J Frailty Aging 2024;13(3)193-202
Published online April 10, 2024, http://dx.doi.org/10.14283/jfa.2024.30

Review

Intrinsic Capacity and Its Biological Basis: A Scoping Review

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Abstract

BACKGROUND: In 2015, the World Health Organization (WHO) introduced the concept of intrinsic capacity (IC) to define healthy aging based on functional capacity. In this scoping review, we summarized available evidence on the development and validation of IC index scores, the association of IC with health-related factors, and its biological basis. The review specifically focused on identifying current research gaps, proposed strategies to leverage biobank datasets, and opportunities to study the genetic mechanisms and gene-environment interactions underlying IC.

METHODS: The literature search was conducted across six databases, including PubMed, CINAHL, Web of Science, Scopus, AgeLine, and PsycINFO, using keywords related to IC.

RESULTS: This review included 84 articles, and most of them (n=38) adopted the 5-domains approach to operationalize IC, utilizing correlated five factors or bifactor structures. Intrinsic capacity has consistently shown significant associations with socio-demographic and health-related outcomes, including age, sex, wealth index, nutrition, exercise, smoking, alcohol use, ADL, IADL, frailty, multimorbidity, and mortality. While studies on the biological basis of the composite IC are limited, with only one study finding a significant association with the ApoE gene variants, studies on specific IC domains — locomotor, vitality, cognitive, psychological, and sensory suggest a heritability of 20-85% of IC and several genetic variants associated with these subdomains have been identified. However, evidence on how genetic and environmental factors influence IC is still lacking, with no available study to date.

CONCLUSION: Our review found that there was inconsistency in the use of standardized IC measurement tools and indicators, but the IC indices had shown good construct and predictive validity. Research into the genetic and gene-to-environment interactions underlying IC is still lacking, which calls for the use of resources from large biobank datasets in the future.

Key words: Intrinsic capacity, healthy aging, functional ability, genetics.

Background

In 2020, one billion of the world's population was 60 years or older, with an increase of 400 million expected between 2021 and 2030 (1-3). As this demographic shift continues, exploring innovative mechanisms to promote healthy aging is an important global health and economic policy agenda. Advocacy for improved health across the lifespan to increase the likelihood of older people being functionally able and capable of doing what they value in older age is increasing.

The World Health Organisation (WHO) redefined Healthy Aging in 2015, taking a life-course approach in preparation for the predicted demographic shift globally. It was redefined as the life-long process of developing and maintaining functional ability (1), determined by intrinsic capacity (IC), the environment, and the interaction between these two factors (1). Intrinsic capacity refers to the composite of an individual's physical and mental capacities across the five domains: locomotor, vitality, cognitive, psychological, and sensory (4). Higher IC levels are associated with decreased disability risk and better overall quality of life (5-7).

In the last two years, four scoping reviews relating to IC have been published (8-11). These reviews have focused on the sensitivity and specificity of WHO's Integrated Care for Older People (ICOPE) step 1 tool in detecting loss of IC (11), demonstrated that IC predicts physical function, frailty, falls and quality of life over time (10), highlighted that there was a lack of consistency in terms of the domains and metrics used across studies (9), and queried if IC was as an underlying latent trait of all capacities rather than an aggregate summary measure of the sub-domain capacities (8). The scoping reviews thus far are yet to address IC's biological (genetic) underpinnings. Intrinsic capacity is influenced by the person's underlying genetic as well as the interaction between the person's genetic make-up and their environment (including lifestyle). Also, research on IC is rapidly increasing, providing a basis for more recent reviews.

Our research group is researching to understand IC genetics better, leveraging existing cohorts where genetic data were collected. Within that context, the primary aim of this scoping review was to explore the existing literature to identify factors (especially genetics) relating to IC and to provide a current overview of knowledge regarding the measurement of IC, along with its predictive and construct validities.

