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# Association of intrinsic capacity with incidence and mortality of cardiovascular disease: Prospective study in UK Biobank

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## Abstract

**Background** The World Health Organization proposed the concept of intrinsic capacity (IC; the composite of all the physical and mental capacities of the individual) as central for healthy ageing. However, little research has investigated the interaction and joint associations of IC with cardiovascular disease (CVD) incidence and CVD mortality in middle- and older-aged adults.

**Methods** Using data from 443 130 UK Biobank participants, we analysed seven biomarkers capturing the level of functioning of five domains of IC to calculate a total IC score (ranging from 0 [better IC] to +4 points [poor IC]). Associations between IC score and incidence of six long-term CVD conditions (hypertension, stroke/transient ischaemic attack stroke, peripheral vascular disease, atrial fibrillation/flutter, coronary artery disease and heart failure), and grouped mortality from these conditions were estimated using Cox proportional models, with a 1-year landmark analysis to triangulate the findings.

**Results** Over 10.6 years of follow-up, CVD morbidity grouped ($n$ = 384 380 participants for the final analytic sample) was associated with IC scores (0 to +4): mean hazard ratio (HR) [95% confidence interval, CI] 1.11 [1.08–1.14], 1.20 [1.16–1.24], 1.29 [1.23–1.36] and 1.56 [1.45–1.59] in men (C-index = 0.68), and 1.17 [1.13–1.20], 1.30 [1.26–1.36], 1.52 [1.45–1.59] and 1.78 [1.67–1.89] in women (C-index = 0.70). In regard to mortality, our results indicated that the higher IC score (+4 points) was associated with a significant increase in subsequent CVD mortality (mean HR [95% CI]: 2.10 [1.81–2.43] in men [C-index = 0.75] and 2.29 [1.85–2.84] in women [C-index = 0.78]). Results of all sensitivity analyses by full sample, sex and age categories were largely consistent independent of major confounding factors ($P < 0.001$).

**Conclusions** IC deficit score is a powerful predictor of functional trajectories and vulnerabilities of the individual in relation to CVD incidence and premature death. Monitoring an individual's IC score may provide an early-warning system to initiate preventive efforts.

**Keywords** biological ageing; biomarkers; incident pathologies; intrinsic capacity; mortality

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# Introduction

With the continuing demographic shift to older populations in almost every country in the world, the global prevalence of multimorbidity and other geriatric syndromes, such as frailty, sarcopenia, depression and dementia, continues to rise, contributing to an ever-increasing demand for healthcare and long-term care.[1] This has led to a growing interest in the biological underpinnings of ageing and how they operate to increase the risk of the chronic diseases prevalent in older age and is guided by an understanding that these risks are driven by 'biological' age, which can vary greatly between individuals of the same chronological age.

To inform countries on how they might respond to these shifts, in 2015, the World Health Organization (WHO) conceptualized a framework for healthy ageing based on functioning rather than the absence of disease[2] and defined healthy ageing as 'the process of building and maintaining the functional ability that enables well-being'. According to this model, functional ability is determined by an individual's intrinsic capacity (IC), the environment they inhabit and the interaction between the individual and their environment. However, beyond proposing that IC comprises all an individual's physical and mental capacities, the WHO did not elaborate on how this concept might be constructed or measured.[3]

Several studies have previously explored associations between ageing and mortality or morbidity by examining the contributions of individual characteristics that might be possible components of IC, such as grip strength or usual walking pace.[4] For example, in a previous analysis of UK Biobank data, Ganna and Ingelsson[5] found that self-reported walking pace is strongly associated with both all-cause and cardiovascular disease (CVD)-related mortality. This is consistent with research suggesting that usual walking pace is associated with health outcomes that extend beyond CVD and all-cause mortality to all-respiratory diseases and chronic obstructive pulmonary disease (COPD) in both men and women.[5] Similarly, an inverse association between grip strength or walking pace and all-cause mortality has been reported for men in a relatively representative sample of the general UK population,[6,7] and this agrees with observations from the PURE study,[8] which reported that lower grip strength was, after adjustment, associated with a hazard ratio (HR) of 1.16 for all-cause mortality.

Nevertheless, the *combined* effect of these and other characteristics is poorly understood. To address this gap, two recent analyses of large and representative English and Chinese cohorts have proposed a structure for the IC construct. Both analyses suggested that the construct comprised five core domains—locomotor, cognitive, sensory and psychological capacities, and an underlying domain the authors termed vitality that might encompass the biological drivers of the ageing process.[9–11] These longitudinal analyses confirmed that IC is a powerful predictor of subsequent loss of both activities of daily living and instrumental activities of daily living, even after accounting for multimorbidities, age and sex.

Evidence of the association between IC and morbimortality is also accumulating. In this context, little research has investigated the interaction and joint associations of IC with a range of specific CVD outcomes. Moreover, most of the studies assessed mortality within a relative short period of time (1–5 years),[4,12–14] and only two previous studies conducted in older US[15] and Singaporean[16] populations demonstrated that lower IC values were associated with an increased risk of mortality over a 10- to 20-year follow-up. It also remains unclear whether the findings are consistent among subpopulations of different age, sex, and racial or ethnic groups. Moreover, in clinical settings, there is pragmatically a limited number of domains or domain-specific measures that can be used, depending on relevance and practicality.[12]

The WHO has suggested that the concept of IC should be considered a dynamic construct, evolving over time.[3] In the present prospective cohort study, we examined the association between IC and mortality, as well as a range of CVD morbidities in nearly half a million adults in the UK Biobank. This knowledge is required if global IC is to act as an early-warning system informing preventive efforts.

