by scores on tests of Logical Memory and Verbal Paired Associates from the WMS-IIIUK, and Digit Span Backwards from the WAIS-IIIUK. *Processing speed* (henceforth *Speed*) was indicated by scores on tests of Digit-Symbol Substitution and Symbol Search from the WAIS-IIIUK, measures of 4-Choice Reaction Time22 and Inspection Time.23 Of these measures of Speed, Inspection Time is the only test requiring no speeded responses. *Crystallized cognitive ability* was measured using scores on the National Adult Reading Test (NART),24 and the Wechsler Test of Adult Reading (WTAR).25 The MMSE was used solely to identify those with likely cognitive impairment or dementia. With the exception of three of the tests for processing speed which required fast motor responses, none of the tests relied on physical function.

*Covariates*

We chose age, socioeconomic position, smoking status, number of chronic physical diseases, depressive symptoms, and inflammatory biomarkers at Wave 1 as potential confounding variables. Assessment details are given in Supplementary text S2.

**Statistical analysis**

The cognitive tests were organized into four domains: Visuospatial ability, Memory, Speed, and Crystallized ability. Within each grouping, we estimated an intercept factor (baseline level of the ability) and a slope factor (change in the ability across the three waves). We did so using latent growth curve modelling in a ‘factors of curves’ format26. Latent-variable models reduce the influence of test-specific measurement error by using the shared variance between the baseline levels and changes in observed scores on multiple cognitive tests to estimate latent (unobserved) variables of cognitive ability baseline and change. Factor models and score estimates, which used full-information maximum likelihood estimation in order to use all the data in the full sample at each wave, were produced using Mplus v7.3.27 Details of the ‘Factors of curves’ structural equation models and mean decline in the cognitive test scores over the three waves are given in Supplementary text S3 and table S1.

Other analyses were carried out in STATA v13.28 We used multinomial logistic regression to calculate relative risks of pre-frailty or frailty at age 76 according to a standard deviation (SD) increment in factor score estimates for baseline of cognitive ability in each domain, and change in cognitive ability in each domain from age 70 to age 76, with adjustment for potential confounding factors. Relationships did not vary by sex, so we pooled the data and adjusted for sex. To reduce potential bias due to attrition, all models included inverse probability weights that make the sample more representative of the cohort at baseline.29 Three of the Speed factor’s tests required fast and accurate motor responses. The fourth, Inspection Time, requires no speeded response. To test whether associations found with the Speed factor were artefacts caused by overlap of components of the frailty phenotype measure—slow walking speed and exhaustion—with the motor aspects of three of these tests, we estimated models where only Inspection Time baseline and slope were used as predictors. Finally, analyses were repeated excluding participants who scored <24 on the MMSE.30

**RESULTS**

Analyses are based on 594 participants with data on all variables of interest. People excluded due to attrition tended to be older, had lower levels of cognitive ability, more depressive symptoms, more chronic physical disease, were more likely to smoke, had higher blood concentrations of c-reactive protein (CRP) and fibrinogen, were less likely to come from a professional or managerial social class, and met more criteria for frailty at age 70. There were no significant differences between those in the sample and those excluded due to missing baseline data, except in level of the cognitive factor ‘speed’ which was lower in the missing-data group (Supplementary table S2).

By age 76, 47.0% of the participants were pre-frail and 14.3% were frail (at age 70, equivalent figures were 45.5% and 4.9% respectively). The increase in prevalence of frailty between these ages is similar to that found previously.31 Among those who were frail at age 76, the most common combination of frailty criteria was exhaustion with low activity or slow walking speed (both occurring in 76.1%). In the sample as a whole, the most common frailty indicator was low activity (30.3%).

Table 1 shows the characteristics of the participants according to frailty status at age 76. Greater frailty at age 76 was associated with older age, more depressive symptoms, more chronic physical disease, being a current smoker, having higher blood concentrations of CRP, and meeting more criteria for frailty at age 70. Greater frailty at age 76 was also associated with lower baseline level of visuospatial ability, memory, speed, and crystallized ability, and with greater decline in memory and speed between ages 70 and 76.