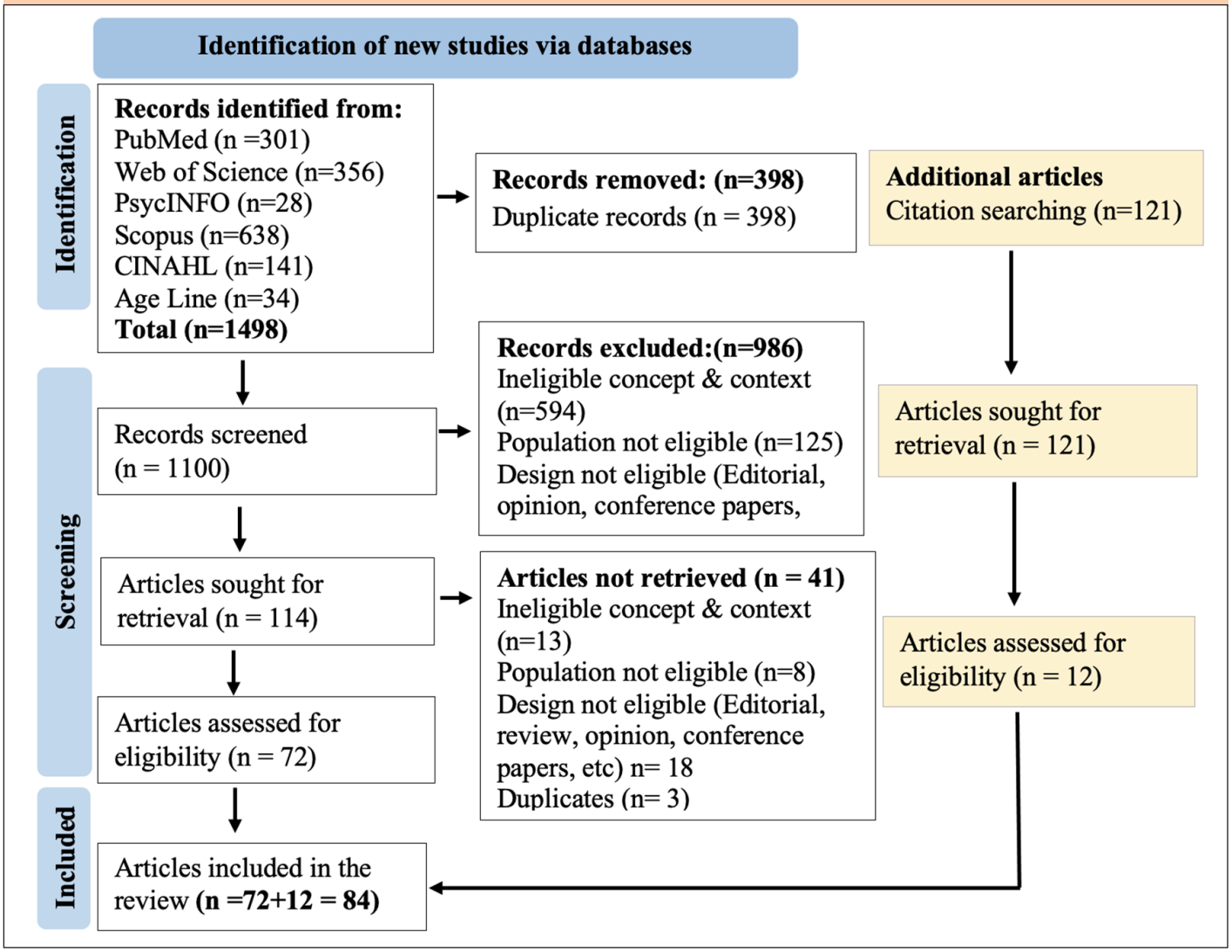
Methods

Scoping Review Framework

We used the Joanna Brigs Institute's (JBI's) Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) and Arksey and O'Malley methodological framework (12-14). The process involved five stages, including defining the purpose, the

Received January 15, 2024
Accepted for publication February 23, 2024

Figure 1. PRISMA flow chart showing the steps of the literature search



research question, and the search terms (Stage 1); identifying relevant studies (stage 2); selecting studies that met the predetermined inclusion criteria (stage 3); mapping and charting the data obtained from the selected studies (stage 4); and collating, summarizing, and reporting of the review findings (stage 5).

