# Chronic loneliness and isolation phenotypes, incident functional impairment and mortality in England between 2004 and 2018

Qian Gao [1,2] ✉, Andrew Steptoe [2] & Daisy Fancourt [2]

Social deficits are potential risk factors for premature mortality. Most research has focused on social deficits measured at single points in time. It remains unclear if the chronicity of loneliness affects its impact on adverse health outcomes. This study assessed the effects of chronic loneliness and isolation in predicting incident functional impairment and all-cause and cause-specific mortality. This longitudinal study used panel data from the English Longitudinal Study of Ageing, including 14 years of follow-up (waves 2–9, in 2004–2018). Social deficits over three waves (4 years) were measured using the UCLA loneliness scale and social isolation index, categorized as not present, fluctuating or chronic. We estimated the all-cause mortality risk with Cox proportional hazard modeling, and the Fine–Gray competing risk modeling was used to test the risk of functional impairment onset and cause-specific mortality. We analyzed 5,131 participants (mean age 67.6 years (s.d. 9.8)) in the mortality cohort (follow-up 9.8 years (IQR: 6.67–10.08)) and 4,279 participants (mean age 67.0 years (s.d. 9.6)) who were functional disability-free at baseline (follow-up 9.8 years (IQR: 7.17–10.17)). Compared with not being lonely/isolated, there was a higher risk of incident functional impairment among those with fluctuating loneliness (sub-hazard ratio (sHR) 1.30, 95% CI: 1.03–1.63) and chronic loneliness (sHR 1.58, 1.12–2.23), as well as chronic social isolation (sHR 1.41, 1.02–1.94). In survival analyses, compared with people who were not lonely/isolated, people experiencing fluctuating loneliness and social isolation had higher risks of all-cause mortality (loneliness HR 1.29, 1.13–1.48; isolation HR 1.15, 1.01–1.31). People with chronic isolation also had higher risks of all-cause mortality (HR 1.27, 1.05–1.55) and cancer-related mortality (sHR 1.69, 1.23–2.31). Over a 14 year follow-up, we found that chronic loneliness and isolation phenotypes were associated with aggravated risks of incident functional impairment and mortality. There was a potential dose–response relationship between chronicity of loneliness phenotypes and functional impairment onset and mortality. Preventing the onset of and transition to chronic loneliness and isolation in older age is a crucial target to support both the healthspan and the lifespan.

[1]School of Public Health, Imperial College London, London, UK. [2]Department of Behavioural Science and Health, Institute of Epidemiology and Health Care, University College London, London, UK. ✉e-mail: q.gao@imperial.ac.uk

Deficits in social relationships have physical and mental health consequences that pose challenges to public health systems. This problem is becoming greater for societies as some aspects of social relationships (such as isolation) can increase as people age, and in some cultures, social engagement has been decreasing over the past two decades[1]. It is estimated that 18–29% of people over the age of 60 live with loneliness or social isolation in the United Kingdom[2,3]. Loneliness is conceptualized as a subjective dissatisfaction with social connectedness and relationships[4], while social isolation objectively measures the absence of proper social interaction and connection[5]. Both subjective loneliness and objective isolation have been recognized as key components of the biopsychosocial frailty phenotype, which adversely affect the development and progression of chronic diseases, such as cardiovascular diseases, late-life cognitive impairment and dementia[6,7], as well as impacting the incidence and progression of mental illnesses such as anxiety and depression and affecting functional capabilities[5,8]. All of these conditions have consequences for health systems at all levels, increasing health-care consumption of primary care[9], outpatient care[10,11] and rehospitalization[10].

To date, much of the research in this space has focused on social deficits without considering the length of time that individuals have experienced them. But chronic loneliness and isolation phenotypes may play a more robust role in shaping adverse health consequences, which could differ from acute and occasional loneliness[12]. Indeed, the evolutionary theory of loneliness posits that lonely or socially isolated individuals are likely to hold negative expectations of meeting social needs and enhanced social deficits, resulting in cycles of more intense and persistent loneliness and isolation[13]. Long-term exposure to loneliness and/or social isolation is linked to biosocial pathogenesis[14,15], and the health hazards can accumulate through persistent psychological stress and unhealthy behaviors[16]. For example, as a persistent psychological stressor, chronic loneliness may result in allostatic overload[17–19] and long-term stress system overactivation[20], as well as dysregulated inflammatory processes[21,22] and upregulated gene transcription of pro-inflammatory control pathways[23].

There is growing research suggesting that these biological pathways involved in chronic social deficits could have implications for the healthspan and lifespan. Several studies have suggested that chronic loneliness is a more harmful predictor of cardiovascular health (for example, lower resting heart rate variability)[24] and incident coronary disease[25] than acute loneliness. Older adults experiencing social deficits are also vulnerable to earlier and faster functional declines[8,26] (setting in motion feedback loops that in turn detrimentally affect social interactions[27]). Social connections appear to help older people remain independent[28]. However, it remains unclear whether chronic loneliness and/or social isolation can drive a higher incidence of functional impairment. Further, previous epidemiological research from multiple countries has identified an increased all-cause mortality risk among older people who report subjective loneliness[26,29–31] or objective social isolation[32,33]. Again, however, it is unclear whether this risk is higher among older adults with chronic social deficits.

Therefore, this study aimed to address this research gap by examining the roles of chronic loneliness and social isolation in predicting the onset of physical functional declines and all-cause and cause-specific mortality over 10-year follow-ups using a nationally representative sample of older adults living in England.

## Results

### Participants

The study consisted of 4,279 participants in the functional disability-free cohort (mean age 67.0 years, s.d. 9.6) and 5,131 participants in the mortality cohort (mean age 67.6 years, s.d. 9.8; Table 1). The disability-free samples had a 20.2% all-cause mortality rate, with 9.83 years of median follow-up (interquartile range (IQR): 7.17–10.17). The all-cause mortality rate was 22.4% in the mortality cohort, with a median follow-up length of 9.83 years (IQR: 6.67–10.08).