Table 2 shows relative risks (RR) (95% CI) for incident pre-frailty or frailty at age 76 according to a SD increment in factor score estimates for baseline level of cognitive ability in each domain. In models adjusted for age, sex and number of frailty criteria present at baseline, higher factor scores for speed were associated with a reduced risk of becoming pre-frail. This association was attenuated and no longer significant after further adjustment for other covariates and for other cognitive factor scores estimates. There were no significant associations between any of the other cognitive factor score estimates’ levels and risk of becoming pre-frail. In initial models, having a higher level of speed or visuospatial ability (but not memory or crystallised ability) was associated with a significantly reduced risk of becoming frail by age 76: RRs for becoming frail per SD increment in cognitive factor score estimates were 0.24 (0.17, 0.35) for speed and 0.63 (0.42, 0.93) for visuospatial ability. Further adjustment in the models of frailty for the other potential confounding factors had only a small attenuating effect on these associations. In a final model with frailty as the outcome, we examined all cognitive factor score estimates simultaneously. In this model, processing speed was the only cognitive domain that was independently associated with risk of becoming frail: for an SD increment in speed, the RR was 0.53 (0.33, 0.85). When we adjusted for change in depressive symptoms, in chronic physical illnesses and in inflammatory markers between wave 1 and wave 3 in place of these measures at wave 1, results were similar: for an SD increment in speed, the RR was 0.46 (0.28, 0.77).

Table 3 shows RRs for incident pre-frailty or frailty according to a SD increment in factor score estimates for the slope of the trajectory of cognitive ability in each domain between age 70 and 76. Higher factor score estimates for change in speed and in visuospatial ability–indicating less decline—were associated with a reduced risk of becoming pre-frail. No other cognitive domain was independently associated with pre-frailty. In initial models, the RRs per SD increment in cognitive factor change were 0.44 (0.32, 0.62) in the case of speed and 0.762 (0.53, 0.98) in the case of visuospatial ability. The association between change in speed and risk of pre-frailty changed little in subsequent models, but the association between change in visuospatial ability and risk of pre-frailty ceased to be significant when adjusted for other cognitive factor score estimates. In initial models of frailty, higher factor score estimates for change in speed and memory—indicating less decline—were associated with reduced risk; RRs for becoming frail per SD increment in cognitive factor change were 0.20 (0.13, 0.32) and 0.48 (0.33, 0.70), respectively. Further adjustment for the other covariates had only a small attenuating effect. In the final model, higher estimates for change in speed was the only cognitive factor score estimate that remained significantly associated with a reduced risk of frailty: for a SD increment, the RR was 0.26 (0.16, 0.42). When we adjusted for change in depressive symptoms, chronic physical illnesses and inflammatory markers between waves 1 and 3 in place of these measures at wave 1, the association between change in speed and risk of frailty was very similar: for an SD increment in speed, the RR was 0.28 (0.17, 0.46).

Table 4 shows RRs for incident pre-frailty or frailty according to SD increments in baseline level and change in Inspection Time. Results were similar to those obtained with the speed factor estimates.

We repeated our analyses excluding those who scored <24 on the MMSE at all three waves (n=27). Results were almost unchanged (data not shown).

We carried out a sensitivity analysis in those who were physically robust at age 70 (n=295). Effect sizes were very similar to those presented in Tables 2 and 3: speed was the only cognitive domain associated with frailty risk in the fully-adjusted models. In this subset, the fully-adjusted RRs of pre-frailty or frailty were 0.78 (0.53, 1.14) and 0.24 (0.09, 0.61) respectively for a SD increment in baseline level of speed, and 0.49 (0.31, 0.79) and 0.23 (0.10, 0.57) respectively for a SD increment in change in speed.

**DISCUSSION**

To our knowledge, only one study has examined the relationship between different cognitive abilities and onset of physical frailty. In 331 women from the Women’s Health and Aging Study, higher initial level of and slower decline in executive function—assessed with a single test—were associated with reduced risk of physical frailty.16 Participants were also assessed for psychomotor speed and immediate and delayed verbal memory—again with single tests. Higher scores for speed, delayed verbal memory only, and general cognitive performance were associated with reduced risk, but there were no significant associations between rate of decline on any cognitive test other than the test of executive function and physical frailty risk. The measure used to assess executive function in that study (the Trail Making Test) may also reflect processing speed,32 therefore conforming to the findings in the current analysis.