Stage 1: Defining the research questions and search terms

This initial phase involved refining the scope and direction of the review based on a preliminary search conducted on Google Scholar. Through this step, we had background information on studies and search terms related to IC measurement, IC measures' validity, health and health-related functional outcomes associated with IC, and its underlying biologic(genetic) basis.

"Generally, the research questions for this review were:

1. What are the IC measurement tools in literature? What are the approaches to computing composite IC scores and assessing the validity of the scores?

This question aims to summarize research findings on IC domains used/found, their indicators, approach to developing composite scores, and the validation of indexes.

2. What are the different sociodemographic, health, and health-related factors associated with intrinsic capacity?

3. Does IC have a biological/genetic basis? What are the biomarkers associated with IC?

Inclusion and exclusion criteria

The Participant, Concept, Context (PCC) approach was employed to develop the eligibility criteria for study inclusion. The inclusion criteria were; studies conducted on human subjects of all ages (populations), focusing on the measurement of IC, its validation, association with socio-economic and health outcomes (concept), and in any setting – whether the studies were conducted in the community or institutional setting (context), published in the English language and published between 01/01/2015 – 20/10/2023. However, abstracts, conference proceedings, commentary, editorials, reviews, and personal opinions were excluded. No research records

were available until WHO experts released the initial article operationalizing IC measurement (15).

Stage 2: Identifying relevant studies (Search strategy)

The literature search was conducted across Six Databases: PubMed, CINAHL, Web of Science, Scopus, AgeLine, and PsycINFO using the mesh terms and keywords "intrinsic capacity", "intrinsic capacity decline", "intrinsic capacity domains", "intrinsic capacity impairment", "intrinsic capacity index", "intrinsic capacity model", and "intrinsic capacity score" in the context of Aging. Each database's detailed search string is presented in Supplementary Table 1 (Supplementary Table- 1).

Stage 3: Selection of relevant articles

Identified articles were imported into Clarivate Analytics EndNote 20 after the completion of the search, and duplicates were removed. Following this, two researchers (MB and AT) independently evaluated the titles and abstracts of the articles against the inclusion criteria. The two assessors thoroughly reviewed the full text of the selected articles. Articles that did not meet the inclusion criteria were excluded, and the reasons for their exclusion were documented and reported. Disagreements that arose during the selection process were resolved through discussion. The search outcomes and procedure for selecting or excluding studies can be observed in the PRISMA-ScR flowchart (Figure 1).

Stage 4: Data extraction and synthesis

Using a data extraction tool, MB and AT collected various information from selected articles, including name of authors, publication year, characteristics of study participants, design and setting of the study, domains of IC measured, method used to calculate composite IC scores, validation approaches, and other relevant information. Supplementary Table 2 provides the data extraction form and the summary of information collected from the articles (Supplementary Table 2). The results collected from these selected articles were presented primarily using narrative descriptions and tables.

Results

Descriptive Summary

Our search strategy yielded 1498 articles, of which 398 were identified as duplicates and, thus, removed. After screening titles and abstracts (Figure 1), 986 publications were excluded, and full-text screening of 114 articles was conducted, resulting in 72 publications for full-text review. With a targeted citation search strategy, we found 12 additional articles relevant to our topic, and the final list for this scoping review was 84 articles.

Of the total 84 articles reviewed, the majority, 77 articles (92%), were published in the last two years, between 2021 and 2023.

The majority (51 articles, 61%) of the publications were carried out using samples sourced from Asia, of which 33 were from China. The remaining studies utilized study participants distributed across other geographical regions, including 20 (24%) studies in Europe (France (n=9), UK (n=4), Belgium (n=3), Spain (n=2), and Netherlands (n=1), and Norway (n=1)), North America (n=3), South America (n=5), New Zealand (n=1) (Supplementary Table-2). Four articles involving study samples from multiple continents. Out of the 84 reviewed articles, 33 were cross-sectional studies, 43 had a longitudinal approach (involving cohort, case-control, or longitudinal designs), and 8 were randomized control trials (Supplementary Table- 2).

Most (64 studies) have explored the validity of IC measurement in different ways. Some studies assessed the predictive validity (16-20) by assessing if IC predicts future health outcomes, whereas others assessed construct validity through the cross-sectional association of IC with socio-demographic variables (21-23), health and health-related functional outcomes (7, 20, 24, 25), mortality (26-29), and quality of life (7).

