Association of intrinsic capacity with functional decline and mortality in older adults: a systematic review and meta-analysis of longitudinal studies

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Summary

Background Together with environmental factors, intrinsic capacity (the composite of all the physical and mental capacities of an individual) has been proposed as a marker of healthy ageing. However, whether intrinsic capacity predicts major clinical outcomes is unclear. We aimed to explore the association of intrinsic capacity with functional decline and mortality in older adults.

Methods In this systematic review and meta-analysis, we conducted a systematic search in MEDLINE (via PubMed), Scopus, and Web of Science from database inception to Feb 14, 2024, of observational longitudinal studies conducted in older adults (age ≥60 years) assessing the association of intrinsic capacity with impairment in basic activities of daily living (BADL) or instrumental activities of daily living (IADL) or risk of mortality. Estimates were extracted by two reviewers (JLS-S and W-HL) and were pooled using three-level meta-analytic models. The quality of each study was independently assessed by two authors (JLS-S and PLV) using the Newcastle–Ottawa Scale for longitudinal studies. Heterogeneity was evaluated using the I^2 indicator at two levels: within-study (level 2) and between-study (level 3) variation. For associations between intrinsic capacity and IADL and BADL, we transformed data (standardised β coefficients and odds ratios [ORs]) into Pearson product moment correlation coefficients (r) using Pearson and Digby formulas to allow comparability across studies. For associations between intrinsic capacity and risk of mortality, hazard ratios (HRs) with 95% CIs were extracted from survival analyses. This study is registered with PROSPERO, CRD42023460482.

Findings We included 37 studies (206 693 participants; average age range 65·3–85·9 years) in the systematic review, of which 31 were included in the meta-analysis on the association between intrinsic capacity and outcomes; three studies (2935 participants) were included in the meta-analysis on the association between intrinsic capacity trajectories and longitudinal changes in BADL or IADL. Intrinsic capacity was inversely associated with longitudinal impairments in BADL (Pearson's r –0·12 [95% CI –0·19 to –0·04]) and IADL (–0·24 [–0·35 to –0·13]), as well as with mortality risk (hazard ratio 0·57 [95% CI 0·51 to 0·63]). An association was also found between intrinsic capacity trajectories and impairment in IADL (but not in BADL), with maintained or improved intrinsic capacity over time associated with a lower impairment in IADL (odds ratio 0·37 [95% CI 0·19 to 0·71]). There was no evidence of publication bias (Egger's test p>0·05) and there was low between-study heterogeneity (I^2=18·4%), though within-study (I^2=63·2%) heterogeneity was substantial.

Interpretation Intrinsic capacity is inversely associated with functional decline and mortality risk in older adults. These findings could support the use of intrinsic capacity as a marker of healthy ageing, although further research is needed to refine the structure and operationalisation of this construct across settings and populations.

Funding None.

Introduction

The ageing of the global population has encouraged research on healthy ageing, which in traditional view has been linked to the absence of major non-communicable conditions (eg, cardiopulmonary diseases or cancer) in older age. However, in 2015, WHO shifted the paradigm of healthy ageing to the maintenance of an individual's functional ability.[1] Within this framework, intrinsic capacity (the composite of all physical and mental capacities of an individual, commonly assessed across five domains: locomotion, cognitive, psychological, vitality, and sensory)[2–5] interacts with the environment to determine functional ability.[6]

The concept of intrinsic capacity has gained attention in the last decade.[7] The clinical and practical relevance of this indicator still heavily rely on its ability to predict major adverse outcomes in older adults, including not only risk of mortality but also functional decline,

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Research in context

Evidence before this study

Together with environmental factors, intrinsic capacity (the composite of all the physical and mental capacities of an individual) influences healthy ageing. However, whether intrinsic capacity predicts major clinical outcomes (eg, functional decline or mortality) remains unclear. We performed a systematic search on this topic in MEDLINE (via PubMed), Scopus, and Web of Science from database inception to Feb 14, 2024, combining the term "intrinsic capacity" with terms related to the outcomes of interest (eg, "mortality", "functional decline", "disability", "activities of daily living"). Articles published in English or Spanish were included. Despite a growing number of studies investigating the longitudinal association between intrinsic capacity and adverse outcomes, evidence remains unclear and fragmented, hindering the widespread adoption of this indicator in real-world scenarios. Moreover, no meta-analytic evidence exists on the topic. We therefore performed a systematic review with subsequent meta-analysis to explore the association of intrinsic capacity with functional decline and risk of mortality in older adults.

Added value of this study

This study is the first to incorporate a quantitative synthesis of evidence on the predictive ability of intrinsic capacity. Our study partly overcomes issues related to heterogeneity across studies and settings in the operationalisation of intrinsic capacity, allowing us to explore the strength of the associations.

Implications of all the available evidence

Although future longitudinal and interventional studies are needed to confirm these findings, and further efforts must be made to standardise the operationalisation of intrinsic capacity, the assessment of this indicator could be useful for risk stratification in older adults. Prioritising the maintenance of intrinsic capacity should be a key focus in the field of healthy ageing.

understood as the inability to perform basic activities of daily living (BADL; ie, ambulating, feeding, dressing, personal hygiene, continence, and toileting) or instrumental activities of daily living (IADL; ie, transportation and shopping, managing finances, shopping and meal preparation, house cleaning and home maintenance, managing communication with others, and managing medication).[8] Despite a growing number of studies investigating the association between intrinsic capacity and adverse outcomes, evidence remains unclear and fragmented, hindering the widespread adoption of this indicator in real-word scenarios.[9]

The purpose of this systematic review and meta-analysis was to synthesise the available evidence on the association of intrinsic capacity with functional decline in older adults, as well as with risk of mortality.

In addition, we explored how intrinsic capacity evolution (trajectories) might determine the outcomes.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, two authors (JLS-S and PLV) systematically searched MEDLINE (via PubMed), Web of Science, and Scopus from inception to Feb 14, 2024 (full search strategy in appendix 3 pp 1–3), combining the search term "intrinsic capacity" with terms related to the outcomes of interest (eg, "mortality", "functional decline", "disability", "activities of daily living"), and screened the titles and abstracts of the potentially eligible studies for suitability. If a study fulfilled the eligibility criteria, the full text was assessed, with disagreements solved by a third reviewer (AL). The reference lists of the included studies were also screened for additional potentially eligible studies. Records were organised and managed with Mendeley (version 1.19.8) and Rayyan.[10]

See Online for appendix 3

We included studies that met the following criteria: published in a peer-reviewed journal; written in English or Spanish; used a longitudinal (prospective or retrospective) observational design; included participants aged 60 years or older; and reported associations between intrinsic capacity (or at least two of its operational domains) and performance in BADL, IADL or mortality risk. In accordance with the WHO definition of older age,[11] the age criterion was amended slightly from the criterion reported in the original study protocol (ie, 65 years or older).