In the present study, both initial level of and decline in memory and speed were associated with frailty risk. Speed seems the more powerful predictor of physical frailty as it was associated with risk independently of covariates and other cognitive domains: for a SD increment in initial level of speed or change in speed (less decline), risk of frailty was reduced by 47% or 74% respectively. To check whether these associations might be produced by overlap between the speed of motor response required by some tests of processing speed and the slow walking speed or exhaustion components of the frailty phenotype, we repeated the analyses using the psychophysical Inspection Time test as the sole measure of processing speed; this test of speed of visual discrimination does not rely on physical reactions. Effect sizes using this single test were smaller than those obtained with the speed factor—for a SD increment in baseline level of or change in Inspection Time, risk of frailty was reduced by 40% or 35% respectively after full adjustment—but these results demonstrate that the link between processing speed and risk of frailty is not artefactual. Processing speed may be an early signal of impending limitations in a number of physical-mental domains, with some underlying shared causes. There is evidence that greater decline in processing speed is associated with greater decline in walking speed,33 and in the current cohort, decline in processing speed, as measured by Inspection Time, was strongly correlated with decline in general cognitive ability.34

The mechanisms underlying associations between domains of cognitive ability, in particular speed, and risk of physical frailty remain unclear. Adjustment for covariates had modest attenuating effects.Neuropathology that has an adverse effect on cognitive function may also influence risk of physical frailty. Support for this comes from findings that rates of change in physical frailty and cognitive function were strongly correlated and that Alzheimer’s disease pathology, macroinfarcts and nigral neuronal loss were associated with prior rates of change in physical frailty and cognitive ability.35 Disruption of connectivity in white matter affects processing speed36, 37 and walking speed.38 Further investigation in this cohort could test whether this is the mechanism underlying our findings. Another explanation might be that some common biological process of cellular senescence underlies the associations. 39 Cellular senescence is a stress response to prevent proliferation of cells exposed to potentially oncogenic stimuli. Senescent cells occur with increasing frequency in older tissues. The secretion of pro-inflammatory cytokines, growth factors and proteases that accompanies cellular senescence may be implicated in cognitive decline and physical frailty.40

The strengths of our study include the characterization of each domain of cognitive function over three waves, enabling us to examine how initial level and change related to onset of physical frailty or pre-frailty. Other strengths are the narrow age range, data on a range of potential confounding factors and the fact that our sample was based on both sexes. One limitation is that for some individuals, decline in cognitive abilities and onset of physical frailty will have begun prior to age 70 making it uncertain whether poorer cognitive ability truly predates later frailty or whether both cognitive and physical health are declining together. Our finding that slower processing speed was as predictive of frailty in the subset of participants who were physically robust as in the sample as a whole suggests that poorer cognitive ability may indeed increase the risk of frailty. A second limitation is that, largely due to attrition, our analyses were based on 54% of participants in the baseline survey. Attrition can result in biased estimates if there are differences in likelihood of follow-up that are related to exposure *and* to outcome. In our analytical sample, higher baseline levels of processing speed were associated with a reduced risk of becoming physically frail. Among those lost to follow-up, the risk of becoming physically frail is likely to have been higher because they tended to be in poorer health and were frailer at baseline (Supplementary table S2). Those lost to follow-up (and those excluded due to missing data) also differ from our analytical sample in having lower levels of processing speed. Our models were weighted to reduce potential bias due to attrition, but the results may underestimate the predictive power of processing speed as regards risk of physical frailty.

The speed with which older people process information and the rate at which this declines may be an important indicator of the risk of becoming physically frail. More research into cognitive-domain specific associations and risk of physical frailty is needed to confirm the importance of different domains for predicting onset of frailty and elucidate the underlying mechanisms.