Some of the studies have inquired into the structural validity of IC (30, 31), sensitivity and specificity analyses (23, 32-34), tested internal consistency using Cronbach alpha (20, 35), performed ROC curve analysis (19), assessed criterion validity through logistic regression analysis (28), and conducted validation analysis by dividing the population into two as 70% for training and 30% validation cohort (26). The WHO has also published an expert consensus article on the measurement and validation of IC, providing a comprehensive working definition of vitality capacity (36).

The association of biological and environmental factors with IC

Biological markers with IC

Eight studies explored the association of IC with aging-related biomarkers. While specific studies estimating the heritability of IC are currently lacking, evidence based on the five IC domains suggests a heritability estimate of 20-85% (37-54). Thus far, only one candidate gene study has been conducted, and this study showed a significant association of IC with ApoE carriage (26).

Research conducted by Lu WH, et al. (2023) showed an increased level of inflammatory markers such as Plasma C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor receptor-1 (TNFR-1), monocyte chemoattractant protein-1 (MCP-1) and growth differentiation factor-15 (GDF-15) in individuals with lower IC (55). Another study by Lee WJ, et al. (2023) found that high serum levels of IL-6, CRP, hyperglycemia, and low dehydroepiandrosterone sulfate (DHEA-S) were associated with low IC (26,

Table 1. Association of intrinsic capacity with health and health-related outcomes

Socio-demographic factors	Lifestyle and behavioral factors	ADL, IADL, frailty, and related factors	Morbidity, mortality, hospitalization, QoL	Biomarkers
Age (7, 20-23, 32, 57, 62-69)	Exercise and (64, 68, 70), physical activity (71-73)	ADL/ADL disability (7, 20, 23-25, 27, 35, 69, 74-81)	multimorbidity (7, 20, 22, 23, 57, 63, 65-67), Charlson index (68)	Allostatic load (62)
Sex (IC lower among women) (7, 20-23, 62, 63, 66, 67)	alcohol consumption (23, 71)	IADL (7, 20, 23-25, 27, 31, 63, 66, 74, 76, 78, 82, 83)	hypertension (32)	Chronic inflammation, hyperglycemia, and DHEA-S (56)
educational status (7, 20, 21, 23, 32, 64, 66-68)	Smoking, tobacco use (23, 68, 71)	frailty (7, 24, 25, 63, 84-88)	Medication adherence (89), Nursing home-acquired pneumonia (90), Polypharmacy (82), Self-rated health (82)	High interleukin (IL)-6, high E-selectin, low serum albumin, and low folate are associated with low IC (26, 59, 60)
economic status (Wealth) (20-22, 62, 64, 65, 67)	Healthy eating (nutritional intervention) (77)	functional ability (28)		Homocysteine (55)
Healthcare costs (91)	Multi-domain interventions (92)	level of physical, social & productive activities(7)	Incidence of death/mortality (10, 27, 28, 35, 56, 65, 74, 81, 93-95)	TNFR1 (57, 59, 60)
marital status (21, 23, 32, 64, 68)	Dietary pattern (96).	Incident dependence (65, 75)	vitality domain impairment, and cognition domain impairment associated with mortality (19)	Plasma N-terminal pro-B-type natriuretic peptide is associated with IC decline (58).
Ethnicity (better FHI for Chinese) (7), IC higher for white race (23), IC lower for black and brown participants (97)	Meat intake (less intake, low IC) (64)	locomotion domain associated with falls (19)	Health-related QoL (5-7, 10, 76), insomnia, memory loss, constipation, slowness, chronic obstructive pulmonary disease, and osteoarthritis were related to IC decline.(64)	APOE+4 Genotype (26)
Housing index (7)	Diet quality index (DQI) (98)	fragility fracture and functional ability (99)	Sleep health (21), Having emotional disorders (21)	GDF-15 (59, 60)
Residence (urban have better IC) (23, 64)	BMI(100)	Nursing home stay (35), Sarcopenia (18)	Hospitalization (27, 90) Hospital-associated complications (95)	CRP (60)
social activities (7)		LSM (30).	Dementia (87)	IF1 (61)
Subjective social status (66)	Perceived stress, health-promoting behaviour (101)	Higher transition to frailty for those with lower IC (88)	Cardiovascular mortality (17) Respiratory disease mortality (16)	
Social engagement (32)		Falls (24), Incontinence (64, 82), Disability (6)	Presence of chronic neurological illness(69)	