The review protocol was preregistered in PROSPERO, CRD42023460482, and we report the study according to the PRISMA statement.[12]

Data analysis

The following data were independently extracted by two reviewers (JLS-S and W-HL) from each study: year of publication, first author, sample size, population characteristics, study design, intrinsic capacity score construct (if applicable) and assessment tools, follow-up duration, method of mortality ascertainment, and definition of functional ability or disability. All these data were tabulated in a Microsoft Excel spreadsheet designed ad hoc, with the template approved after discussion between two researchers (JLS-S and W-HL).

The quality of each study was independently assessed by two authors (JLS-S and PLV) using the Newcastle–Ottawa Scale for longitudinal studies (appendix 3 pp 4–5), which has a maximum score of 9 points. Studies were classified as having a high (≥5 points) or low (<5 points) quality.[13]

Given the variability in exposure and outcome definitions among studies, we transformed data (standardised β coefficients and odds ratios [ORs]) into

Pearson product moment correlation coefficients (*r*) using Pearson and Digby formulas[14,15] to allow comparability across studies (appendix 3 p 6). According to the McGrath and Meyer classification, associations were categorised as weak ($r \leq 0 \cdot 10$), moderate ($0 \cdot 10 < r < 0 \cdot 37$), or large ($r \geq 0 \cdot 37$).[16] For associations between intrinsic capacity and risk of mortality, hazard ratios (HRs) with 95% CIs were extracted from survival analyses.

Due to the hierarchical data structure (with some studies providing separate effect estimates for each intrinsic capacity domain), and in order to identify the effect size within studies, we applied three-level random-effects meta-analysis models[17] (appendix 3 p 13) as well as correlated and hierarchical effects models assuming dependent effect size estimates.[18] The levels correspond to: the individual participant aggregated effect size, resulting from pooling individual domain-specific effect sizes; the individual study (cluster) effect sizes; and the aggregated cluster effect (pooled estimate). To address the dependence of effect size assessments, we used the sandwich (robust covariance matrix) estimator and defined a high correlation ($r=0 \cdot 70$) based on the National Institute for Health and Care Excellence guidelines.[18] The correlated and hierarchical effects model was primarily selected for reporting and interpretation of results, except when the three-level model showed a similar pooled estimate with narrower 95% CI, which indicates greater precision. Model fit analyses are detailed in appendix 3 (p 8). To explore differential associations by sex and the time window for intrinsic capacity prediction, we conducted multiple meta-regression models to investigate the potential moderating effect of the proportion of female participants included in the studies or the length of follow-up (months). Publication bias was assessed by visualisation of funnel plot asymmetry and quantitatively using Egger's regression test. Heterogeneity was evaluated using the I^2 indicator at two levels: within-study (level 2) and between-study (level 3) variation. Finally, to facilitate clinical interpretation, we conducted additional analyses that only included studies reporting risk estimates based on categorical exposures (ie, low *vs* high intrinsic capacity). Following Cochrane recommendations,[19] we expressed the risk estimates as risk differences across a range ($0 \cdot 10$, $0 \cdot 45$, and $0 \cdot 60$) of assumed comparator risks for BADLs and IADLs, and as assumption of median survival time (10 years) for mortality. The absolute risk differences were then expressed as number of persons (per 1000) who could avoid the relevant condition if having a high intrinsic capacity. All analyses were conducted using R (version 4.0.3).

Role of the funding source

There was no funding source for this study.

Results

37 studies were included in the systematic review (figure 1), of which 31 were suitable for meta-analysis.

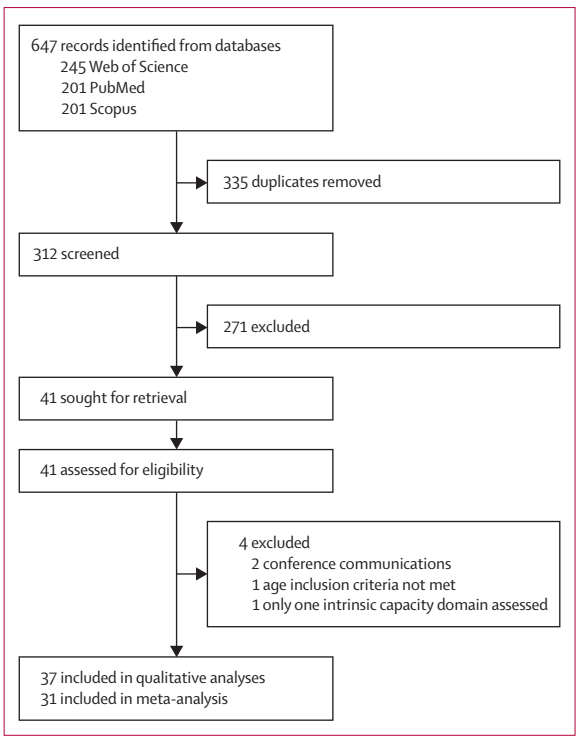

Figure 1: **PRISMA flow diagram of the study selection**

Articles that were not included after full-text reading (and the reasons for exclusion) are summarised in appendix 3 (p 7).

The 37 included studies comprised a total of 206 693 participants (132 490 [64%] female, weighted mean age 74·2 years [range 65·3–85·9]; table 1). Individual study sample sizes ranged from 100 to 117 105 participants, with 34 (92%) studies including a single cohort and three (8%) including multi-country cohorts. The majority of studies (24 [65%]) were conducted in the general older adult population, and seven studies (19%) focused solely on older adults living in the community, four studies (11%) focused on older adults in nursing homes or senior communities, and two studies (5%) were done in older adults in a hospital setting. All included studies were deemed to be high quality according to the Newcastle–Ottawa Scale for longitudinal studies (appendix 3 pp 9–10).