**Table 1 | Characteristics of study samples**

| Characteristics | Functional disability-free cohort (*n*=4,279) | Mortality cohort (*n*=5,131) |
|---|---|---|
| **Age (mean (s.d.))** | 67.0 (9.6) | 67.6 (9.8) |
| **Sex** | | |
| Female | 2,379 (55.6%) | 2,868 (55.9%) |
| Male | 1,900 (44.4%) | 2,263 (44.1%) |
| **Education** | | |
| No or basic qualifications | 1,337 (31.3%) | 1,735 (33.8%) |
| General Certificate of Secondary Education/O level/ qualification at age 16 | 1,172 (27.4%) | 1,356 (26.4%) |
| A levels/higher education/ qualification at age 18 | 1,010 (23.6%) | 1,195 (23.3%) |
| Degree/further higher qualification | 760 (17.7%) | 845 (16.5%) |
| **Household income (mean (s.d.))** | 339.3 (262.9) | 330.1 (249.3) |
| **Employment** | | |
| Unemployed or retired | 2,862 (66.9%) | 3,626 (70.7%) |
| Actively working | 1,417 (33.1%) | 1,505 (29.3%) |
| **Sedentary lifestyle** | | |
| Less than weekly | 620 (14.5%) | 1,039 (20.3%) |
| Weekly and more frequent | 3,659 (85.5%) | 4,092 (79.7%) |
| **Chronic illness** | | |
| Yes | 2,110 (49.3%) | 2,877 (56.1%) |
| None | 2,169 (50.7%) | 2,254 (43.9%) |
| **Persistent pain** | | |
| Yes | 926 (21.6%) | 1,467 (28.6%) |
| No | 3,353 (78.4%) | 3,664 (71.4%) |
| **Depression** | | |
| Yes | 819 (19.1%) | 1,177 (22.9%) |
| No | 3,460 (80.9%) | 3,954 (77.1%) |
| **Loneliness** | | |
| No loneliness | 2,617 (61.2%) | 3,028 (59.0%) |
| Fluctuating loneliness | 1,427 (33.3%) | 1,767 (34.4%) |
| Chronic loneliness | 235 (5.5%) | 336 (6.6%) |
| **Social isolation** | | |
| No isolation | 2,257 (52.8%) | 2,682 (52.3%) |
| Fluctuating isolation | 1,662 (38.8%) | 1,970 (38.4%) |
| Chronic isolation | 360 (8.4%) | 479 (9.3%) |
| **Baseline functional impairment** | | |
| ADLs disability | 0 | 1,019 (19.9%) |
| No disability | 4,279 (100%) | 4,112 (80.1%) |
| **Median length of follow-up (years (IQR))** | 9.83 (7.17–10.17) | 9.83 (6.67–10.08) |
| **Mortality rate per 1,000 person-years** | 24.22 (22.65–25.89) | 27.14 (25.61–28.76) |
| **All-cause death** | 864 (20.2%) | 1,148 (22.4%) |
| **Cause-specific death** | | |
| Cancer | 314 (7.3%) | 385 (7.5%) |
| CVD | 245 (5.7%) | 333 (6.5%) |
| Respiratory disease | 126 (3.0%) | 174 (3.4%) |
| Other cause | 179 (4.2%) | 256 (5.0%) |

ADL, activity of daily living.

**Table 2 | Associations between chronic and fluctuating loneliness and social isolation and incident functional impairment**

| Incident functional impairment | Loneliness (sHR, 95% CI) | | Social isolation (sHR, 95% CI) | |
|---|---|---|---|---|
| | Fluctuating loneliness | Chronic loneliness | Fluctuating social isolation | Chronic social isolation |
| Unadjusted | 1.77 (1.44–2.17) | 2.39 (1.73–3.32) | 1.53 (1.24–1.88) | 1.88 (1.37–2.59) |
| Model 1 | 1.61 (1.30–1.98) | 2.06 (1.47–2.88) | 1.22 (0.98–1.52) | 1.57 (1.14–2.17) |
| Model 2 | 1.30 (1.03–1.63) | 1.58 (1.12–2.23) | 1.09 (0.88–1.36) | 1.41 (1.02–1.94) |

Reference group: no loneliness/social isolation. We conducted the Fine–Gray competing risk model. Model 1 was adjusted for age, sex, education, household income, employment and sedentary lifestyle; Model 2 was additionally adjusted for depression, persistent pain and long-term illness.
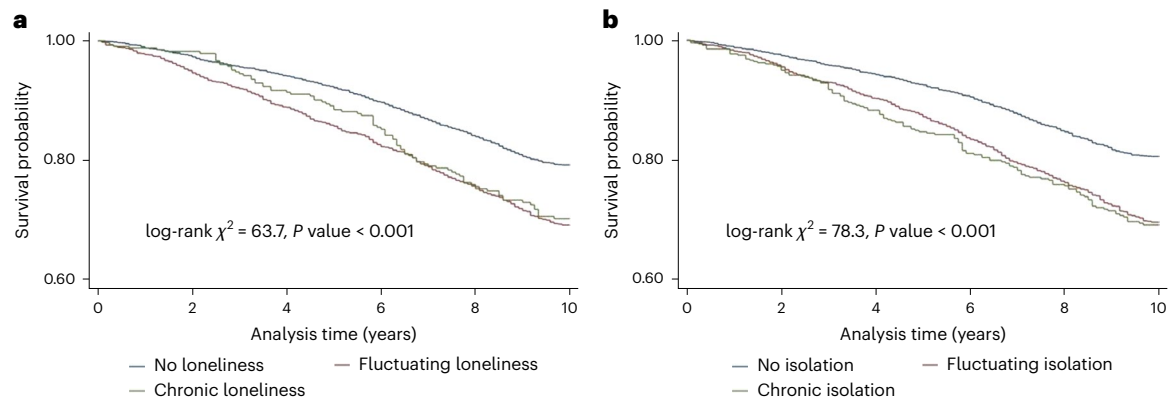


**Fig. 1 | Kaplan–Meier survival curve for 10-year all-cause mortality by different patterns of loneliness and social isolation. a**, Loneliness. **b**, Social isolation. Kaplan–Meier survival curves were graphed, and two-sided log-rank tests were conducted to compare the differences in curves across patterns of loneliness/isolation over 4 years.