# Material and methods

## *Study design and participants*

UK Biobank (www.ukbiobank.co.uk) is a prospective population-based cohort study that included 502 640 participants (age range 37–76 years) from 22 assessment centres across England, Scotland and Wales, between 2007 and 2010.[17] Participants completed a touchscreen questionnaire and a nurse-led interview and had physical measurements taken, as described in detail elsewhere.[18] UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent for data collection, analysis and linkage, which was conducted in accordance with the principles of the Declaration of Helsinki. Among the 502 640 participants, we excluded 179 participants for loss to follow-up or withdrawal of consent from the study. Other exclusion criteria included missing data for exhaustion ($n$ = 14 142), sleep duration ($n$ = 888), hearing difficulty ($n$ = 20 480), slow walking pace ($n$ = 3797), weight loss ($n$ = 8905) and low grip strength ($n$ = 10 732), resulting in 443 130 participants included in the baseline analyses (*Table S1*).

## Procedures

An IC score was derived drawing on measures reflecting four of the five domains proposed by Beard et al.[2,10,11] (one for psychological capacity, two for sensory capacity, two for vitality and one for locomotor capacity). We were unable to include a measure for cognitive capacity as this was not included in the Biobank assessment. *Table 1* shows our definitions alongside those of WHO and published studies.[3,13,19,20] When possible, these adaptations were based on previously validated versions of the IC construct (*Table S2*).[8,9,21,22]

The *Psychological* domain included self-reported exhaustion ('Over the past two weeks, how often have you felt tired or had little energy?', response: more than half of the days, nearly every day = 1 point; not at all/several days = 0 points) and sleep duration ('About how many hours sleep do you get in every 24 hours?, please include naps', response: short <7 h/day or long >9 h/day = 1; healthy 7–9 h/day = 0 points). The *Sensory* domain included vision problems, which were measured with self-reported data considering eye/eyelid problems (non-cancer illness) and hearing impairment, which was measured with self-reported ('Do you have any difficulty with your hearing?', response: yes, I am completely deaf = 1 point; no = 0 points). The *Vitality* domain was operationalized via grip strength, which was assessed by mean handgrip strength (kilograms) through the use of a hydraulic hand dynamometer (Jamar J00105), and the mean of the right and left values was expressed in absolute units (kilograms), and by sex and body mass index (BMI) adjusted cut-offs (below cut-off = 1 point; above cut-off = 0 points) according to Fried et al.,[23] and weight loss self-reported ('Compared with one year ago, has your weight changed?', response: yes—lost weight = 1 point; no—weight the same, yes—gain weight = 0 points). *Locomotor* capacity was assessed from walking pace, which was self-reported with participants being asked, 'How would you describe your usual walking pace?' (response: slow pace = 1 point; steady average pace or brisk pace = 0 points). In this study, we used a similar approach to the screening tool of the Integrated Care for Older People (ICOPE) Handbook[3] derived by summing a dichotomized score for each of the four domains with 1 point being assigned if any measure in that domain experienced impairments and 0 points if the measure(s) has retained capacity. Similar approaches to IC scoring have been reported elsewhere.[16] A total IC deficit score was obtained by adding up the scores from the four domains, giving a possible maximum score of 7 indicating the worst IC, whereas 0 indicating the best. Responses 'more than four factors' were combined because of the low number of responses in category 'six factors' ($n$ = 471) or 'seven factors' ($n$ = 29), creating an IC deficit score; categorical variable was then derived to form 0, 1, 2, 3 or +4 factors. The objective of this categorization is to show the number of affected domains as an ordinal variable, rather than summarized in a continuous variable, with the idea that

**Table 1** Descriptive cross-sectional analysis of baseline variables

| | | Male ($n$ = 203 414) | | | Female ($n$ = 239 716) | | |
|---|---|---|---|---|---|---|---|
| | Total ($n$ = 443 130) | 37–56 years ($n$ = 76 899) | 56–65 years ($n$ = 76 131) | >65 years ($n$ = 50 384) | 37–56 years ($n$ = 95 950) | 56–65 years ($n$ = 92 199) | >65 years ($n$ = 51 567) |
| **IC factors, *n* (%)** | | | | | | | |
| Exhaustion | 53 968 (12.18) | 9672 (12.58) | 7411 (9.73) | 3990 (7.92) | 16 484 (17.18) | 11 309 (12.27) | 5102 (9.89) |
| Sleep duration | 116 986 (26.40) | 22 658 (29.46) | 20 299 (26.66) | 11 375 (22.58) | 23 054 (24.03) | 25 532 (27.69) | 14 068 (27.28) |
| Eye problems | 18 759 (4.23) | 1954 (2.54) | 3668 (4.82) | 3373 (6.69) | 1996 (2.08) | 4180 (4.53) | 3588 (6.96) |
| Hearing difficulty | 112 960 (25.49) | 16 085 (20.92) | 25 276 (33.20) | 20 802 (41.29) | 15 621 (16.28) | 21 252 (23.05) | 13 924 (27.00) |
| Slow walking pace | 67 954 (15.34) | 12 174 (15.83) | 11 266 (14.80) | 6780 (13.46) | 15 815 (16.48) | 14 464 (15.69) | 7455 (14.46) |
| Weight loss | 33 697 (7.60) | 3479 (4.52) | 6029 (7.92) | 5456 (10.83) | 5543 (5.78) | 7677 (8.33) | 5513 (10.69) |
| Low grip strength | 86 683 (19.56) | 7793 (10.13) | 12 523 (16.45) | 11 983 (23.78) | 13 040 (13.59) | 23 668 (25.67) | 17 676 (34.28) |
| **IC scoring, *n* (%)** | | | | | | | |
| 0 factors (ref, better IC) | 149 322 (33.70) | 29 540 (38.41) | 24 016 (31.55) | 13 405 (26.61) | 39 348 (41.01) | 29 287 (31.76) | 13 726 (26.62) |
| 1 factor | 160 719 (36.27) | 28 282 (36.78) | 28 728 (37.73) | 19 086 (37.88) | 32 865 (34.25) | 33 116 (35.92) | 18 642 (36.15) |
| 2 factors | 86 458 (19.51) | 13 427 (17.46) | 15 477 (20.33) | 11 423 (22.67) | 15 546 (16.20) | 18 749 (20.34) | 11 836 (22.95) |
| 3 factors | 32 983 (7.44) | 4258 (5.54) | 5555 (7.30) | 4577 (9.08) | 5809 (6.05) | 7699 (8.35) | 5085 (9.86) |
| +4 factors (deficit IC) | 13 648 (3.08) | 1392 (1.81) | 2355 (3.09) | 1893 (3.76) | 2382 (2.48) | 3348 (3.63) | 2278 (4.42) |