Intrinsic capacity was operationalised as the sum of impaired domains (ie, a discrete variable) in 17 (46%) studies or as a composite score (ie, continuous variable) in 16 (43%) studies. All studies assessed intrinsic capacity through at least four operational domains (34 [92%] included five domains and three [8%] included four domains). There was large variability in the tools used to assess the different intrinsic capacity domains. Out of the 60 instruments used to assess locomotion in the included studies, the most commonly used instruments were the gait speed test (present in 15 [25%] studies), five-times sit-to-stand

	Country	Population	n	Age, years	Sex, female	Follow-up, months	Exposure	Outcome	Outcome tool	Outcome definition
Beard et al, 2019[20]	UK	Older adults from the general population	2352	70·5 (7·9)	55%	24	Intrinsic capacity composite score	BADL disability, IADL disability	6-item BADL, 7-item IADL	Score evolution
Beard et al, 2022[21]	China	Older adults from the general population	2915	>60	NR	24	Intrinsic capacity composite score	BADL disability, IADL disability	6-item BADL, 5-item IADL	Score evolution
Campbell et al, 2023[22]	UK	Older adults from the general population	2348	70·8 (7·9)	55%	96	Intrinsic capacity composite score	BADL disability, IADL disability, mortality	6-item BADL, 7-item IADL, national mortality records	Score evolution
Charles et al, 2020[23]	Belgium	Nursing home residents	604	82·9 (9·1)	73%	36	Low *vs* high intrinsic capacity*	Mortality, BADL change	Medical charts, Katz Index	Increase of ≥1 point in the Katz Index
Chen et al, 2022[24]	Taiwan	Nursing home residents	9448	77·1 (9·6)	60%	36	Intrinsic capacity trajectories	BADL disability	NR	<30 out of 100 points
Cheong et al, 2022[25]	Singapore	Older adults from the general population	1906	66·6 (7·6)	63%	69·6	Intrinsic capacity composite score	Mortality	National death registry	NA
González-Bautista et al, 2021[26]	France	Community-dwelling older adults	759	75·2 (4·3)	64%	60	Low *vs* high intrinsic capacity*	BADL change, IADL change	Katz BADL Index, Lawton IADL Index	Increase of ≥1 difficulties
González-Bautista et al, 2023[27]	Peru, Mexico, China, India, Cuba, Dominican Republic, Puerto Rico (USA), Venezuela	Older adults from the general population	14 923	74·5 (7·1)	63%	50·4	Low *vs* high intrinsic capacity	Mortality, disability	Interview, WHODAS 2.0	NR
Jia et al, 2023[28]	China	Community-dwelling older adults	808	67·8 (5·1)	60%	36	Intrinsic capacity trajectories	BADL disability, IADL disability	Katz BADL Index, Lawton IADL Index	Having difficulties in ≥1 item
Koivunen et al, 2023[29]	Netherlands	Older adults from the general population	1319	70·3 (7·8)	50%	72	Intrinsic capacity composite score	Mortality, BADL change	Death registries of the relevant municipalities, 6-item BADL	Score evolution (range 0–30)
Lee et al, 2023[30]	Taiwan	Older adults from the general population	1839	63·9 (9·3)	53%	120	Intrinsic capacity composite score	Mortality	Telephone calls every 3 months	NA
Lee et al, 2024[31]	Taiwan	Older adults from the general population	1009	61·0 (7·4)	52%	78	Intrinsic capacity composite score	Disability	Functional Autonomy Measurement System	Having difficulties in ≥1 item
Liu et al, 2021[32]	China	Older adults living in a senior community	227	83·8 (4·4)	59%	24	Low *vs* high intrinsic capacity*	BADL disability	Katz Index	Increase of ≥1 difficulties
Locquet et al, 2022[33]	Belgium	Older adults from the general population	481	73·4 (6·1)	60%	60	Intrinsic capacity composite score	Mortality	Annual interview or telephone calls	NA
Lu et al, 2023[34]	China	Community-dwelling older adults	220	84·0 (4·4)	58%	36	Intrinsic capacity composite score	Mortality	Face-to-face or telephone interviews and medical records	NA
Lu et al, 2021[35]	China	Community-dwelling older adults	2081	79·6 (8·0)	56%	36	Intrinsic capacity composite score	IADL disability	Lawton Index (9 items)	Score evolution (range 0–18)
Meng et al, 2022[36]	Taiwan	Older adults from the general population	839	65·3 (9·4)	54%	48	Low *vs* high intrinsic capacity	Mortality	National death registry	NA
Nagae et al, 2023[37]	Japan	Older adults in hospital	296	84·7 (5·4)	57%	0·046	Intrinsic capacity composite score	In-hospital mortality	Medical charts	NA
Prince et al, 2021[38]	Peru, Mexico, China, India, Cuba, Dominican Republic, Puerto Rico (USA), Venezuela	Older adults from the general population	12 939	74·2	62%	NA	Low *vs* high intrinsic capacity	Mortality	WHODAS 2.0 (disability)	NA
Ramírez-Vélez et al, 2023[39]	UK	Older adults from the general population	117 105	68·4 (1·9)	0	120·72	Low *vs* high intrinsic capacity	Cardiovascular mortality	National mortality records	NA
Salinas-Rodríguez et al, 2022[40]	Mexico	Older adults	2735	66·8 (9·8)	61%	90	Intrinsic capacity trajectories	ADL change	WHODAS 2.0 (12 items)	Score from 0 (no disability) to 100 (complete disability)

(Table 1 continues on next page)