In the mortality cohort, the prevalence of chronic loneliness and isolation were 6.6% and 9.3%, respectively; 34.4% of the participants had fluctuating loneliness, and 38.4% had fluctuating isolation. Chronic loneliness and isolation were slightly less prevalent in the disability-free cohort, with 5.5% and 8.4% of the sample reporting the issues.

### Incident functional impairment
Compared with no loneliness, chronic loneliness (sub-hazard ratio (sHR): 1.58, 95% confidence interval (CI) 1.12–2.23) and fluctuating loneliness (sHR: 1.30, 1.03–1.63) were associated with increased risk of incident functional impairment (Table 2). These results were found when adjusting for social confounders and were maintained (albeit slightly attenuated) when additionally adjusting for health-related confounders. Fluctuating social isolation was not consistently associated with functional impairment when adjusting for confounders, but older adults with chronic social isolation had higher risks of developing new functional impairment cases (sHR: 1.41, 1.02–1.94).

### All-cause and cause-specific mortality
In survival analyses, crude Kaplan–Meier curves showed that the fluctuating and chronic social isolation group had lower 10-year survival rates than the not isolated group (Fig. 1), with evidence of a slight dose–response relationship depending on chronicity. The pattern for loneliness was less clear, with a clear higher survival rate for the not lonely group but inconsistent patterns over time between fluctuating and chronic loneliness and survival rates. The results were consistent in cause-specific mortality analyses (Supplementary Fig. 1).

In the fully adjusted Cox proportional model, compared with no social isolation, chronic isolation had the most elevated all-cause mortality risks (hazard ratio (HR) 1.27, 1.05–1.55), followed by fluctuating isolation (HR 1.15, 1.01–1.31) (Table 3). Fluctuating loneliness had a higher all-cause mortality risk than no loneliness (HR 1.29, 1.13–1.48). However, the adverse effects of chronic loneliness on all-cause mortality were attenuated after adjustment for health-related confounders. In the cause-specific mortality analyses, social isolation (especially chronic social isolation) was related to higher cancer-related mortality risk and respiratory-related mortality risk, while loneliness was related to higher cardiovascular disease (CVD) mortality (although results were less robust for chronic loneliness).

### Discussion
Over the 14-year follow-up of a nationally representative sample of older adults in England, we found that social isolation and loneliness were both related to incident functional impairment and mortality risk. Chronic isolation and loneliness had stronger associations with both outcomes than fluctuating isolation and loneliness, suggesting that temporal patterns and longevity of these experiences are important risk factors. We saw differences in patterns of cause-specific mortality, with cancer and respiratory disease mortality linked more to social isolation and CVD mortality to loneliness, suggesting different bio-behavioral pathways. Results were consistent when accounting for sociodemographic factors. Some results were attenuated when taking into account health-related factors, which could indicate some partial mediation of associations. It is notable, however, that many of the key results were still maintained (especially for chronic social deficits) even when adjusting for these factors, highlighting that results are not merely due to pre-existing associations between social deficits and mental and physical health symptoms.

Notably, we provide new evidence that chronic loneliness and isolation are related to higher functional impairment and mortality risks than fluctuating patterns. The chronic phenotype appears more detrimental to health, with a dose–response relationship between chronicity and outcomes, suggesting that adverse health effects of loneliness and isolation may accumulate over time and drive poorer health outcomes[12]. Indeed, prolonged loneliness could cumulatively damage functional ability and longevity through long-term unhealthy behaviors (for example, sedentary lifestyle)[16], prolonged stress system overactivation[20] and chronic inflammation[21,23]. The slightly higher mortality risk for fluctuating subjective loneliness above chronic loneliness may have resulted from the small number of participants who reported chronic loneliness in our study.

**Table 3 | Associations between changes in loneliness and social isolation, and all-cause and cause-specific mortality**

| All-cause mortality | Loneliness | | Social isolation | |
|---|---|---|---|---|
| | Fluctuating loneliness, HR | Chronic loneliness, HR | Fluctuating social isolation, HR | Chronic social isolation, HR |
| Unadjusted | 1.61 (1.43–1.82) | 1.51 (1.21–1.89) | 1.68 (1.48–1.90) | 1.74 (1.44–2.11) |
| Model 1 | 1.46 (1.29–1.66) | 1.32 (1.05–1.65) | 1.22 (1.07–1.38) | 1.38 (1.14–1.67) |
| Model 2 | 1.29 (1.13–1.48) | 1.11 (0.87–1.40) | 1.15 (1.01–1.31) | 1.27 (1.05–1.55) |
| **Cancer mortality** | | | | |
| Unadjusted | 0.93 (0.75–1.16) | 1.11 (0.75–1.64) | 1.36 (1.10–1.69) | 1.84 (1.35–2.51) |
| Model 1 | 0.93 (0.74–1.17) | 1.09 (0.74–1.62) | 1.27 (1.01–1.58) | 1.72 (1.26–2.35) |
| Model 2 | 0.85 (0.67–1.08) | 0.95 (0.62–1.44) | 1.23 (0.98–1.54) | 1.69 (1.23–2.31) |
| **CVD mortality** | | | | |
| Unadjusted | 1.79 (1.43–2.25) | 1.94 (1.32–2.85) | 1.78 (1.42–2.24) | 1.48 (1.01–2.17) |
| Model 1 | 1.44 (1.13–1.84) | 1.59 (1.05–2.41) | 1.26 (0.98–1.61) | 1.14 (0.77–1.68) |
| Model 2 | 1.29 (1.00–1.67) | 1.38 (0.90–2.12) | 1.18 (0.92–1.52) | 1.07 (0.72–1.59) |
| **Respiratory disease mortality** | | | | |
| Unadjusted | 1.93 (1.42–2.64) | 1.70 (0.96–2.99) | 1.70 (1.23–2.36) | 2.24 (1.43–3.53) |
| Model 1 | 1.47 (1.05–2.05) | 1.49 (0.85–2.62) | 1.17 (0.83–1.65) | 1.66 (1.03–2.67) |
| Model 2 | 1.28 (0.90–1.81) | 1.24 (0.69–2.25) | 1.11 (0.79–1.57) | 1.55 (0.96–2.48) |

Reference group: no loneliness/social isolation. We applied the Cox proportional hazards model to estimate the effects of loneliness and social isolation on all-cause mortality and the Fine–Gray competing risk model to assess their roles in cause-specific mortality. The proportional hazard assumption was assessed using the Schoenfeld residuals test. Model 1 was adjusted for age, sex, education, household income, employment and sedentary lifestyle; Model 2 was additionally adjusted for depression, persistent pain and long-term illness.