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Conflict of Interest checklist:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Elements of Financial/Personal Conflicts** | **CRG** | **SJR** | **CC** | **JMS** | **IJD** |
|  | **Yes** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **No** |
| **Employment or Affiliation** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
|  |  |  |  |  |  |  |  |  |  |  |
| **Grants/Funds** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
|  |  |  |  |  |  |  |  |  |  |  |
| **Honoraria** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
|  |  |  |  |  |  |  |  |  |  |  |
| **Speaker Forum** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
|  |  |  |  |  |  |  |  |  |  |  |
| **Consultant** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
|  |  |  |  |  |  |  |  |  |  |  |
| **Stocks** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
|  |  |  |  |  |  |  |  |  |  |  |
| **Royalties** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
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| **Expert Testimony** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
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| **Board Member** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
|  |  |  |  |  |  |  |  |  |  |  |
| **Patents** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |
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| **Personal Relationship** |  | **No** |  | **No** |  | **No** |  | **No** |  | **No** |

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**Author Contributions:** CRG and IJD conceived the study; IJD & JMS were responsible for the recruitment of the cohort and collection of data; SJR and CRG analysed the data; CRG drafted the first version of the manuscript; all authors contributed to the interpretation of data and the final version of the manuscript.

**Sponsor’s Role:** None

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**Table 1: Characteristics of the Study Sample According to Frailty Status at Age 76**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **Not frail (n=230)** | **Pre-frail****(n=279)** | **Frail****(n=85)** | **P value for difference1** |
| *At age 70* |  |  |  |  |
| Age (yrs), mean (SD)  | 69.4 (0.83) | 69.5 (0.81) | 69.7 (0.77) | <0.001 |
| Depressive symptom score, median (IQR) | 1 (0-2) | 1 (0-2) | 2 (1-3) | <0.001 |
| Number of frailty criteria, median (IQR) | 0 (0-1) | 0 (0-1) | 2 (1-2)  | <0.001 |
| Number of chronic diseases, median (IQR) | 0 (0-1) | 1 (0-1) | 1 (1-2) | <0.001 |
| Fibrinogen (g/L), median (IQR) | 3.1 (2.7-3.5) | 3.2 (2.8-3.5) | 3.2 (2.9-3.7)  | 0.142 |
| C-reactive protein (mg/L), median (IQR) | 1.5 (1.5-5) | 3 (1.5-6) | 4 (1.5-7) | 0.020 |
| Female, no (%) | 108 (47.0) | 139 (49.8) | 44 (51.7) | 0.698 |
| Current smoker, no (%) | 11 (4.78) | 17 (6.09) | 11 (12.9) | 0.031 |
| Professional/managerial social class, no (%) | 144 (62.6) | 166 (59.5) | 47 (55.3) | 0.481 |
| *Cognitive factor score estimates for baseline level*  |  |  |  |  |
| Visuospatial ability, mean (SD) | 0.32 (0.85) | 0.17 (0.84) | -0.42 (0.92) | <0.001 |
| Memory, mean (SD) | 0.24 (0.79) | 0.12 (0.80) | -0.29 (0.82) | <0.001 |
| Speed, mean (SD) | 0.46 (0.81) | 0.18 (0.76) | -0.54 (1.01) | <0.001 |
| Crystallized ability, mean (SD) | 0.23 (0.94) | 0.12 (0.93) | -0.29 (1.07) | <0.001 |
| *Cognitive factor score estimates for slope*  |  |  |  |  |
| Visuospatial ability, mean (SD) | -0.02 (0.50) | -0.04 (0.51) | -0.01 (0.56) | 0.850 |
| Memory, mean (SD) | 0.10 (0.68) | -0.03 (0.75) | -0.28 (0.82) | <0.001 |
| Speed, mean (SD) | 0.23 (0.54) | -0.01 (0.69) | -0.42 (0.81) | <0.001 |
| Crystallized ability, mean (SD) | -0.02 (0.87) | -0.03 (1.08) | 0.003 (0.66) | 0.964 |

1 From ANOVA, Kruskal-Wallis or chi-square tests as appropriate

**Table 2: Relative Risks1 (95% CI) for Incident Physical Pre-Frailty and Frailty at Age 76 According to Baseline Level of Cognitive Function at Age 70, 73 and 76**