	Country	Population	n	Age, years	Sex, female	Follow-up, months	Exposure	Outcome	Outcome tool	Outcome definition
(Continued from previous page)										
Sánchez-Rodríguez et al, 2023[41]	Belgium	Community-dwelling older adults	534	73·5 (6·2)	60%	108	Low *vs* high intrinsic capacity*	Mortality	National death registry	NA
Sánchez-Sánchez et al, 2022[42]	France	Nursing home residents	371	85·9 (7·3)	71%	12	Intrinsic capacity composite score	Mortality, BADL change	Medical charts, Katz Index	Score evolution
Stolz et al, 2022[43]	USA	Community-dwelling older adults	754	78·4 (5·3)	67%	66	Intrinsic capacity composite score	Mortality, BADL disability	Local obituaries and informants, 4-item BADL scale	Need for assistance in any BADL lasting >3 months
Tay et al, 2023[44]	Singapore	Community-dwelling older adults	809	67·6 (6·8)	76%	12	Intrinsic capacity composite score	BADL disability, IADL disability	Barthel Index, Lawton Index	Loss of >2 points
Waris et al, 2022[45]	India	Older adults from the general population	100	71·9 (6·0)	36%	6	Intrinsic capacity composite score	BADL disability	Barthel Index (10 items)	A decrease ≥1 point
Yu et al, 2023[46]	China	Older adults from the general population	775	69·0 (6·4)	70%	24	Intrinsic capacity composite score	IADL change	Lawton IADL Index	Score evolution
Yu et al, 2022[47]	China	Older adults from the general population	756	69·3 (6·6)	69%	12	Intrinsic capacity trajectories	BADL disability, IADL disability	Katz Index, Lawton Index	Score in wave 2 below the lower 95% CI limit
Yu et al, 2021[48]	China	Older adults	756	69·3 (6·6)	69%	12	Low *vs* high intrinsic capacity*	BADL disability, IADL disability	Katz Index, Lawton Index	Having difficulties in ≥1 item
Yu et al, 2021[49]	Hong Kong	Older adults	1475	72·2 (5·1)	50%	84	Intrinsic capacity composite score	IADL change	5-item IADL scale	Score evolution (range 0–15)
Yu et al, 2023[50]	China	Older adults	1371	74·6	78·7%	36	Intrinsic capacity trajectories	IADL disability	Lawton Index (5 items)	Having difficulties in ≥1 item
Yu et al, 2022[51]	Hong Kong	Older adults	1671	75·7 (7·9)	79·2%	36	Low *vs* high intrinsic capacity	IADL disability	Lawton Index (5 items)	Having difficulties in ≥1 item
Yu et al, 2022[52]	Hong Kong	Older adults	846	79·7	51%	96	Low *vs* high intrinsic capacity	Mortality	National death registry	NA
Zeng et al, 2021[53]	China	Older adults in hospital	329	NR	41%	12	Intrinsic capacity composite score	Mortality, BADL disability, IADL disability	Medical records, Barthel Index, Lawton Index	Decrease of ≥1 point
Zhang et al, 2023[54]	China	Older adults from the general population	1788	75·4 (3·9)	53·4%	48	Low *vs* high intrinsic capacity	Mortality, IADL change	Regional death registry, Lawton Index (range 8–24)	NR
Zhang et al, 2023†[55]	Japan	Older adults from the general population	794	69·8	49%	128	Low *vs* high intrinsic capacity	Mortality	National death registry	NA
Zhang et al, 2023‡[55]	Taiwan	Older adults from the general population	1358	69·6	66·1%	36	Low *vs* high intrinsic capacity	Mortality	Telephone calls every 3 months	NA
Zhao et al, 2021[56]	China	Older adults	6663	74·2 (5·5)	60·9%	12	Low *vs* high intrinsic capacity	BADL disability	Barthel Index	Having limitations in ≥1 item

Data are n, %, mean, mean (SD), or range. ADL=activities of daily living. BADL=basic activities of daily living. IADL=instrumental activities of daily living. NA=not applicable. NR=not reported. WHODAS=WHO Disability Assessment Schedule. *Estimates were computed by pooling intrinsic capacity individual domains risks. †Data from the National Institute for Longevity Sciences–Longitudinal Study of Aging (Japan). ‡Data from the Longitudinal Aging Study of Taipei (Taiwan).

Table 1: **Characteristics of included studies**

	Domains assessed	Locomotion	Cognition	Psychology	Sensory	Vitality	Intrinsic capacity composite score
Beard et al, 2019[20]	5	2·4 m usual walking speed; 5-time chair-rise time; balance test	Verbal fluency—animal naming test; delayed verbal memory; attention—letter cancellation task	8-item CES-D score; 4-item scale for sleep disturbance	Self-rated distance and near vision; self-rated hearing	Handgrip strength; FEV; dehydroepiandrosterone; IGF-1; haemoglobin	Factor score using CFA
Beard et al, 2022[21]	5	2·5 m usual walking speed; 5-time chair-rise time; balance test	Delayed word recall; serial 7 test; time orientation; redraw ability	9-item CES-D score; sleep length and quality	Self-rated distance and near vision; self-rated hearing	Handgrip strength; FEV; haemoglobin	Factor score using CFA
Campbell et al, 2023[22]	5	Walking speed; 5-time chair-rise time; balance test	Immediate and delayed word recall; time orientation	CES-D; Satisfaction With Life Scale	Self-rated vision; self-rated hearing	Handgrip strength; BMI; waist circumference	Score generated from IRT
Charles et al, 2020[23]	5	4 m walking speed; 5-time chair-rise time; balance test	Time orientation; three-word recall	EQ-5D—anxiety or depression; CES-D—fatigue	Self-reported Strawbridge questionnaire	Handgrip strength; BMI; MNA; abdominal circumference	..
Chen et al, 2022[24]	5	Self-reported need of assistant aids	SPMSQ	10-item CES-D	Vision status; hearing status	BMI	Latent classes of intrinsic capacity trajectories using the latent class linear mixed model
Cheong et al, 2022[25]	5	Timed up and go; 6 m fast-pace walking speed; knee extension strength; Tinetti POMA	MMSE	GDS-15	LogMAR scoring; whisper test	FEV; ENIGMA; Nutritional Screening Initiative; energy level measured by 12-item Short Form Survey	Factor score using principal component analysis
González-Bautista et al, 2021[26]	6*	5-time chair-rise time	Time and space orientation; word recall	Two items from GDS-15 (feeling unhappy and loss of interests)	Self-reported visual problems; self-reported difficulty in hearing whisper voice (part of Hearing Handicap Inventory for the Elderly—screening version)	Self-reported weight loss; self-reported appetite loss	Sum of impaired intrinsic capacity domains (0–6)
González-Bautista et al, 2023[27]	6*	5 m usual walking speed	Community Screening Instrument for Dementia COGSCORE	EURO-D depression scale	Self-reported visual problems or interviewer-identified functional blindness; self-reported or interviewer-identified hearing problems and deafness	Self-reported weight loss; mid-upper-arm circumference	Latent statuses of intrinsic capacity impairments using the latent transitions model
Jia et al, 2023[28]	5	SPPB	SPMSQ	GDS-15	Self-reported visual impairment; self-reported hearing impairment	MNA short form	Transitions in number of intrinsic capacity domain impairments
Koivunen et al, 2023[29]	5	6 m fast-space walking speed; tandem-position standing balance test	Coding task	General self-efficacy scale	Self-rated vision; self-rated hearing	Handgrip strength	Average of five domains, rescaled as 0–100
Lee et al, 2023[30]	5	6 m gait speed test	MMSE	CES-D	Self-reported visual impairment; self-reported hearing impairment	MNA	Average of five domains, rescaled as 0–100
Lee et al, 2024[31]	5	6 m gait speed test	MMSE	CES-D	Self-reported visual impairment; self-reported hearing impairment	MNA	Average of five domains, rescaled as 0–100
Liu et al, 2021[32]	5	Chair-rise time	Time and space orientation; three-word recall	Two items from GDS-15 (feeling depressed and loss of interests)	Self-reported visual impairment; self-reported hearing impairment	Self-reported weight loss; self-reported appetite loss	Sum of dichotomised domain measures (0–9)
Locquet et al, 2022[33]	4	SPPB	MMSE	GDS-15	..	MNA	Composite Z score
Lu et al, 2023[34]	6*	SPPB	MMSE	GDS-15	Visual and hearing impairment through face-to-face assessment	MNA short form	Sum of impaired intrinsic capacity domains (0–6)
Lu et al, 2021[35]	5	Handgrip strength; self-reported walking steadiness	Montreal Cognitive Assessment	GDS-15	Self-rated vision; self-rated hearing	FRAIL scale	Factor score using CFA