Further, we found a distinction between loneliness and social isolation in cause-specific mortality, with social isolation (especially the chronic phenotype) associated with higher cancer-related mortality risk and respiratory-related mortality risk, while loneliness was related to higher CVD-related mortality. The loneliness–CVD findings support previous studies showing increased risk of CVD due to loneliness-based activation of psychological pathways (depression, stress, anger and hostility), adverse immune responses (atypical neuroendocrine stress responses, increased inflammation and enhanced oxidative stress), cardiometabolic pathways (blood pressure, heart rate variability, increased vascular resistance and changes in gut microbiota) and potential epigenetic changes, in addition to behavioral factors such as physical inactivity, body mass index and substance use[34]. Indeed, we have previously found that loneliness as opposed to social isolation is associated with increased hospital admissions for CVD events as well as increased risk for incident CVD outcomes, including incident CVD events[35] and mortality[36]. Similarly, the social isolation results support past findings suggesting that social isolation (but not loneliness) increases the risk of respiratory disease admissions, potentially due to risk factors such as smoking[35,37,38].

The findings for cancer do reflect some past literature failing to find associations between loneliness and cancer-related mortality (after adjusting for confounders)[39]. However, previous findings of a relationship for social isolation with cancer-related mortality are mixed[36,40]. Nonetheless, our findings of a relationship that is dose-dependent on chronicity could be due to some shared mechanistic pathways. Social isolation can influence cancer progression and survival through activated tumorigenic markers[41], higher vascular endothelial growth factor and pro-inflammatory biomarkers that contributed to tumor angiogenesis[42,43]. However, these pathways can also be activated via loneliness, and it is notable that loneliness was not linked to cancer survival, suggesting additional mechanistic pathways are also at play. Instead, socially isolated individuals may receive less social encouragement to seek medical advice about early symptoms of cancer, leading to late cancer detection and a higher risk of developing advanced cancer. Similarly, a supportive social network and connections could potentially improve cancer outcomes through facilitating cancer recovery and functional independence (including adherence to cancer treatments)[44]. As socioemotional selectivity theory illustrates, time perception may affect social network and preferred social partners. For example, cancer survivors may prioritize social connections such as family communications in the wake of diagnoses[45]. While our research adjusted for existing chronic illness, future studies could seek to disentangle whether existing health conditions such as cancer lead people to adjust their social behaviors, potentially leading to a reverse-causal finding.

A key contribution of this study is in providing evidence on chronic social deficits, where previous studies have often relied on single time-point measurements. Consistent with previous findings[26,29,32,33], both subjective loneliness and objective isolation were associated with increased premature mortality risk in this study. However, aligning with previous UK Biobank findings showing that isolation but not loneliness was related to higher all-cause mortality after full adjustment[46], after accounting for health-related confounders, we found that chronic loneliness is no longer an independent risk factor for all-cause mortality, suggesting that the harmful effect of chronic subjective loneliness on mortality may be attributable to mental and physical health. Loneliness is related to worsening health status[5], which could mediate the association between chronic loneliness and premature mortality. However, our findings suggest that people with chronic loneliness and social isolation are more likely to develop functional impairment onset, illustrating that chronic phenotypes may have a significant role in accumulating harmful effects on functional abilities. This confirms and supplements previous evidence that loneliness and social isolation are linked with worsening functional declines in later life[8,26]. Lacking a socially supportive environment can potentially hinder access to resources and develop coping strategies, leading to incident functional ability declines among older adults[44].

This investigation in England provides insights into associations of chronic loneliness and social isolation with the incidence of functional impairment and all-cause and cause-specific mortality using a nationally representative sample. English Longitudinal Study of Ageing (ELSA) data provide comprehensive information on social demographic and health-related confounders. Nevertheless, there are several limitations in current estimates. First, this is an observational study, so causality cannot be demonstrated. Although we considered an extensive

set of confounders, it is possible for residual confounding to remain. For example, our population-based survey data limited the possibility of taking into account clinically validated mental health diagnoses, many of which are likely to co-exist with loneliness and isolation phenotypes. We considered depression with a validated and widely applied scale (above-threshold depression scores) in the modeling, but we cannot rule out the potential overestimation/underestimation of the current effect sizes. Second, most of our measures were collected through self-report, which may introduce response bias. In addition, findings of cause-specific mortality analyses (three types of causes) may be affected by statistical power, so they are presented as exploratory. However, the results are consistent with all-cause mortality analyses. Finally, the magnitude of risk aggravation could also be varied depending on the different measurements of loneliness applied (single versus multiple item measures)[30]. Future studies could explore the consistency of findings in other studies with different measurement approaches.

## Conclusion

The study sheds light on the effects of chronic loneliness and social isolation on predicting incident functional impairment and premature mortality, highlighting the importance of addressing chronic loneliness phenotypes to better support healthy ageing. Our findings indicate that both subjective loneliness and objective social isolation might increase the risks of functional impairment and mortality risk, with social isolation (especially the chronic phenotype) associated with higher all-cause and cancer-related mortality risks and loneliness related to higher risks for all-cause and CVD-related mortality independent of sociodemographic and health status. Preventing the onset and transition to chronic loneliness phenotypes in older age is vital to facilitating disease management and recovery. Chronic loneliness and social isolation could be targets for policy and public health practice in the future, especially in developing interventions to help older people maintain functional ability and healthy longevity.

## Methods

### Study sample

ELSA was designed to recruit a representative sample of adults aged 50 years and older living in private households in England. The ELSA survey was started in 2002 and then followed up every 2 years[47]. In this study, we used data from wave 2 (in 2004) as this is the first wave that provides loneliness and social isolation measures. We initially included participants who had completed the loneliness/social isolation information in waves 2–4 ($n = 6,004$).