*Note*: Descriptive analyses of the data were presented as absolute and relative frequency (%). $\chi^2$ test for trend: $P < 0.001$ for all variables. Abbreviation: IC, intrinsic capacity.

this would facilitate identification and/or monitoring of people in the community with priority conditions associated with declines in IC. This terminology will ensure that higher scores reflect a greater number of deficits.

We calculated age from dates of birth and baseline assessment, categorized as 37–56, 56–65 and +65 years. Participants defined their own ethnicity within the following major categories: 'White', 'mixed', 'Asian or Asian British', 'Black or Black British', 'Chinese' or 'other ethnic group'. Socio-economic status was classified by the Townsend score in quartiles, based on preceding national census data (a higher quartile implied higher levels of socio-economic deprivation).[24] Alcohol intake was based on self-reported frequency of alcohol intake (never; special occasions only; one to three times per month; one to four times per week; or daily or almost daily). Dietary information was collected through the Oxford WebQ, a web-based 24-h recall questionnaire that considers mean consumption of fresh fruit (piece per day), dried fruit (piece per day) and cooked/salad vegetables (heaped tablespoons per day).[25] Smoking status was self-reported as never, former or current smoker. Physical activity was self-reported and classified as none or light activity with a frequency of once per week or less = no, and medium or heavy activity, or light activity more than once per week = yes.[26] Self-reported TV viewing time was assessed by asking the following question: 'In a typical day, how many hours do you spend watching TV? (Put 0 if you do not spend any time doing it.)' Self-reported daily recreational computer (CPU) use time was assessed for all participants by asking the following question: 'In a typical day, how many hours do you spend using the computer? (Do not include using a computer at work; put 0 if you do not spend any time doing it.)' Durations of $1 \leq 3$ h (reference category, no) and $>3$ h = yes were categorized based on previously published categories.[27] Height (metres) and weight (kilograms) were measured by staff at the UK Biobank study centre. BMI was then calculated from the weight and height measurements (kilograms per square metre).

## Outcomes

The outcomes in the present study were CVD mortality and incident disease grouped as CVD, with the exposure variable being the number of factors reported, which was summed and IC scoring categorized as 0, 1, 2, 3 or +4 factors. We used the link to national mortality records by the UK Biobank data analysts. Participant follow-up started at inclusion in the UK Biobank study (2006–2010 or 31 December 2010) and follow-up ended on 31 December 2021, or we censored death for all participants. The mean follow-up period was 10.6 years. We extracted the underlying (primary) cause of death, coded according to the International Classification of Diseases, Tenth Revision (ICD-10) from death certification data, classified as CVD (I05–I89). The incident disease outcomes were the CVD conditions reported by participants organized into a list of six long-term conditions (LTCs) based on previously published literature on multimorbidity established for a large epidemiological study in Scotland through systematic review, the Quality and Outcomes Framework, NHS Scotland and an expert panel, and subsequently amended for UK Biobank.[28,29] Additionally, a wide range of grouped cardiovascular disease (CVD) conditions were included, namely hypertension, stroke/transient ischemic attack (TIA), peripheral vascular disease, atrial fibrillation/flutter, coronary artery disease (CAD), and heart failure. The six LTCs were classified based on LTC count into no LTCs, 1 LTC, 2 LTCs, 3 LTCs, 4 LTCs, 5 LTCs and 6 LTCs, as previously described by Hanlon et al.[29] Responses '5–6 LTCs' were combined because of low number of responses in category 'six LTCs' ($n$ = 224), creating a six-category LTCs as 1 LTC, 2 LTCs, 3 LTCs, 4 LTCs and 5–6 LTCs. Among the 443 130 participants included at baseline, the present study excluded participants with baseline CVD ($n$ = 58 750), leaving 384 380 participants for the final analytic sample. Baseline CVD was ascertained by self-reported information and hospital records.

## Analysis plan

All analyses were planned before inspection of the data in keeping with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[30] Descriptive or unadjusted analyses included all available data for eligible participants. Categorical variables are presented as participant numbers and percentages. Means and standard deviations (SDs) are presented for continuous variables. First, baseline prevalence was summarized for IC factors and scoring (0 to +4 factors). Second, baseline characteristics (sex, age, ethnicity, socio-economic status [Townsend score by quartiles], frequency of alcohol intake, dietary intake [consumption of fresh/dried fruit and cooked/salad vegetables], smoking status, physical activity, time spent using TV/CPU and BMI [BMI category], by IC scoring) were compared using the $\chi^2$ test for categorical variables and analysis of variance test for continuous variables.