(Table 2 continues on next page)

	Domains assessed	Locomotion	Cognition	Psychology	Sensory	Vitality	Intrinsic capacity composite score
(Continued from previous page)							
Meng et al, 2022[36]	5	Usual walking speed; repeated chair-rise time	SPMSQ; language and three-item recall, part of MMSE	10-item CES-D	Snellen Chart (visual acuity); self-reported hearing loss	Handgrip strength; BMI	Aggregate dichotomised domain measures using various weightings (0–12)
Nagae et al, 2023[37]	5	Mobility category of the Barthel Index	MMSE	GDS-15	Physician-assessed visual and hearing impairment	MNA short form	Sum of five domain measures (0–10); individual domains were rescaled to 0–2
Prince et al, 2021[38]	5	5 m usual walking speed	Community Screening Instrument for Dementia COGSCORE	EURO-D depression scale	Self-reported visual problems or interviewer-identified functional blindness; self-reported or interviewer-identified hearing problems and deafness	Self-reported weight loss; mid-upper-arm circumference	Sum of impaired intrinsic capacity domains
Ramírez-Vélez et al, 2023[39]	4	Self-reported slow usual walking speed	..	Self-reported exhaustion; self-reported sleep duration	Self-reported visual problems; self-reported hearing difficulty	Self-reported weight loss; handgrip strength	Sum of impaired intrinsic capacity domains
Salinas-Rodríguez et al, 2022[40]	5	4 m usual walking speed	Immediate and delayed verbal recall; forward and backward digit span; verbal fluency—animal naming test	Presence of depression, determined by depressive symptoms or medication use	Self-reported visual impairment; self-reported hearing impairment	Handgrip strength; BMI	Score generated from IRT and rescaled to 0–100
Sánchez-Rodríguez et al, 2023[41]	4	SPPB	MMSE	GDS-15	..	Malnutrition determined by MNA short form or Global Leadership Initiative of Malnutrition criteria	..
Sánchez-Sánchez et al, 2022[42]	5	SPPB	Hodkinson Abbreviated Mental Test	10-item GDS	Self-reported visual impairment; self-reported hearing impairment	MNA short form	Composite score
Stolz et al, 2022[43]	5	20-ft walking speed; three-time chair-rise time; balance test, part of the SPPB	MMSE	11-item CES-D	Jaeger chart (near-vision acuity); hearing impairment assessed by audioscope	Handgrip strength; maximum peak expiratory flow value	Average of five domains, rescaled as 0–100
Tay et al, 2023[44]	5	SPPB; 6MWT	MMSE; subjective memory problems	GDS-15; EQ-5D—anxiety or depression	Self-reported visual impairment; self-reported hearing impairment	MNA short form; appendicular skeletal muscle mass	Sum of five domain measures (0–10); individual domains were rescaled to 0–2
Waris et al, 2022[45]	5	Classified as the domain strength, including 4 m usual walking speed, 6MWT, handgrip strength, IGF-1, and haemoglobin	Saint Louis University Mental Status	GDS-15; 7-item General Anxiety Disorder	Snellen Chart (visual acuity); hearing impairment assessed by hear check device (audiometer)	BMI; MNA short form	Factor score using exploratory factor analysis
Yu et al, 2023[46]	6*	5-time chair-rise test	SPMSQ	Two items of CES-D	Self-reported visual impairment; self-reported hearing impairment	Weight loss; self-reported decline in food intake	Sum of dichotomised domain measures (0–6)
Yu et al, 2022[47]	6*	5-time chair-rise test	SPMSQ	Two items of CES-D	Self-reported visual impairment; self-reported hearing impairment	Weight loss; appetite loss	Intrinsic capacity patterns identified by latent class analysis

(Table 2 continues on next page)

	Domains assessed	Locomotion	Cognition	Psychology	Sensory	Vitality	Intrinsic capacity composite score
(Continued from previous page)							
Yu et al, 2021[48]	6*	5-time chair-rise test	SPMSQ	Two items of CES-D	Self-reported visual impairment; self-reported hearing impairment	Weight loss; self-reported decline in food intake	..
Yu et al, 2021[49]	5	6MWT; 5-time chair-rise time; balance test	MMSE	GDS-15	Snellen Chart (visual acuity); Frisby stereo test (visual disparity)	Handgrip strength; ratio of body fat to appendicular skeletal muscle mass	Factor score using CFA
Yu et al, 2023[50]	5	Two items of mobility difficulty from FRAIL scale	AMIC	Three questions related to life satisfaction, meaning in life, and feelings of happiness	Self-rated vision ability; self-rated hearing ability	Self-reported weight loss; difficulty in lifting and carrying 10 lbs	Factor score using CFA
Yu et al, 2022[51]	6*	Two items of mobility difficulty from FRAIL scale	AMIC	Three questions related to life satisfaction, meaning in life, and feelings of happiness	Self-rated vision ability; self-rated hearing ability	Self-reported weight loss	Sum of impaired intrinsic capacity domains (0–6)
Yu et al, 2022[52]	5	Three items of mobility, including: need walking aid to walk, able to walk steadily, and able to take stairs	12-item Clifton Assessment Schedule	GDS-15	Self-rated vision ability; self-rated hearing ability	Weight loss; BMI	Sum of impaired intrinsic capacity domains (0–5)
Zeng et al, 2021[53]	5	4 m usual walking speed; balance subset of POMA scale	MMSE	GDS-15	Self-rated vision ability self-rated hearing ability	Handgrip strength; MNA short form	Sum of dichotomised domain measures (0–5)
Zhang et al, 2023[54]	5	Timed up and go	Hasegawa Dementia Scale—Revised	GDS-15	Self-reported visual impairment; self-reported hearing impairment	MNA short form	Sum of five domain measures (0–10); individual domains were rescaled to 0–2
Zhang et al, 2023†[55]	6*	Slow gait speed according to AWGSOP	Seven items from MMSE	CES-D	Self-reported visual impairment; air-conduction pure-tone thresholds for both ears using diagnostic audiometers in a soundproof booth	≥5% over a 2-year period or lack of appetite (CES-D question)	..
Zhang et al, 2023‡[55]	6*	Low performance in the 5 sit-to-stand test according to AWGSOP	Nine items from Montreal Cognitive Assessment	CES-D	Poor vision affecting daily activities; self-reported hearing impairment affecting daily activities	Loss of more than 3 kg in the last 3 months or loss of appetite, assessed through the question: "Have you eaten less in the past 3 months due to poor appetite?"	..
Zhao et al, 2021[56]	5	Tinetti POMA	MMSE	GDS-15	Self-reported visual impairment; self-reported hearing impairment	MNA	Sum of impaired intrinsic capacity domains (0–5)