Abbreviations: FHI-Functional health index, DQI – Diet quality index, BMI – Body mass index, ADL-Activities of daily living, IADL-Instrumental activities of daily living, LSM – Life space mobility, QoL – Quality of life, DHEA-S - dehydroepiandrosterone sulfate, TNFR1- Serum Tumor necrosis factor receptor 1 level, APOE+4 - apolipoprotein E gene, GDF-15 - Growth differentiation factor 15, CRP - C-reactive protein, IF1-Mitochondrial inhibitory factor 1.

56). Lower levels of serum albumin and folate (26), high homocysteine (55), Tumor Necrosis Factor Receptor 1 level (TNFR1) (57), Plasma N-Terminal Pro-B-Type Natriuretic Peptide level (58), or E-selectin (26) and increased allostatic load (26) were significantly associated with low IC. Recent studies have also reported associations between IC and plasma biomarkers reflecting inflammation (such as CRP, IL-6, TNFR-1, and MCP-1) and mitochondrial impairment (such as GDF-15, IF1) such that elevated levels of plasma interleukin-6 (IL-6), tumor necrosis factor receptor-1 (TNFR-1), CRP, growth differentiation factor-15 (GDF-15) and IF1 were associated with lower IC or faster decline in IC (59-61). Details of all factors associated with intrinsic capacity are presented in Table 1 (Table 1).

Lifestyle and socio-economic factors with IC

Exercise and lifestyle choices play a crucial role in IC, with studies revealing significant associations. Smoking is linked to lower IC (23, 64, 68, 70-73), as is alcohol consumption (23, 71), and reduced meat intake (64). Interventional and cohort studies, respectively, underscore the positive impact of healthy eating (77) and fruits and vegetables and protein-rich diets on IC (96). A multidomain intervention has also been shown to enhance IC (102).

The exploration of socio-economic factors demonstrates noteworthy associations with IC. Age is inversely correlated, with lower IC found in older age (7, 20-23, 32, 57, 62-69), and women tend to exhibit lower IC (7, 20-23, 62, 63, 66, 67). Lower educational status (7, 20, 21, 23, 32, 64, 66-68), low economic status (20-22, 62, 64, 65, 67, 91), unmarried status (21, 23, 32, 64, 68), and urban residence are associated with lower IC.; however, being white race was associated with a higher IC (23, 64), and higher IC was observed in Chinese individuals compared to non- Chinese in Singapore (23, 97).

Social factors also play a role in IC. Lower social engagement, lower subjective social status, fewer social activities, and lower housing index are linked to lower IC (7, 32, 66).

Mortality and morbidity with IC

IC is a significant predictor of various health outcomes. It predicts multimorbidity (20, 65), mortality (10, 27, 28, 35, 56, 65, 74, 81, 93-95), quality of life (5, 6, 10, 76), risk of dementia (87), cardiovascular diseases mortality (17), respiratory disease mortality (16), hospitalization (27), and complications related to hospitalization (95). Conversely, multimorbidity predicts declines in IC (68). In addition to predictive relationships,