To evaluate the validity of the criteria used in our IC definition, we examined the impact of each individual variable and IC scoring (0 to +4 points) on morbidity (LTCs and CVD grouped) as well as mortality outcomes specifically related to CVD. This assessment was conducted using separate hazard ratios (HRs) and 95% confidence intervals (CIs), with the data stratified by sex (men and women). Models were developed a priori to investigate the impact of incremental adjustments, in line with a previous study.[31] Model 1 was unadjusted. Model 2 was adjusted for age, deprivation index, ethnicity, alcohol intake and dietary intake. Model 3 (fully adjusted) was adjusted as in Model 2 but also included lifestyle

factors (smoking status, physical activity levels, time spent using TV/CPU and BMI category). The incremental effect of an increasing number of IC factors was assessed by comparing the HRs for the presence of one, two, three or four indicators, using the zero factors as the reference group. To minimize the potential contribution of reverse causality to the findings, we did a landmark analysis excluding events occurring within 1 year after recruitment.

We also conducted sensitivity analyses. First, we repeated all analyses stratified by sex and age categories, to assess whether the morbidity and mortality risk differed across age ranges and between sexes (Models 1–3). Similarly, we used the individual IC factors rather than the score in the models to evaluate whether the estimated contribution was similar to that of the main analysis. Second, a weighted IC deficit score was constructed to account for variable magnitudes of the associations between different outcomes (stratified by age categories and sex). Third, to assess the predictive ability of individual IC factors and IC scoring, we calculated Harrell's C-index (which estimates the probability of concordance between observed and predicted responses), and we then compared the ability to predict different outcomes.[32] We checked the proportional hazard assumption by tests based on Schoenfeld's residuals. Lastly, subgroup analyses (also stratified by age categories and sex) were done along with tests for statistical interactions between predictors (adverse health outcomes) and IC scoring, to assess if the association of the IC approach was modified by other covariates. The proportional hazard assumption was checked using Schoenfeld's residuals. R 3.6.1 was used to perform the analyses (using the packages 'forestplot' and 'survival'). A $P$ value $< 0.05$ was considered statistically significant.

## Results

Among the 443 130 baseline participants (mean age 58.4 years), 149 322 (33.7%) had zero factors (within the six individual ICs studied), 160 719 (36.2%) had one factor, 86 458 (19.5%) had two factors, 32 983 (7.4%) had three factors and 13 648 (3%) had four or more IC factors. The majority of participants were female (54%) and under 65 years of age (76.9%). Eye problems, hearing difficulty, weight loss and low grip strength were found to increase with age, while exhaustion, sleep duration and slow walking pace were more prevalent among younger participants. Descriptive cross-sectional sample analysis of baseline variables for IC factors and IC scoring is shown in *Table 1*.

The unadjusted baseline characteristics for participants according to IC scoring are shown in *Table S1*. Participants meeting the criteria for +4 IC factors were more likely to be male and to a have low income (Quartile 4) compared with those in the zero factors group. Also, participants with unhealthy levels of salad vegetable intake or fresh/dried fruit intake were current smokers, those with high physical activity levels had higher levels of time spent TV/CPU and those higher BMI were more prevalent among adults meeting the criteria for +4 IC factors.

The baseline prevalence of IC deficit scores across the different levels of the six LTCs in the cross-sectional analysis is shown in *Figure S1*. The prevalence of each factor increased with increasing numbers of LTCs. LTCs were also more common in the IC scores: 11.8% of participants meeting the criteria for +4 IC factor deficit score were multimorbid compared with 37% of participants meeting the criteria for zero IC factor deficit score. For those with 5–6 LTCs, zero IC factors were prevalent in 17.4% of participants, whereas the proportion with at least zero LTCs was 2.1% in the zero factors group versus 15.6% in the 3 LTCs group. Results of all sensitivity analyses were largely consistent by full sample, sex and age categories (*Figure S2*).

Each CVD included in this study, such as hypertension, stroke/TIA stroke, peripheral vascular disease, atrial fibrillation/flutter, CAD and heart failure, was associated with a significantly greater hazard of three or four IC factors compared with no or one IC factor in both men and women (*Tables S3* and *S4*). Overall, the incidence CVD disease (grouped as 6 LTCs) analyses taking detailed account of the aforementioned confounders (Model 3) showed an estimated HR (mean [95% CI]) for each one point higher in the IC deficit score of 1.11 [1.08–1.14], 1.20 [1.16–1.24], 1.29 [1.23–1.36] and 1.56 [1.45–1.59], respectively, in men (C-index = 0.68), and 1.17 [1.13–1.20], 1.30 [1.26–1.36], 1.52 [1.45–1.59] and 1.78 [1.67–1.89] in women (C-index = 0.70) (*Figure 1D*). Results of all sensitivity analyses were largely consistent by full sample, sex and age categories (*Figure 1A–C* and *Table S5*) among ($n$ = 384 380) participants for the final analytic subsample, independent of major confounding factors ($P < 0.001$).

During a median follow-up period of 10.6 years, per participant, there were 27 251 deaths censored (31 December 2022). Of these, 5265 deaths (19.3%) were primarily attributed to CVD. Analyses of the CVD mortality associated with IC scoring, adjusted for age, deprivation index, ethnicity, alcohol use, dietary intake, smoking status, physical activity levels, time spent using TV/CPU and BMI status, are shown in *Figure 2A–D*. Results indicated that the higher IC deficit score (+4 points) was associated with a significant increase in CVD mortality (mean HR [95% CI]: 2.10 [1.81–2.43] and 2.29 [1.85–2.84] in men [C-index = 0.75] and women [C-index = 0.78], respectively; *Figure 2D*) after adjustment for age, deprivation index, ethnicity and several other health, lifestyle and dietary factors. Much stronger effects were estimated for CVD mortality, which were 2.85 [1.87–4.33] and 2.30 [1.22–4.35] in men (37–56 years) [C-index = 0.65] and women (37–56 years) [C-index = 0.65], respectively (*Figure 2A*). The associations were similar in all analyses stratified by sex and age categories, without adjustment