AMIC=Abbreviated Memory Inventory for the Chinese. AWGSOP=Asian Working Group on Sarcopenia in Older People. CES-D=Center for Epidemiological Studies—Depression. ENIGMA=Elderly Nutritional Indicators For Geriatric Malnutrition Assessment. FEV=forced expiratory volume. CFA=confirmatory factor analysis. GDS=Geriatric Depression Scale. IRT=item response theory. LogMAR=logarithm of the minimum angle of resolution. MMSE=mini-mental state examination. MNA=Mini Nutritional Assessment. POMA=Performance-Oriented Mobility Assessment. SPMSQ=Short Portable Mental Status Questionnaire. SPPB=short physical performance battery. FRAIL=Fatigue, Resistance, Ambulation, Illness, and Loss of Weight. 6MWT=6 min walking test. *Vision and hearing analysed separately. †Data from the National Institute for Longevity Sciences–Longitudinal Study of Aging (Japan). ‡Data from the Longitudinal Aging Study of Taipei (Taiwan).

Table 2: **Operationalisation of intrinsic capacity in included studies**

test (13 [22%] studies), and balance performance-based tests (nine [15%] studies). Of the 50 tools used for the evaluation of cognitive domain, the most commonly used assessments were global cognition scores (derived from the Mini-Mental State Examination or Montreal Cognitive Assessment; present in 29 [58%] studies), memory (six [12%] studies), and time or spatial orientation tools (five [10%] studies). Of the 42 tools used to assess the psychological domain, depressive symptom screening instruments, such as different versions of the Geriatric Depression Scale (16 [38%] studies) or the Center of Epidemiological Studies of Depression Scale (14 [33%] studies) were the most common tools. Of the 33 different tools used to assess the sensory domain, self-reported visual or hearing limitations (26 [79%] studies) or direct hearing or visual acuity assessment (five [15%] studies) were most commonly used. Finally, of the 54 instruments that assessed the vitality domain across studies, the most commonly used were the Mini-Nutritional Assessment scores (14 [26%] studies), self-reported recent loss of appetite or weight (13 [24%] studies), or handgrip strength (ten [18·5%] studies). Estimates of the association between impaired individual domains and outcomes were provided in five (14%) studies. Nine (24%) studies compared high versus low intrinsic capacity levels, whereas five (14%) used intrinsic capacity trajectories (ie, longitudinal changes over time) as the exposure. Regarding the outcomes, 24 (65%) studies analysed the association between intrinsic capacity and performance in activities of daily living as a dichotomous outcome, with 13 (35%) evaluating impairment in BADL and 11 (30%) impairment in IADL. Four (11%) studies assessed changes in the ability to perform BADL, four (11%) studies assessed changes in the ability to perform IADL, and three (8%) studies assessed changes in overall activities of daily living scores. Additionally, 20 (54%) studies assessed mortality risk, with 18 (49%) focusing on all-cause mortality, one (3%) on in-hospital mortality, and one (3%) on cardiovascular mortality. The mean follow-up duration was 38·7 months (range 6–96) for ADL-related outcomes and 67·4 months (0·6–168) for mortality. The definitions used to operationalise intrinsic capacity in the different studies are detailed in table 1, and the methods used to assess intrinsic capacity are described in table 2.

Intrinsic capacity had a moderate inverse association with longitudinal impairments in BADL (r –0·12 [95% CI –0·19 to –0·04], p=0·0031; figure 2), with no evidence of publication bias (Egger's test p>0·05; appendix 3 p 14) and low between-study heterogeneity (I^2 18·2%) despite large within-study heterogeneity (I^2 77·1%; appendix 3 p 15). Subanalyses of studies with categorical exposure (ie, high *vs* low intrinsic capacity) corroborated the observed inverse association between intrinsic capacity and longitudinal impairments in BADL (OR 0·56 [95% CI 0·35 to 0·87]). Assuming a baseline risk of impairment in BADL of 0·45, a higher intrinsic capacity was associated with 145 per 1000 individuals (95% CI 93 to 191) fewer cases of BADL decline. Risk differences assuming other comparator risks (0·10 and 0·60) are presented in appendix 3 (p 12). The meta-regression results revealed a weaker association between intrinsic capacity and impairment in BADL in those studies with longer follow-up periods (β 0·03, p=0·04; appendix 3 p 18), but no moderating effect was observed in those studies with a greater proportion of female participants.