To explore the relationship with functional decline, we limited the sample to participants free of physical disabilities at baseline (wave 4; definition follows) ($n = 4,857$). To enable analysis of competing risks of disability with death, we then excluded those who did not consent to linkage with the UK Office for National Statistics data ($n = 244$) and with missingness in covariates ($n = 334$), leading to a final sample ($n = 4,279$).

To explore the relationship with mortality, we linked the records with the UK Office for National Statistics to ascertain death dates and vital status and excluded loss to follow-up samples ($n = 274$). The study also excluded those with missingness in covariates ($n = 599$), providing a final analytical sample of 5,131. Details of the study sample selection process are shown in Supplementary Fig. 2.

### Measures

**Outcomes.** Incident functional impairment was defined as developing impairments in one or more ADLs at follow-up waves (2010–2018), consisting of getting in or out of bed, walking across a room, bathing or showering, using the toilet, dressing (including putting on shoes and socks) and eating, such as cutting food[48].

All-cause and cause-specific mortality data were ascertained from the National Health Service central data registry, including deaths from cancer, CVD, respiratory disease and other causes using ICD-10 (International Classification of Diseases, 10th Revision)[49] codes. Vital status was followed up until March 2018.

**Exposures.** Loneliness was measured by a validated three-item version of the UCLA (University of California at Los Angeles) loneliness scale[50,51], measuring whether individuals felt (1) lack of companionship, (2) left out and (3) isolated from others, with a sum score ranging from 3 to 9 and a cut-off score of ≥6 to indicate loneliness[2].

For social isolation, we used the five-item index of social isolation, which captures social contactlessness in domains: (1) unmarried/not cohabiting or living alone, (2) no engagement in any groups, clubs or other social organizations and less than monthly contact (via face-to-face, phone or written/e-mail contact) with children, family members and friends. It has been applied and validated in ELSA[2,51,52]. The overall scores range from 0 to 5, and those with a score of ≥3 were categorized as socially isolated[50].

In this study, we measured changes in loneliness/social isolation over the first three waves (2004–2008) and generated new three-category loneliness and social isolation variables: no loneliness/isolation (not lonely/socially isolated in any waves), fluctuating loneliness/isolation (reported loneliness/isolation in one or two waves) and chronic loneliness/isolation (reported loneliness/isolation in all waves).

**Covariates.** We considered baseline (wave 2, in 2004) sociodemographic characteristics, including age, sex (male, female), educational attainment (no qualifications or basic qualifications, General Certificate of Secondary Education or O level or qualification at age 16, A levels or higher education or qualification at age 18, degree or further higher qualification), equivalized household income[53] and employment status (employed versus unemployed or retired). We also adjusted for health-behavior confounders such as sedentary lifestyle (less than weekly engagement versus weekly and more frequently engagement in mild, moderate or vigorous sports or activities).

We further considered that some health-related factors could act as confounders, including long-standing chronic illness (one or more of cancer, chronic obstructive pulmonary disease, arthritis, stroke, diabetes, angina), depression (measured using the eight-item Center for Epidemiologic Studies Depression Scale with a score of ≥3 to indicate depression (yes/no)[54]) and persistent pain (moderate or severe chronic pain (yes/no)). However, it is also plausible that all of these lie on the causal pathway; hence, adjusting for them could result in partial mediation of findings. Therefore, we included them only in a final model to compare the effects of their inclusion on the findings[55].

### Statistical analysis

To examine the relationship with incident physical functional disability, we identified the onset of ADL disability as a 'competing outcome' in the functional disability-free cohort and conducted the Fine–Gray competing risk model[56] (additionally adjusting for competing risk of death). To examine the relationship between social deficits and mortality, we applied the Cox proportional hazards model to estimate the effects of chronic loneliness and social isolation on all-cause mortality and the Fine–Gray competing risk model to assess their roles in cause-specific mortality. The proportional hazard assumption was assessed using the Schoenfeld residuals test. Kaplan–Meier survival curves were graphed, and log-rank tests were conducted to compare the differences in curves across patterns of loneliness/isolation over 4 years. In modeling, we adjusted for baseline age, sex, education, household income, employment and sedentary lifestyle at baseline (wave 4) in Model 1. Model 2 then additionally adjusted for baseline depression, persistent pain and long-term illness, but this was treated as a comparison model given the potential risk of partial mediation of findings. All analyses were performed using STATA 17.0.

## Ethics and inclusion statement

This work analyzed the English Longitudinal Study of Ageing. The research is locally relevant, and all co-authors are from the United Kingdom. All co-authors have agreed on their roles and responsibilities ahead of research. This research complies with the Declaration of Helsinki. ELSA Wave 9 received ethical approval from the South Central-Berkshire Research Ethics Committee on 10 May 2018 (17/SC/0588). ELSA Wave 8 received ethical approval from the South Central-Berkshire Research Ethics Committee on 23 September 2015 (15/SC/0526). ELSA Wave 7 received ethical approval from the National Research Ethics Service Committee South Central-Berkshire on 28 November 2013 (13/SC/0532). ELSA Wave 6 received ethical approval from the National Research Ethics Service Committee South Central-Berkshire on 28 November 2012 (11/SC/0374). ELSA Wave 5 received ethical approval from the Berkshire Research Ethics Committee on 21 December 2009 (09/H0505/124). ELSA Wave 4 received ethical approval from the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee on 12 October 2007 (07/H0716/48). ELSA Wave 3 received ethical approval from the London Multi-Centre Research Ethics Committee on 27 October 2005 (05/MRE02/63). ELSA Wave 2 received ethical approval from the London Multi-Centre Research Ethics Committee on 12 August 2004 (MREC/04/2/006). Informed consent was acquired from all participants.

## Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

## Data availability

ELSA data are available through registration with the UK data service (https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=200011).

## Code availability

All data analyses used open-source STATA code (that is, Cox proportional hazards model and Fine–Gray competing risk model).