|  |  |  |  |
| --- | --- | --- | --- |
| **Cognitive factor score estimate for baseline level** | **Relative risks (95% CI), adjusted for age, sex, & components of frailty present at age 70** | **Relative risks (95% CI), further adjusted for depressive symptoms, chronic physical diseases, social class, inflammatory biomarkers & smoking status at age 70** | **Relative risks (95% CI), further adjusted for other cognitive factor score estimates**  |
|  | **Pre-frailty** | **Frailty** | **Pre-frailty** | **Frailty** | **Pre-frailty** | **Frailty** |
| Visuospatial ability, per SD | 1.01 (0.79, 1.30) | 0.63 (0.42, 0.93) | 0.99 (0.76, 1.30) | 0.64 (0.41, 0.98) | 1.05 (0.78, 1.63) | 0.81 (0.50, 1.31) |
| Memory, per SD | 1.03 (0.78, 1.04) | 0.81 (0.55, 1.21) | 1.04 (0.78, 1.40) | 0.81 (0.52, 1.26) | 1.01 (0.73, 1.38) | 0.86 (0.52, 1.40) |
| Speed, per SD | 0.66 (0.52, 0.84) | 0.24 (0.17, 0.35) | 0.84 (0.64, 1.10) | 0.49 (0.32, 0.76) | 0.82 (0.61, 1.09) | 0.53 (0.33, 0.85) |
| Crystallized ability, per SD | 1.10 (0.87, 1.40) | 1.06 (0.77, 1.46) | 1.14 (0.87, 1.51) | 1.21 (0.81, 1.81) | 1.15 (0.86, 1.54) | 1.40 (0.90, 2.18) |

1All estimates are weighted to adjust for attrition since baseline

**Table 3: Relative Risks1 (95% CI) for Incident Physical Pre-Frailty and Frailty at Age 76 According to Change in Cognitive Function Between Age 70 and 76**

|  |  |  |  |
| --- | --- | --- | --- |
| **Cognitive factor score estimates for slope** | **Relative risks (95% CI), adjusted for age, sex, & components of frailty present at age 70** | **Relative risks (95% CI), further adjusted for depressive symptoms, chronic physical diseases, social class, inflammatory biomarkers & smoking status at age 70** | **Relative risks (95% CI), further adjusted for other cognitive factor score estimates**  |
|  | **Pre-frailty** | **Frailty** | **Pre-frailty** | **Frailty** | **Pre-frailty** | **Frailty** |
| Visuospatial ability, per SD | 0.72 (0.53, 0.98) | 0.65 (0.40, 1.06)  | 0.71 (0.52, 0.98) | 0.65 (0.39, 1.06) | 0.82 (0.59, 1.15) | 0.95 (0.56, 1.63) |
| Memory, per SD | 0.80 (0.62, 1.03) | 0.48 (0.33, 0.70) | 0.79 (0.61, 1.02) | 0.49 (0.33, 0.72) | 0.93 (0.70, 1.24) | 0.75 (0.48, 1.15) |
| Speed, per SD | 0.44 (0.32, 0.62) | 0.20 (0.13, 0.32) | 0.47 (0.34, 0.65) | 0.22 (0.15, 0.36) | 0.50 (0.35, 0.70) | 0.26 (0.16, 0.42) |
| Crystallized ability, per SD | 0.93 (0.77, 1.12) | 0.91 (0.69, 1.19) | 0.92 (0.776 1.11) | 0.90 (0.68, 1.18) | 0.93 (0.77, 1.13) | 0.92 (0.69, 1.24) |

1All estimates are weighted to adjust for attrition since baseline

**Table 4: Relative Risks1 (95% CI) for Incident Physical Pre-Frailty and Frailty at Age 76 According to Baseline Level of and Change in Inspection Time Between Age 70 and 76**

|  |  |  |  |
| --- | --- | --- | --- |
| **Inspection Time baseline level or slope** | **Relative risks (95% CI), adjusted for age, sex, & components of frailty present at age 70** | **Relative risks (95% CI), further adjusted for depressive symptoms, chronic physical diseases, social class, inflammatory biomarkers & smoking status at age 70** | **Relative risks (95% CI), further adjusted for other cognitive factor score estimates**  |
|  | **Pre-frailty** | **Frailty** | **Pre-frailty** | **Frailty** | **Pre-frailty** | **Frailty** |
| Inspection Time level, per SD | 0.76 (0.62, 0.93) | 0.56 (0.42, 0.76) | 0.77 (0.63, 0.934) | 0.58 (0.43, 0.79) | 0.76 (0.62, 0.93) | 0.60 (0.44, 0.83) |
|  |  |  |  |  |  |  |
| Inspection Time slope, per SD | 0.87 (0.63, 1.21) | 0.60 (0.38, 0.97) | 0.86 (0.62, 1.20) | 0.61 (0.38, 0.79) | 0.86 (0.61, 1.20) | 0.65 (0.40, 1.01) |
|  |  |  |  |  |  |  |