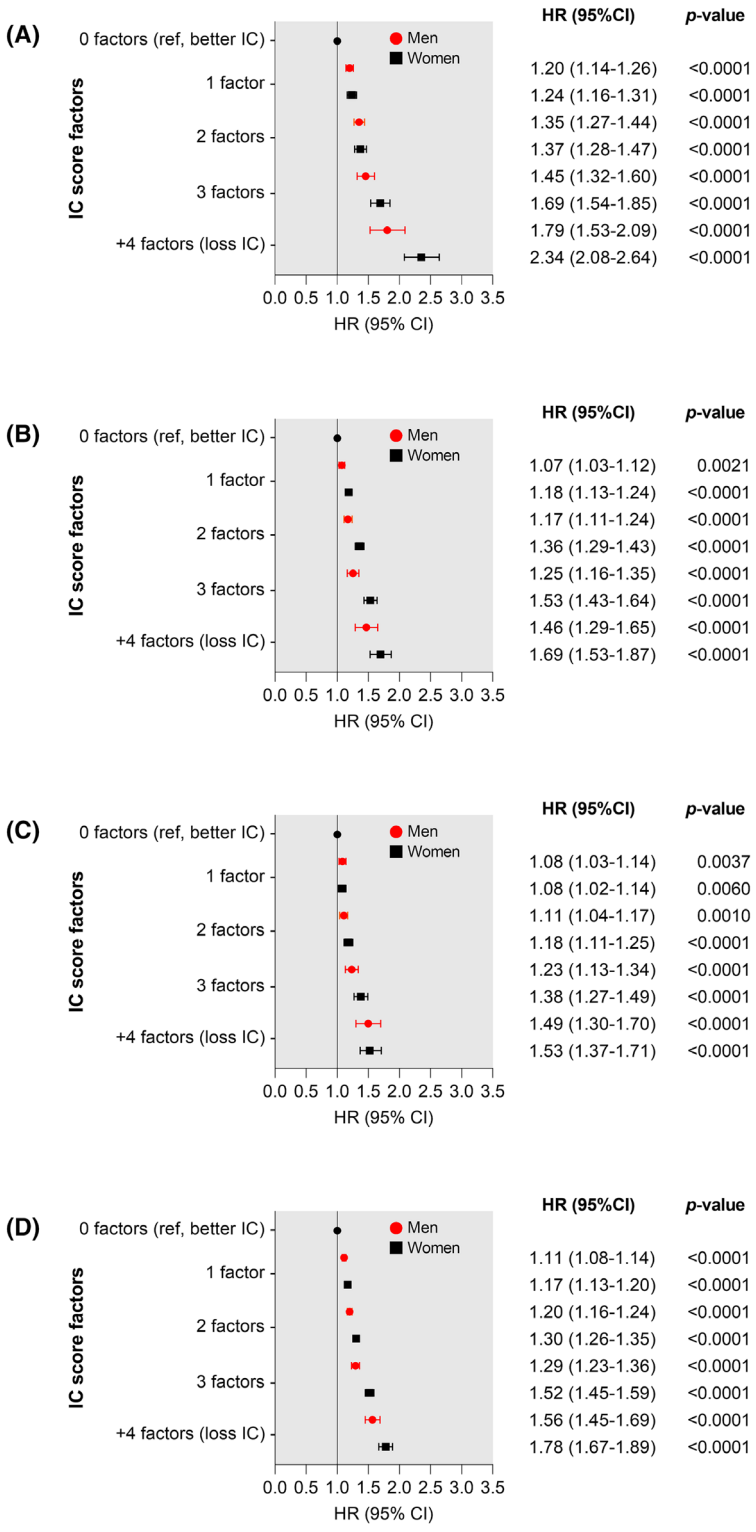


**Figure 1** Association between incident cardiovascular disease (CVD) and intrinsic capacity (IC) deficit scores by sex, age categories (37–55, 55–65 and +65 years) and full sample. Data are presented as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). (A) 37–55 years, (B) 55–65 years, (C) +65 years and (D) full sample. All analyses were adjusted for age, deprivation index, ethnicity, alcohol use, dietary intake, smoking status, physical activity, time spent using TV/CPU and body mass index category. The incremental effect of an increasing number of IC factors was assessed by comparing the HRs for the presence of 1, 2, 3 or +4 factors, using the zero factors group as the reference group. The global incidence CVD was derived from cause-specific disease as hypertension, stroke/transient ischaemic attack stroke, peripheral vascular disease, atrial fibrillation/flutter, coronary artery disease and heart failure.