## References

1. Kannan, V. D. & Veazie, P. J. US trends in social isolation, social engagement, and companionship—nationally and by age, sex, race/ethnicity, family income, and work hours, 2003–2020. *SSM Popul. Health* **21**, 101331 (2023).
2. Steptoe, A., Shankar, A., Demakakos, P. & Wardle, J. Social isolation, loneliness, and all-cause mortality in older men and women. *Proc. Natl Acad. Sci. USA* **110**, 5797–5801 (2013).
3. Yang, K. & Victor, C. Age and loneliness in 25 European nations. *Ageing Soc.* **31**, 1368–1388 (2011).
4. Perlman, D. & Peplau, L. A. in *Encyclopedia of Mental Health* Vol. 2 (ed. Friedman, H.) 571–581 (Academic Press, 1998).
5. National Academies of Sciences, Engineering, and Medicine *Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System* (National Academies Press, 2020); https://doi.org/10.17226/25663
6. Panza, F. et al. Depressive and biopsychosocial frailty phenotypes: impact on late-life cognitive disorders. *J. Alzheimers Dis.* **94**, 879–898 (2023).
7. Teo, N. et al. A bio-psycho-social approach for frailty amongst Singaporean Chinese community-dwelling older adults— evidence from the Singapore Longitudinal Aging Study. *BMC Geriatr.* **19**, 350 (2019).
8. Shankar, A., McMunn, A., Demakakos, P., Hamer, M. & Steptoe, A. Social isolation and loneliness: prospective associations with functional status in older adults. *Health Psychol.* **36**, 179–187 (2017).
9. Sirois, F. M. & Owens, J. A meta-analysis of loneliness and use of primary health care. *Health Psychol. Rev.* https://doi.org/10.1080/17437199.2021.1986417 (2021)
10. Newall, N., McArthur, J. & Menec, V. H. A longitudinal examination of social participation, loneliness, and use of physician and hospital services. *J. Aging Health* **27**, 500–518 (2014).
11. Gerst-Emerson, K. & Jayawardhana, J. Loneliness as a public health issue: the impact of loneliness on health care utilization among older adults. *Am. J. Public Health* **105**, 1013–1019 (2015).
12. Morr, M., Liu, X., Hurlemann, R., Becker, B. & Scheele, D. Chronic loneliness: neurocognitive mechanisms and interventions. *Psychother. Psychosom.* **91**, 227–237 (2022).
13. Hawkley, L. C. & Capitanio, J. P. Perceived social isolation, evolutionary fitness and health outcomes: a lifespan approach. *Phil. Trans. R. Soc. B* **370**, 20140114 (2015).
14. Horwitz, R. I. et al. Biosocial pathogenesis. *Psychother. Psychosom.* **91**, 73–77 (2022).
15. Quadt, L., Esposito, G., Critchley, H. D. & Garfinkel, S. N. Brain-body interactions underlying the association of loneliness with mental and physical health. *Neurosci. Biobehav. Rev.* **116**, 283–300 (2020).
16. Cacioppo, J. T., Cacioppo, S., Capitanio, J. P. & Cole, S. W. The neuroendocrinology of social isolation. *Annu. Rev. Psychol.* **66**, 733–767 (2015).
17. Seeman, T. et al. Social relationships and allostatic load in Taiwanese elderly and near elderly. *Soc. Sci. Med.* **59**, 2245–2257 (2004).
18. Seeman, T. E., Singer, B. H., Ryff, C. D., Dienberg Love, G. & Levy-Storms, L. Social relationships, gender, and allostatic load across two age cohorts. *Psychosom. Med.* **64**, 395–406 (2002).
19. Brooks, K. P. et al. Social relationships and allostatic load in the MIDUS study. *Health Psychol.* **33**, 1373–1381 (2014).
20. McEwen, B. S. Protective and damaging effects of stress mediators. *N. Engl. J. Med.* **338**, 171–179 (1998).
21. Hawkley, L. C. & Cacioppo, J. T. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. *Ann. Behav. Med.* **40**, 218–227 (2010).
22. Gao, Q., Bone, J. K., Finn, S. & Fancourt, D. The reciprocal associations between social deficits, social engagement, and inflammation: longitudinal evidence comparing venous blood samples and dried blood spots and mapping the modifying role of phenotypic and genotypic depression. *Brain Behav. Immun.* **119**, 120–128 (2024).
23. Cole, S. W. et al. Social regulation of gene expression in human leukocytes. *Genome Biol.* **8**, R189 (2007).
24. Roddick, C. M. & Chen, F. S. Effects of chronic and state loneliness on heart rate variability in women. *Ann. Behav. Med.* **55**, 460–475 (2021).
25. Thurston, R. C. & Kubzansky, L. D. Women, loneliness, and incident coronary heart disease. *Psychosom. Med.* **71**, 836–842 (2009).
26. Perissinotto, C. M., Stijacic Cenzer, I. & Covinsky, K. E. Loneliness in older persons: a predictor of functional decline and death. *Arch. Intern. Med.* **172**, 1078–1083 (2012).
27. Donovan, N. J. & Blazer, D. Social isolation and loneliness in older adults: review and commentary of a National Academies report. *Am. J. Geriatr. Psychiatry* **28**, 1233–1244 (2020).
28. Guida, J. L. et al. Social relationships and functional impairment in aging cancer survivors: a longitudinal social network study. *Gerontologist* **60**, 607–616 (2020).
29. Courtin, E. & Knapp, M. Social isolation, loneliness and health in old age: a scoping review. *Health Soc. Care Community* **25**, 799–812 (2017).

30. Shiovitz-Ezra, S. & Ayalon, L. Situational versus chronic loneliness as risk factors for all-cause mortality. *Int. Psychogeriatr.* **22**, 455–462 (2010).

31. Gao, Q. et al. Loneliness among older adults in Latin America, China, and India: prevalence, correlates and association with mortality. *Int. J. Public Health* https://doi.org/10.3389/ijph.2021.604449 (2021).

32. Naito, R. et al. Social isolation as a risk factor for all-cause mortality: systematic review and meta-analysis of cohort studies. *PLoS ONE* **18**, e0280308 (2023).

33. Holt-Lunstad, J., Smith, T. B., Baker, M., Harris, T. & Stephenson, D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspect. Psychol. Sci.* **10**, 227–237 (2015).

34. Paul, E., Bu, F. & Fancourt, D. Loneliness and risk for cardiovascular disease: mechanisms and future directions. *Curr. Cardiol. Rep.* **23**, 68 (2021).

35. Valtorta, N. K., Kanaan, M., Gilbody, S. & Hanratty, B. Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing. *Eur. J. Prev. Cardiol.* **25**, 1387–1396 (2018).