1All estimates are weighted to adjust for attrition since baseline

**Supplementary text S1: Operationalising the Fried phenotype of frailty criteria**

Height and weight were measured with a portable stadiometer and electronic scales, respectively. Body mass index (BMI) was calculated as weight (in kilograms)/height (in metres)2. Weight loss was defined as current BMI <18.5 kg/m2 or, at wave 3 only, loss of weight of 10% or more since the wave 1 examination. Maximum handgrip strength was measured three times on each side using a dynamometer; the best of these measurements was used for analysis. Weakness was defined as maximum grip strength in the lowest 20% of the distribution, taking account of sex and BMI. Exhaustion was considered present if the participant responded ‘very often’ or ‘nearly all the time’ to the question ‘I feel as if I’m slowed down’, taken from the Hospital Anxiety and Depression Scale.1 Walking speed was assessed by measuring the time taken to walk a distance of 6 metres at maximum speed. Slow walking speed was defined as a walking speed in the lowest 20% of the distribution, taking account of sex and height. Participants were asked to indicate their usual level of physical activity on a 6-point scale, ranging from ‘moving only in connection with necessary (household) chores’ to ‘keep-fit/heavy exercise or competitive sport several times a week’. Low physical activity was defined as activity in the lowest sex-specific 20% of the distribution.

**Reference**

1. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica* 1983;67:361-70

**Supplementary text S2: Assessment of covariates**

Socioeconomic position was derived from the participant’s highest reported occupation (or their spouse’s if it was higher) and was classified into five social class categories: professional, managerial, skilled non-manual, skilled manual, and semi-skilled/unskilled. Participants provided information during an interview on whether they had been diagnosed with diabetes, stroke, cardiovascular disease, high blood pressure or cancer; we derived a variable for number of chronic physical diseases present. Participants provided information at interview on whether they were a current smoker, ex-smoker or had never smoked. Symptoms of depression were assessed using the depression subscale of the Hospital Anxiety and Scale (HADS-D)1. As one item from this subscale—‘I feel as if I’m slowed up’—was used as an indicator of exhaustion when deriving the frailty phenotype, we excluded this item when calculating the total depression score. Blood samples were taken for the measurement of C-reactive protein (CRP) and fibrinogen.

**Reference**

1. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica* 1983;67:361-70

**Supplementary table 1: Slope means for each cognitive test across the three waves (age 70 to age 76).**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cognitivedomain | Cognitive test | *b* | SE | *p* |
| Visuospatial ability | Matrix Reasoning | −.156 | .023 | < .001 |
| Block Design | −.415 | .038 | < .001 |
| Spatial Span | −.027 | .007 | < .001 |
| Memory | Verbal Paired Associates | −.197 | .043 | < .001 |
| Logical Memory  | .105 | .089 | .238 |
| Digit Span Backward | −.023 | .011 | .030 |
| Speed | Symbol Search | −.149 | .029 | < .001 |
| Digit-Symbol Substitution | −.703 | .047 | < .001 |
| Inspection Time | −.493 | .065 | < .001 |
| Choice Reaction Time | −.071 | .004 | < .001 |
| Crystallized ability | NART | −.026 | .017 | .134 |
| WTAR | −.079 | .016 | < .001 |

As shown in Supplementary Table 1, there was significant mean decline in all but two of the cognitive tests between age 70 and age 76; the tests of memory showed less decline, possibly due to some of their content (which was identical wave-to-wave) being recalled from the previous wave by some of the participants. The tests of speed showed, on average, the largest declines across the waves.