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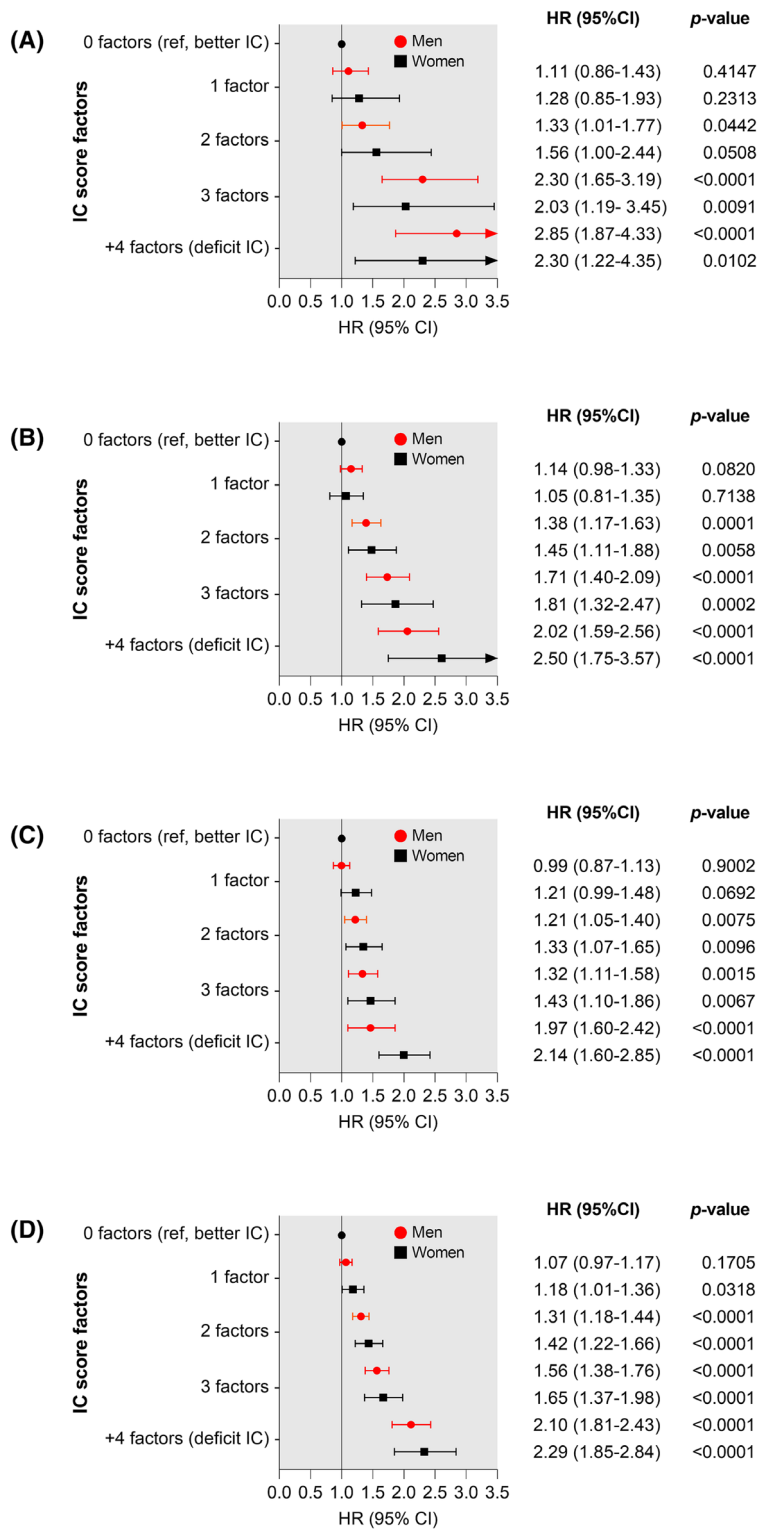


**Figure 2** Hazard ratios (HRs) for cardiovascular disease (CVD) mortality and intrinsic capacity (IC) deficit scores by sex, age categories (37–55, 55–65 and +65 years) and full sample. Data are presented as HRs and corresponding 95% confidence intervals (CIs). (A) 37–55 years, (B) 55–65 years, (C) +65 years and (D) full sample. All analyses were adjusted for age, deprivation index, ethnicity, alcohol use, dietary intake, smoking status, physical activity, time spent using TV/CPU and body mass index category. The incremental effect of an increasing number of IC factors was assessed by comparing the HRs for the presence of 1, 2, 3 or +4 factors, using the zero factors group as the reference group. The global incidence CVD was derived from cause-specific disease as hypertension, stroke/transient ischaemic attack stroke, peripheral vascular disease, atrial fibrillation/flutter, coronary artery disease and heart failure.


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in Model 1, and after further adjustment, the magnitude of associations was slightly attenuated in Models 2 and 3 (*Table S6*). The C-indices for the most adjusted models containing IC scoring demonstrated moderate-to-strong discrimination (Model 3, ranging from 0.66 to 0.78), with good calibration (*Table S6*).

## Discussion

In this prospective cohort analysis in middle- and older-aged adults, we observed that worse IC was strongly associated with increased risk of subsequent incidence and mortality from CVD. The observed associations were consistent between sexes and remained robust after adjustment for age, deprivation index, ethnicity and several other health, lifestyle and dietary factors.

The finding of a direct association between poorer IC and adverse health outcomes is consistent with previous studies.[4,12–14,33] The IC deficit score showed a graded relationship with CVD mortality risk and survival outcomes, which suggests that accumulation of impairments of different domains in IC is linked with increasingly higher risk of mortality. Our findings are in line with those reported in a study by Prince et al.[34] who found that having experienced one or more declines in IC domain at baseline was associated with a 66% increased risk of mortality after 3–5 years of follow-up in a population cohort. IC declines have also been associated with mortality by Stolz et al.[15] who showed that a 1-point lower IC value was associated with a 5% increase in mortality among community-dwelling older people without activities of daily living disability at baseline. Similarly, a longitudinal cohort study of older people by Yu et al.[16] showed that compared with those in the lowest (best) quartile of IC, those in the highest (worst) quartile had a 1.48-fold (95% CI [1.21–1.82]) higher risk of mortality, after adjustment for sociodemographic variables.

Our analysis included much younger age groups than most previous research.[1,11,35] Not only were the associations we observed in younger adults consistent with our findings in older age groups but also the discrimination ability of IC scoring to predict CVD mortality and multimorbidity was highest in the youngest category of participants. While these findings need to be treated with caution, they suggest that assessment of IC may have value at earlier phases of the life course than previously proposed. Additionally, when comparing the C-indices, the predictive ability of IC scoring differed negligibly in the different adjusted models. This would suggest that when an IC approach is implemented in clinical practice, any of the terms to express IC scoring would be valid; however, the use of summed and IC scoring categorized as zero, one, two, three or at least four factors may be the simplest way forward.