36. Naito, R. et al. Impact of social isolation on mortality and morbidity in 20 high-income, middle-income and low-income countries in five continents. *BMJ Glob. Health* **6**, e004124 (2021).

37. Bu, F., Philip, K. & Fancourt, D. Social isolation and loneliness as risk factors for hospital admissions for respiratory disease among older adults. *Thorax* **75**, 597–599 (2020).

38. Bu, F., Zaninotto, P. & Fancourt, D. Longitudinal associations between loneliness, social isolation and cardiovascular events. *Heart* **106**, 1394–1399 (2020).

39. Kraav, S.-L. et al. The effects of loneliness and social isolation on all-cause, injury, cancer, and CVD mortality in a cohort of middle-aged Finnish men. A prospective study. *Aging Ment. Health* **25**, 2219–2228 (2021).

40. Fleisch Marcus, A., Illescas, A. H., Hohl, B. C. & Llanos, A. A. M. Relationships between social isolation, neighborhood poverty, and cancer mortality in a population-based study of US adults. *PLoS ONE* **12**, e0173370 (2017).

41. Kroenke, C. H. A conceptual model of social networks and mechanisms of cancer mortality, and potential strategies to improve survival. *Transl. Behav. Med.* **8**, 629–642 (2018).

42. Grivennikov, S. I. & Karin, M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. *Ann. Rheum. Dis.* **70**, i104–i108 (2011).

43. Guthrie, G. J. K., Roxburgh, C. S. D., Horgan, P. G. & McMillan, D. C. Does interleukin-6 link explain the link between tumour necrosis, local and systemic inflammatory responses and outcome in patients with colorectal cancer? *Cancer Treat. Rev.* **39**, 89–96 (2013).

44. Thompson, T., Rodebaugh, T. L., Pérez, M., Schootman, M. & Jeffe, D. B. Perceived social support change in patients with early stage breast cancer and controls. *Health Psychol.* **32**, 886–895 (2013).

45. Fisher, C. L. & Nussbaum, J. F. Maximizing wellness in successful aging and cancer coping: the importance of family communication from a socioemotional selectivity theoretical perspective. *J. Fam. Commun.* **15**, 3–19 (2015).

46. Elovainio, M. et al. Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study. *Lancet Public Health* **2**, e260–e266 (2017).

47. Steptoe, A., Breeze, E., Banks, J. & Nazroo, J. Cohort profile: the English Longitudinal Study of Ageing. *Int. J. Epidemiol.* **42**, 1640–1648 (2013).

48. Rippon, I. & Steptoe, A. Is the relationship between subjective age, depressive symptoms and activities of daily living bidirectional? *Soc. Sci. Med.* **214**, 41–48 (2018).

49. WHO. *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (2019); https://icd.who.int/browse10/2019/en

50. Crowe, C. L. et al. Associations of loneliness and social isolation with health span and life span in the US Health and Retirement Study. *J. Gerontol. A* **76**, 1997–2006 (2021).

51. Davies, K., Maharani, A., Chandola, T., Todd, C. & Pendleton, N. The longitudinal relationship between loneliness, social isolation, and frailty in older adults in England: a prospective analysis. *Lancet Healthy Longev.* **2**, e70–e77 (2021).

52. Shankar, A., McMunn, A., Banks, J. & Steptoe, A. Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychol.* **30**, 377–385 (2011).

53. Banks, J. et al. *Financial Circumstances, Health and Well-Being of the Older Population in England: ELSA 2008 (Wave 4)* (PurePrint Group, 2010).

54. Karim, J., Weisz, R., Bibi, Z. & ur Rehman, S. Validation of the eight-Item Center for Epidemiologic Studies Depression Scale (CES-D) among older adults. *Curr. Psychol.* **34**, 681–692 (2015).

55. VanderWeele, T. J. Principles of confounder selection. *Eur. J. Epidemiol.* **34**, 211–219 (2019).

56. Fine, J. P. & Gray, R. J. A proportional hazards model for the subdistribution of a competing risk. *J. Am. Stat. Assoc.* **94**, 496–509 (1999).

## Author contributions

Q.G. and D.F. conceived and designed the study. Q.G. acquired and verified the data, conducted data analyses and wrote the draft of the paper. A.S. and D.F. contributed to the conceptualization, interpretation, review and critical revision of the paper. All authors reviewed and approved the final paper.

## Competing interests

The authors declare no competing interests.

## Additional information

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s44220-025-00436-0.

**Correspondence and requests for materials** should be addressed to Qian Gao.

**Peer review information** *Nature Mental Health* thanks Francesco Panza and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Corresponding author(s): Qian Gao

Last updated by author(s): Apr 11, 2025

# Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

## Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

| n/a | Confirmed | |
|---|---|---|
| ☐ | ☒ | The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ | The statistical test(s) used AND whether they are one- or two-sided<br>*Only common tests should be described solely by name; describe more complex techniques in the Methods section.* |
| ☐ | ☒ | A description of all covariates tested |
| ☐ | ☒ | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ | For null hypothesis testing, the test statistic (e.g. $F$, $t$, $r$) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br>*Give P values as exact values whenever suitable.* |
| ☒ | ☐ | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ | Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated |

*Our web collection on statistics for biologists contains articles on many of the points above.*

## Software and code

Policy information about availability of computer code

| Data collection | No software was used for data collection. |
|---|---|
| Data analysis | All data analyses used open-source STATA code (i.e. Cox proportional hazards model and Fine-Gray competing risk model). All analyses were performed using STATA 17.0. |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

## Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:
- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

ELSA data was available through registration with the UK data service (https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=200011).

# Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](). See also policy information about [sex, gender (identity/presentation), and sexual orientation]() and [race, ethnicity and racism]().

| | |
|---|---|
| Reporting on sex and gender | The ELSA datasets had collected sex information. We reported the distribution of sex in Table 1. The fully adjusted Cox proportional hazards model and Fine-Gray competing risk model have adjusted for sex and other confounders  (Tables 2-3). |
| Reporting on race, ethnicity, or other socially relevant groupings | The study reported the distribution of participants' educational levels, household income, and employment status in Table 1 and models adjusted for these factors (Tables 2-3). |
| Population characteristics | The study consisted of 4279 participants in the functional disability-free cohort (67.0 years, SD=9.6) and 5131 participants in the mortality cohort (mean age=67.6 years, SD=9.8). The disability-free samples had a 20.2% all-cause mortality rate, with 9.83 years of median follow-up (IQR 7.17 to 10.17). The all-cause mortality rate was 22.4% in the mortality cohort, with a median follow-up length of 9.83 years (IQR 6.67 to 10.08). In the mortality cohort, the prevalence of chronic loneliness and isolation were 6.6% and 9.3%, respectively. 34.4% of the participants had fluctuating loneliness, and 38.4% with fluctuating isolation. Chronic loneliness and isolation were slightly less prevalent in the disability-free cohort, with 5.5% and 8.4% of the sample reporting the issues. The characteristics of study samples are reported in Table 1. |
| Recruitment | The English Longitudinal Study of Ageing (ELSA) was designed to recruit a representative sample of adults aged 50 years and older living in private households in England. The ELSA survey was started in 2002 and then followed up every two years. This study is a secondary data analysis of ELSA, and the detailed information about data collection has been described elsewhere (see data availability source in the manuscript). |
| Ethics oversight | ELSA Wave 9 received ethical approval from the South Central-Berkshire Research Ethics Committee on May 10, 2018 (17/SC/0588). ELSA Wave 8 received ethical approval from the South Central-Berkshire Research Ethics Committee on September 23, 2015 (15/SC/0526). ELSA Wave 7 received ethical approval from the National Research Ethics Service Committee South Central-Berkshire on November 28, 2013 (13/SC/0532). ELSA Wave 6 received ethical approval from the National Research Ethics Service Committee South Central-Berkshire on November 28, 2012 (11/SC/0374). ELSA Wave 5 received ethical approval from the Berkshire Research Ethics Committee on December 21, 2009 (09/H0505/124). ELSA Wave 4 received ethical approval from the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee on October 12, 2007 (07/H0716/48). ELSA Wave 3 received ethical approval from the London Multi-Centre Research Ethics Committee on October 27, 2005 (05/MRE02/63). ELSA Wave 2 received ethical approval from the London Multi-Centre Research Ethics Committee on August 12, 2004 (MREC/04/2/006). Informed consent was acquired from all participants. |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

# Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences    ☒ Behavioural & social sciences    ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf]()

# Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

| | |
|---|---|
| Study description | This quantitative study examined the roles of chronic loneliness and social isolation in predicting the onset of physical functional declines and all-cause and cause-specific mortality over 10-year follow-ups using a nationally representative sample of older adults living in England. |
| Research sample | The study used a nationally representative sample of older adults living in England, including study participants from different sociodemographic characteristics and health conditions. The English Longitudinal Study of Ageing (ELSA) survey was started in 2002 and then followed up every two years. ELSA is a national cohort study of more than 11,000 older participants aged 50+ living in England. In this study, we used data from wave 2 (in 2004), as this is the first wave that provides loneliness and social isolation measures. ELSA waves 2-9 were analysed. We linked the records with the UK Office for National Statistics (ONS) data to ascertain death dates and vital status and excluded loss to follow-up samples. Finally, the study consisted of 4279 participants in the functional disability-free cohort and 5131 participants in the mortality cohort. The proportion of gender and age distribution, etc., is reported in Table 1. Details of the study sample selection process are shown in Supplementary Figure 2. |
| Sampling strategy | The English Longitudinal Study of Ageing (ELSA) was designed to recruit a representative sample of adults aged 50 years and older living in private households in England. Further information on the sampling strategy can be found in the data resource. To enable analysis of mortality, we linked the records with the UK ONS, in which we excluded those who did not consent to linkage with the ONS data. The sample is sufficient as ELSA is a national study, and the age group reflects the ageing population. |

| | |
|---|---|
| Data collection | This study is a secondary data analysis of the ELSA, and no data collection was involved in this study. Data collection procedures can be found in the data resource. |
| Timing | This longitudinal study used panel data from the English Longitudinal Study of Ageing (ELSA), including 14 years of follow-up (waves 2-9, 2004-2018): Wave 2 (2004/05), Wave 3 (2006/2007), wave 4 (2008/09), Wave 5 (2010/11), Wave 6 (2012/13), Wave 7 (2014/15), Wave 8 (2016/17), and Wave 9 (2018/19). |
| Data exclusions | The study excluded data where participants had not responded to all measures (Functional disability-free cohort n=334; Mortality cohort n=599). The missingness was largely due to loss to follow-up and non-response. To enable data analysis of mortality, we also excluded those who did not consent to linkage with the UK Office for National Statistics (ONS) data (Functional disability-free cohort n=244; mortality cohort n=274). The exclusion criteria were pre-established. |
| Non-participation | To explore the relationship with functional decline, we limited the sample to participants free of physical disabilities at baseline (wave 4; see 'measures' below for definition) (n=4857). To enable analysis of competing risks of disability with death, we then excluded those who did not consent to linkage with the UK Office for National Statistics (ONS) data (n=244) and with missingness in covariates (n=334), leading to a final sample (n=4279). To explore the relationship with mortality, we linked the records with the UK ONS to ascertain death dates and vital status and excluded loss to follow-up samples (n=274). The study also excluded those with missingness in covariates (n=599), providing a final analytical sample of 5131. Details of the study sample selection process are shown in Supplementary Figure 2. |
| Randomization | This longitudinal study adjusted for age, sex, education, household income, employment, sedentary lifestyle, depression, persistent pain, and long-term illness in modelling. |

# Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

## Materials & experimental systems

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ Antibodies |
| ☒ | ☐ Eukaryotic cell lines |
| ☒ | ☐ Palaeontology and archaeology |
| ☒ | ☐ Animals and other organisms |
| ☒ | ☐ Clinical data |
| ☒ | ☐ Dual use research of concern |
| ☒ | ☐ Plants |

## Methods

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ ChIP-seq |
| ☒ | ☐ Flow cytometry |
| ☒ | ☐ MRI-based neuroimaging |

## Plants

| | |
|---|---|
| Seed stocks | *Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.* |
| Novel plant genotypes | *Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.* |
| Authentication | *Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.* |