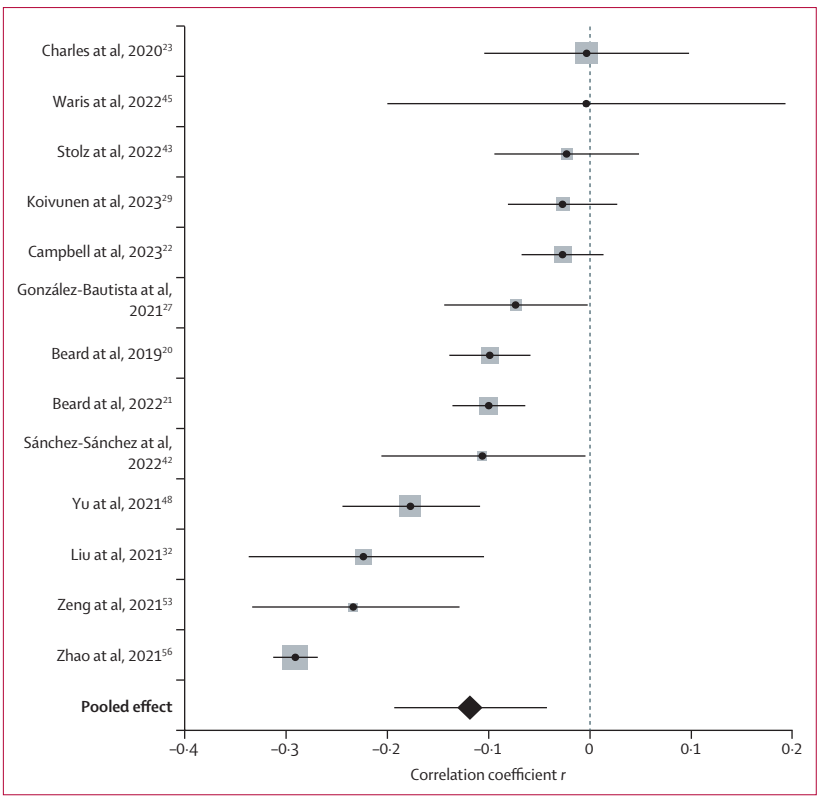

Figure 2: **Association between intrinsic capacity and impairment in basic activities of daily living**
Bars indicate 95% CIs.

Intrinsic capacity had a moderate inverse association with longitudinal impairment in IADL (r –0·24 [95% CI –0·35 to –0·13], p=0·044; figure 3), with no evidence of publication bias (Egger's test p>0·05, appendix 3 p 14) or between-study heterogeneity (I^2 0·0%), but with high heterogeneity within studies (I^2 98·0%; appendix 3 p 16). Subanalyses of studies using a categorical definition of intrinsic capacity confirmed that a higher intrinsic capacity was inversely associated with longitudinal impairment in IADL compared with a lower intrinsic capacity (OR 0·49 [95% CI 0·26 to 0·92]). With an assumed comparator risk of 0·45, a higher intrinsic capacity was associated with 168 per 1000 individuals (95% CI 55 to 259) fewer cases of decline in IADL (appendix 3 p 11). Meta-regression analyses showed a stronger inverse association between intrinsic capacity and impairment in IADL in those studies with a greater

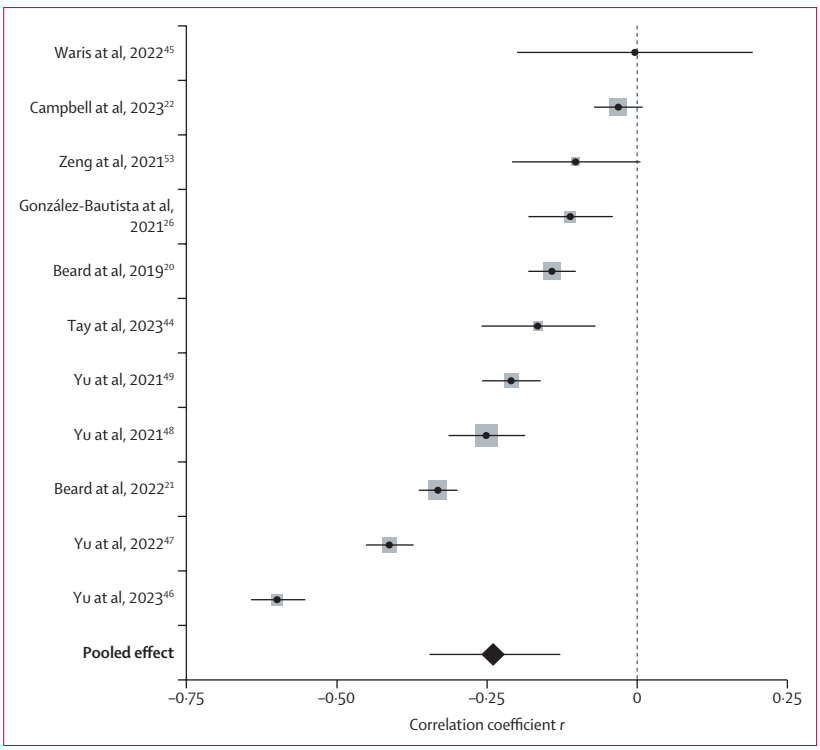

Figure 3: **Association between intrinsic capacity and impairment in instrumental activities of daily living**
Bars indicate 95% CIs.

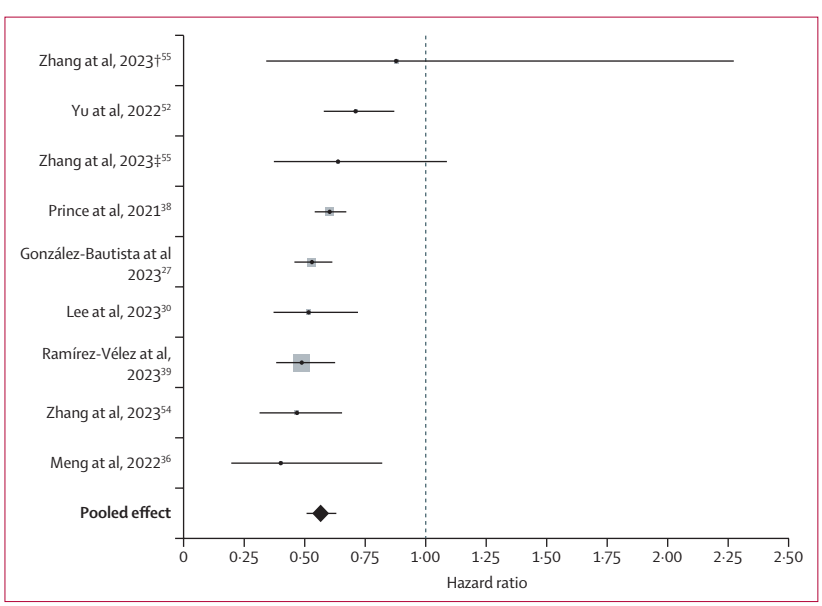

Figure 4: **Association between intrinsic capacity and mortality**
Bars indicate 95% CIs.†Data from the National Institute for Longevity Sciences–Longitudinal Study of Aging (Japan). ‡Data from the Longitudinal Aging Study of Taipei (Taiwan).

proportion of female participants (β –0·008, p=0·047; appendix 3 p 19), but study follow-up duration did not influence the effect estimates.