The largest previous study involving younger adults included 7106 participants aged 50 years or older from the cross-sectional Mexican Health and Aging Study in Mexico.[36] Analysing the number of affected domains, the majority of the population aged 50 years or older had at least one domain affected (88%), reaching over 90% in the oldest group. If confirmed by other research, this might help earlier identification of individuals at risk of poor health trajectories and create innovative opportunities for clinical and public health intervention. The association with adverse health outcomes was also stronger for those with impairments in multiple IC factors compared with those with a higher number of diseases or cause-specific disease groups. This suggests that a function-centred approach (driven by positive health attributes) such as IC might better predict LTCs across the life-course than disease-based approaches such as multimortality.

### *Strengths and limitations of this study*

The present study has important strengths, including the large sample size (and number of deaths), which allowed stratification by sex and age categories with sufficient statistical power. The extensively phenotyped population also allowed a comprehensive investigation into possible confounding influences on the association between the IC approach and adverse CVD outcomes. In addition, we constructed an overall IC deficit score to comprehensively evaluate the complex relations of IC factors and adverse health outcomes. We also conducted a series of sensitivity analyses to test the robustness of the findings and evaluated individual and IC factors.

Nevertheless, we also acknowledge several limitations. First, information on IC factors was mainly self-reported and was only measured once, making measurement errors inevitable. Also, this is a secondary analysis from a study not designed to assess IC, selecting those questions that more closely reflect the nature of IC and its domains. Many commonly used measures of IC and the entire subdomain of cognitive capacity were not included in the dataset and could not be considered in our analysis. Moreover, key measures such as gait speed relied on self-report. Future studies with repeated objectively assessed measurements are needed. Second, an IC deficit score derived from a sum of the number of healthy IC factors assumes that all IC factors had equal effects on health outcomes, which might not be true. However, there is no consensus yet on how to measure IC. A number of varying mathematical algorithms have been suggested, such as an integrated approach using bi-factor modelling to estimate factor scores[10,11,16] and a summation of the individual domain scores that were based on the distribution of the study sample (e.g., *Z*-scores) or pre-determined threshold values that reflect the transition from one state to


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another.[4,13–15] In this study, we used the summation approach to operationalize IC. Our approach is nonetheless relatively easy to adopt and may readily be administered in community settings, and comparable approach of the IC deficit score has been reported elsewhere.[16] However, the comparison of these approaches has been limited, particularly when it comes to utilizing IC for predicting morbidity or mortality for CVD. The disparity of different methods used for computation of a composite IC deficit score also reduces the ability to make direct comparisons between studies, and we highlight the need for more epidemiological research to validate these findings in different populations. Third, the follow-up duration was relatively short (10.6 years), and those who died during the study period might have had serious disease at baseline. Fourth, owing to the nature of post hoc subgroup analyses, the sample size in each subgroup was not calculated before data collection, and the results should be interpreted cautiously. Fifth, the UK Biobank had a low response rate, and participants are not representative of the overall UK population (i.e., participants in our study were majority White race, educated and from less socially disadvantaged areas). Finally, although we controlled for key personal characteristics, and several other health, lifestyle and dietary factors, residual confounding was still possible and causal inference cannot be made because of the nature of observational studies.

## Conclusions

This analysis suggests that impaired levels of the new WHO construct of IC are significantly associated with higher risks of mortality and a wide range of adverse CVD outcomes. These findings could have important public health implications, as the multidimensional IC construct is easily measured, inexpensive and highly reproducible in clinical practice and appears to include information not considered by measures such as the extent of multimorbidity. Assessment of IC holds great promise to transform geriatric care worldwide including in regions without well-established geriatric medicine. Future research, with appropriately designed randomized controlled trials, is warranted to determine whether the current observations reflect a causal association and, if so, these findings could have import implications for WHO recommendations.

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## Conflict of interest statement

We declare no competing interests.

## Data availability statement

This research has been conducted using the UK Biobank Resource under Application Number 73008.

## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

## References

1. Pagès A, Costa N, González-Bautista E, Mounié M, Juillard-Condat B, Molinier L, et al. MAPT/DSA Group Screening for deficits on intrinsic capacity domains and associated healthcare costs. *Arch Gerontol Geriatr* 2022;**100**:104654.
2. Beard JR, Officer A, de Carvalho IA, Sadana R, Pot AM, Michel JP, et al. The World report on ageing and health: a policy framework for healthy ageing. *Lancet* 2016;**387**: 2145–2154.
3. *Integrated Care for Older People (ICOPE): Guidance for Person-Centred Assessment and Pathways in Primary Care*. Geneva: World Health Organization; 2019. (WHO/FWC/ALC/19.1). https://www.who.int/publications/i/item/WHO-FWC-ALC-19.1
4. Zeng X, Shen S, Xu L, Wang Y, Yang Y, Chen L, et al. The impact of intrinsic capacity on adverse outcomes in older hospitalized patients: a one-year follow-up study. *Gerontology* 2021;**67**:267–275.
5. Ganna A, Ingelsson E. 5 year mortality predictors in 498,103 UK Biobank participants: a prospective population-based study. *Lancet* 2015;**386**:533–540.
6. Celis-Morales CA, Gray S, Petermann F, Iliodromiti S, Welsh P, Lyall DM, et al. Walking pace is associated with lower risk of all-cause and cause-specific mortality. *Med Sci Sports Exerc* 2019;**51**:472–480.
7. Celis-Morales CA, Welsh P, Lyall DM, Steell L, Petermann F, Anderson J, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ* 2018;**361**:k1651.
8. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr, Orlandini A, et al. Prospective Urban Rural Epidemiology (PURE) Study investigators. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet* 2015;**386**:266–273.
9. Cesari M, Araujo de Carvalho I, Amuthavalli Thiyagarajan J, Cooper C, Martin FC, Reginster JY, et al. Evidence for the domains supporting the construct of intrinsic capacity. *J Gerontol A Biol Sci Med Sci* 2018;**73**:1653–1660.