**Supplementary table 2: Characteristics at wave 1 of participants included and excluded from the analytical sample**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **Included in analytical sample** |  | **P for difference: those in sample *vs* excluded due to attrition1** | **P for difference: those in sample *vs* those excluded due to missing data1** |
|  | **Yes** **(n=594)** | **No, due to attrition (n=394)** | **No, due to missing data (n=1032)** |  |  |
| Age (yrs), mean (SD) | 69.5 (0.82) | 69.6 (0.84) | 69.6 (0.88) | 0.047 | 0.166 |
| Depressive symptom score, median (IQR) | 1 (0-2) | 1 (0-3) | 1 (0-3) | 0.007 | 0.090 |
| Number of frailty criteria, median (IQR) | 1 (0-1) | 1 (0-2) | 0 (0-1) | <0.001 | 0.848 |
| No of chronic diseases, median (IQR) | 1 (0-1) | 1 (0-2) | 1 (0-2) | 0.003 | 0.322 |
| Fibrinogen (g/L), median (IQR) | 3.2 (2.8-3.6) | 3.3 (2.9-3.8) | 3.3 (2.9-3.6) | 0.002 | 0.251 |
| C-reactive protein (mg/L), median (IQR) | 3 (1.5-5) | 4 (1.5-8) | 4 (1.5-7) | 0.001 | 0.054 |
| Female, % | 49.0 | 47.9 | 44.7 | 0.311 | 0.417 |
| Current smoker, % | 6.57 | 19.0 | 10.7 | <0.001 | 0.135 |
| Professional/managerial social class, % | 60.1 | 47.9 | 55.3 | <0.001 | 0.380 |
| *Cognitive factor score estimates for level*  |  |  |  |  |  |
| Visuospatial ability, mean (SD) | 0.14 (0.89) | -0.23 (0.87) | 0.07 (0.91) | <0.001 | 0.470 |
| Memory, mean (SD) | 0.11 (0.82) | -0.19 (0.78) | 0.10 (0.93) | <0.001 | 0.989 |
| Speed, mean (SD) | 0.18 (0.88) | -0.24 (0.87) | -0.17 (0.89) | <0.001 | <0.001 |
| Crystallized ability, mean (SD) | 0.10 (0.94) | -0.14 (1.00) | -0.07 (1.11) | <0.001 | 0.111 |

1 From t-tests, Kruskal-Wallis tests, or chi-square tests as appropriate. 2maximum number on which these analyses are based

**Supplementary text S3: ‘Factors of curves’ structural equation models of the cognitive ability test scores**

To estimate the ‘factors of curves’ model, individual latent growth curve models across the three testing waves (approximate mean ages 70, 73, and 76 years) were estimated for each of the cognitive tests, and the resulting latent intercept and slope factors for each test were used as indicators of higher-order domain intercepts and slopes (thus, we factor-analysed the individual tests’ growth curves). For example, the latent intercepts and latent slopes for Matrix Reasoning, Block Design, and Spatial Span (Forwards and Backwards) were used as indicators of the higher-order level and slope of Visuospatial ability (*mutatis mutandis* for the remaining three cognitive domains). The parameters on the slope factor for each test were set to the precise gap in years between each testing wave (2.98 years on average between waves 1 and 2; 6.75 years on average between waves 1 and 3).

The results reported in the main document come from growth curves with their intercept set at the final wave (such that the cognitive decline slope occurred prior to the intercept), though estimating the growth curves with their intercept at the first wave made little difference to the results. The domain factors we extracted are reliable indices of each participant’s cognitive baseline for that domain and the extent of their cognitive change in it from age 70 to age 76. We extracted the factor score estimates from the models and used them in subsequent models predicting (pre-)frailty status. Note that some slopes had residual variances estimated as negative since they were near-zero; we fixed them to zero and thus assumed that all their variance was associated with the general factor of slope.

The final model that was used to estimate the factor scores had excellent fit to the data (Visuospatial *χ*2(54) = 168.24, *p* < .001, Root Mean Square of Approximation (RMSEA) = 0.044, Comparative Fit Index (CFI) = 0.976, Tucker-Lewis Index (TLI) = 0.970; Memory *χ*2(27) = 128.16, *p* < .001, RMSEA = 0.059, CFI = 0.975, TLI = 0.967; Speed *χ*2(56) = 158.22, *p* < .001, RMSEA = 0.041, CFI = 0.985, TLI = 0.982; Crystallized *χ*2(28) = 68.29, *p* < .001, RMSEA = 0.036, CFI = 0.996, TLI = 0.995). That is, the cognitive predictor variables we used were a good fit to the three waves of data in the study.