Three studies (2935 participants) were included in the meta-analysis on the association between intrinsic capacity trajectories and longitudinal changes in BADL or IADL. Although no significant association was found between intrinsic capacity trajectories and changes in BADL (OR 0·38 [95% CI 0·02–7·13]), maintained or increased intrinsic capacity was inversely associated with impairment in IADL compared with individuals with a decline in this variable (0·37 [0·19–0·71]).

Intrinsic capacity was inversely associated with the risk of mortality (HR 0·57 [95% CI 0·51–0·63]; figure 4), with no evidence of publication bias (Egger's test p>0·05) and low between-study (I^2 18·4%) but substantial within-study (I^2 63·2%) heterogeneity (appendix 3 p 17). When expressing these risk estimates as absolute risk, and assuming a median survival time of 10 years for the comparator (ie, individuals with low intrinsic capacity), older people with a high intrinsic capacity would live a median of 17·7 years (95% CI 15·9–19·7) longer. None of the included studies explored the association between intrinsic capacity trajectories and mortality.

Discussion

The main findings of this systematic review and meta-analysis is that baseline intrinsic capacity is inversely associated with longitudinal impairment in BADL or IADL and with risk of mortality in older adults. Additionally, maintaining or increasing intrinsic capacity over time appears to be inversely associated with disability in IADL (but not in BADL). However, the low number of studies available for this analysis precludes drawing strong conclusions. Although further efforts are needed to standardise the assessment of intrinsic capacity, our findings overall show the predictive ability of intrinsic capacity for adverse events in older adults. These results highlight the potential role of this indicator within the healthy ageing framework and suggest that preventing intrinsic capacity decline could contribute to the preservation of functional ability and could extend lifespan, with implications at both the individual and societal levels.

To serve as a marker of healthy ageing, a construct must be able to predict relevant clinical and functional outcomes. Our findings suggest that preserving intrinsic capacity plays a role in attenuating age-associated functional decline and risk of mortality. Our study builds on two previous scoping reviews (without meta-analyses) by Zhou and colleagues[57] and Yang and colleagues,[58] which suggested a link between intrinsic capacity and clinical outcomes, health-care resource use, quality of life, and mortality risk in older adults. However, in contrast to these previous reviews, the available evidence was synthesised quantitatively in the present study, thereby overcoming (at least partly) issues related to heterogeneity across studies and settings in the operationalisation of intrinsic capacity and allowing assessments of the strength of associations.

Intrinsic capacity has previously been shown to have superior predictive ability, compared to comorbidities, in

predicting adverse outcomes in older adults.[28,34,56] These findings align with the shift from a disease-focused to a function-focused perspective in the care of older adults, as advocated by WHO,[7] and, together with the present findings, support the use of intrinsic capacity for monitoring the health of older adults. Thus, from a theoretical standpoint, the concept of intrinsic capacity could contribute to reshaping the care of older adults by emphasising optimal functioning over the life course, aligning with the new paradigm of healthy ageing.[7]

Some methodological aspects of the intrinsic capacity construct must be considered, particularly its structure and operational definition, which remain a matter of debate.[59] Another open question is which specific domains should form this construct. We observed that a large amount of heterogeneity in the results of our meta-analysis is attributable to within-study variability. Such variability is likely to stem from studies reporting effect estimates for different intrinsic capacity domains, suggesting that not all domains are similarly associated with adverse outcomes. For instance, one study showed significant disparities in the association of the individual intrinsic capacity domains with mortality or functional impairment, indicating an uneven contribution to adverse outcome risk.[26] Therefore, further evidence is needed to determine which specific domain has superior predictive ability and whether the composite construct has greater clinical or prognostic value than the different individual domains. Furthermore, because studies have used divergent methods for constructing composite intrinsic capacity scores (eg, sum of impaired domains, rescaling of individual domains, or average Z score), the most valid approach for computing these scores remains to be identified. Additionally, more research is needed to establish the optimal measurement of intrinsic capacity and its individual domains across various settings and populations, as the sensitivity of certain measurement tools might vary depending on participant characteristics (eg, cognitive or functional status).[60]

The present study is not without limitations. A fundamental issue in the literature on intrinsic capacity, and consequently in our work, is the diverse operationalisation of intrinsic capacity across studies. Most studies were not originally designed for assessing intrinsic capacity, resulting in heterogeneous methods for defining this indicator. In addition to hampering comparability between studies,[61–63] such heterogeneity precluded a meta-analysis that included all studies, thereby impairing the generalisability of our results. Additionally, despite our efforts to include all data available on longitudinal intrinsic capacity trajectories as exposure variables, the low number of studies, together with the short follow-up periods, hinders our ability to draw firm conclusions about the associations of intrinsic capacity trajectories with outcomes. We noted an association between intrinsic capacity trajectories and the decline in IADL, but not in BADL. This somewhat unexpected finding might be due, at least in part, to a greater premature loss over time of IADL compared with the simpler (BADL) tasks, but could also be attributed to insufficient follow-up time. Following WHO recommendations for defining older age, we included studies of individuals aged 60 years or older, thereby deviating slightly from the original protocol; however, this is unlikely to have greatly affected our findings given that only two studies included participants with a mean age of less than 65 years,[30,31] which constituted only 1·3% of the total sample in the present analysis.[30,31] Additionally, because more than 90% of participants included in our analyses were recruited from the general older adult population, caution is warranted when extrapolating our observations to more specific settings such as in hospitals or nursing homes. Further research is needed to determine the optimal measure of intrinsic capacity across various settings and populations and to explore the effects of prospective monitoring on relevant outcomes in the long term. This understanding is essential for enabling the widespread implementation of intrinsic capacity assessment into health-care systems.[64]

In conclusion, intrinsic capacity is inversely associated with functional decline (ie, longitudinal impairment in BADL and IADL), as well as with mortality risk, in older adults. Therefore, though future longitudinal and interventional studies are needed, as well as further efforts to standardise the way in which intrinsic capacity is operationalised, intrinsic capacity assessment could be useful for risk stratification in older adults. Moreover, preservation of intrinsic capacity should be a key focus in the pursuit of healthy ageing.

Contributors

JLS-S and PLV conceptualised the study, performed the systematic search, and accessed and verified all the underlying data. JLS-S and W-HL extracted the data. DG-G and BdPC analysed the data. DG-G produced the figures. JLS-S wrote the original draft of the manuscript with the help of PLV. All authors contributed to the writing and revision of the manuscript, had full access to all the data in the study, and were responsible for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The datasets analysed during the study are available from the corresponding author upon reasonable request by email.

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