10. Beard JR, Jotheeswaran AT, Cesari M, Araujo de Carvalho I. The structure and predictive value of intrinsic capacity in a longitudinal study of ageing. *BMJ Open* 2019;**9**:e026119.
11. Beard JR, Si Y, Liu Z, Chenoweth L, Hanewald K. Intrinsic capacity: validation of a new WHO concept for healthy aging in a longitudinal Chinese study. *J Gerontol A Biol Sci Med Sci* 2022;**77**:94–100.
12. Cheong CY, Yap P, Nyunt MSZ, Qi G, Gwee X, Wee SL, et al. Functional health index of intrinsic capacity: multi-domain operationalisation and validation in the Singapore Longitudinal Ageing Study (SLAS2). *Age Ageing* 2022;**51**:afac011.
13. Charles A, Buckinx F, Locquet M, Reginster JY, Petermans J, Gruslin B, et al. Prediction of adverse outcomes in nursing home residents according to intrinsic capacity proposed by the World Health Organization. *J Gerontol A Biol Sci Med Sci* 2020; **75**:1594–1599.
14. Locquet M, Sanchez-Rodriguez D, Bruyère O, Geerinck A, Lengelé L, Reginster JY, et al. Intrinsic capacity defined using four domains and mortality risk: a 5-year follow-up of the SarcoPhAge cohort. *J Nutr Health Aging* 2022;**26**:23–29.
15. Stolz E, Mayerl H, Freidl W, Roller-Wirnsberger R, Gill TM. Intrinsic capacity predicts negative health outcomes in older adults. *J Gerontol A Biol Sci Med Sci* 2022; **77**:101–105.
16. Yu R, Lai ETC, Leung G, Ho SC, Woo J. Intrinsic capacity and 10-year mortality: findings from a cohort of older people. *Exp Gerontol* 2022;**167**:111926.
17. Collins R. What makes UK Biobank special? *Lancet* 2012;**379**:1173–1174.
18. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;**12**: e1001779.
19. Gutiérrez-Robledo LM, García-Chanes RE, González-Bautista E, Rosas-Carrasco O. Validation of two intrinsic capacity scales and its relationship with frailty and other outcomes in Mexican community-dwelling older adults. *J Nutr Health Aging* 2021;**25**: 33–40.
20. Ramírez-Vélez R, Correa-Bautista JE, García-Hermoso A, Cano CA, Izquierdo M. Reference values for handgrip strength and their association with intrinsic capacity domains among older adults. *J Cachexia Sarcopenia Muscle* 2019;**10**:278–286.
21. Gonzalez-Bautista E, Andrieu S, Gutiérrez-Robledo LM, García-Chanes RE, de Souto BP. In the quest of a standard index of intrinsic capacity. A critical literature review. *J Nutr Health Aging* 2020;**24**:959–965.
22. George PP, Lun P, Ong SP, Lim WS. A rapid review of the measurement of intrinsic capacity in older adults. *J Nutr Health Aging* 2021;**25**:774–782.
23. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146–M156.
24. Townsend P. Deprivation. *J Soc Policy* 1987;**16**:125–146.
25. Liu B, Young H, Crowe FL, Benson VS, Spencer EA, Key TJ, et al. Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. *Public Health Nutr* 2011;**14**:1998–2005.
26. Celis-Morales CA, Lyall DM, Anderson J, Iliodromiti S, Fan Y, Ntuk UE, et al. The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. *Eur Heart J* 2017;**38**:116–122.
27. Hunter RF, Murray JM, Coleman HG. The association between recreational screen time and cancer risk: findings from the UK Biobank, a large prospective cohort study. *Int J Behav Nutr Phys Act* 2020;**17**:97.
28. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Research Support, Non-U.S. Gov't. *Lancet* 2012;**380**:37–43.
29. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health* 2018;**3**:e323–e332.
30. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;**61**:344–349.
31. Zhang YB, Chen C, Pan XF, Guo J, Li Y, Franco OH, et al. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. *BMJ* 2021;**373**:n604.
32. Wolbers M, Blanche P, Koller MT, Witteman JC, Gerds TA. Concordance for prognostic models with competing risks. *Biostatistics* 2014;**15**:526–539.
33. Ma L, Chhetri JK, Zhang Y, Liu P, Chen Y, Li Y, et al. Integrated Care for Older People screening tool for measuring intrinsic capacity: preliminary findings from ICOPE pilot in China. *Front Med (Lausanne)* 2020; **7**:576079.
34. Prince MJ, Acosta D, Guerra M, Huang Y, Jacob KS, Jimenez-Velazquez IZ, et al. Intrinsic capacity and its associations with incident dependence and mortality in 10/66 Dementia Research Group studies in Latin America, India, and China: a population-based cohort study. *PLoS Med* 2021;**18**:e1003097.
35. Meng LC, Huang ST, Peng LN, Chen LK, Hsiao FY. Biological features of the outcome-based intrinsic capacity composite scores from a population-based cohort study: pas de deux of biological and functional aging. *Front Med (Lausanne)* 2022; **9**:851882.
36. Gutiérrez-Robledo LM, García-Chanes RE, Pérez-Zepeda MU. Screening intrinsic capacity and its epidemiological characterization: a secondary analysis of the Mexican Health and Aging Study. *Rev Panam Salud Publica* 2021;**45**:e121.
37. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2021. *J Cachexia Sarcopenia Muscle* 2021;**12**:2259–2261.