Table 2. Variables used to define/measure intrinsic capacity and/or domains

Cognition capacity	Locomotion capacity	Vitality capacity	Psychological capacity	Sensory capacity
Memory (self-reported) (24, 28, 73, 96)	Balance (20, 23, 28, 66, 67, 71, 86, 98, 109)	Dehydroepiandrosterone (DHEA(S)) (20)	CES-D/Modified (20, 25, 26, 28, 29, 35, 55, 56, 67, 71, 72, 75, 97, 109)	Self-reported/rated hearing capacity (20, 23-25, 28, 55, 62, 74-76, 82, 85, 94, 105, 106, 109-111)
Verbal fluency/semantic verbal fluency (6, 20, 23, 70, 97)	Muscle Strength/ Hand grip strength (7, 20, 31, 112)	FEV1 (7, 20, 67, 72)	Sleep/Sleep Score (16, 17, 20, 67)	Self-reported/rated visual capacity (20, 23, 24, 28, 55, 62, 72, 74-76, 82, 85, 94, 105, 106, 109-111)
MMSE/Modified MMSE (7, 18, 19, 24-26, 28-30, 34, 35, 56, 57, 59-62, 64, 66, 68, 69, 72, 74, 77, 79, 84-86, 88, 93, 95, 98, 103, 107)	Gait speed (6, 16, 17, 20, 23, 25, 26, 28, 33, 55, 56, 62, 65-67, 70, 71, 74, 77, 86-88, 96-98, 100, 109, 112)	Hand grip strength (6, 16, 17, 23, 25, 26, 28-30, 35, 55, 59-62, 66, 67, 70, 72, 74, 77, 86, 88, 96-98, 102, 111)	GDS-15/Modified (7, 18, 19, 23, 24, 30, 31, 34, 55, 57, 59-64, 66, 68-70, 74, 77, 79, 81, 84-86, 88, 90, 93-96, 98, 101, 102, 105-107, 112, 113)	Self-reported hearing problems/impairment (6, 16-19, 22, 26, 30, 31, 33, 56, 57, 64, 65, 67, 68, 71, 79, 81, 84, 96, 101, 103, 113-115)
Recall three words/word recall test (33, 55, 58, 63, 67, 91, 108, 109, 114-116)	Chair stand/rise test (20, 25, 26, 28, 30, 33, 58, 62, 63, 66, 67, 70, 76, 77, 83, 86, 88, 91, 98, 101, 108, 114-116)	MNA or its short form (18, 19, 24, 25, 29, 30, 32, 34, 55, 56, 68, 74, 77, 79-81, 84, 85, 88, 90, 93, 95, 96, 100, 101, 105-107, 113)	Self-reported satisfaction with life (Evaluative, hedonic, and eudemonic) (22, 55, 62, 73, 82)	Self-reported visual problems/impairment (6, 16, 17, 19, 21, 22, 26, 30, 31, 33, 56-58, 63-65, 67-69, 71, 79, 81, 84, 87, 91, 96, 101, 103, 108, 112-117)
Attention (20, 96)	Pick pencil test (62)	Peak flow test (PEF) (35, 62)	Locus of control (62)	Strawbridge questionnaire for hearing & vision (29)
Delayed verbal memory (6, 20, 70)	Sarcopenia (103)	Haemoglobin (20, 67)	Social participation (21, 62)	Whisper test for hearing (7, 21, 32, 58, 63, 69, 80, 83, 91, 108, 116)
Orientation in time and space (21, 23, 33, 55, 58, 63, 83, 91, 101, 102, 108, 114-117)	Prevalence of falls (103)	BMI (6, 26, 29, 55, 57, 62, 64, 69, 71, 75, 94, 109)	Yesavage geriatric depression scale and mental problems (103)	Snellen chart (logMAR) (7, 25, 26, 32, 66, 80, 86, 98, 107)
Immediate memory (6, 70)	Impaired ADL (103)	Loss of appetite (33, 58, 63, 76, 83, 91, 103, 108, 110, 114-116)	EuroQol-5D / modified (24, 29, 30)	Stereopsis (66, 86, 98)
visuospatial memory (70, 96)	Mobility/upper mobility/lower mobility (21, 55, 73, 103, 117)	Weight loss (21-23, 33, 57, 58, 63, 65, 73, 76, 82, 83, 87, 91, 94, 103, 108, 110, 112, 114-117)	GAD-7 (23, 70)	Near vision using Jaeger chart (35)
Free & cued selective reminding test (102)	SPPB test (18, 19, 24, 25, 29, 30, 32, 34, 35, 55, 57, 59, 60, 64, 68, 72, 80, 81, 84, 85, 90, 93, 102, 103, 105-107, 111)	Abdominal circumference (29)	Feeling down, depressed, or hopeless (ICOPE item) (21, 33, 58, 76, 83, 91, 108, 110, 114-117)	Hearing impairment using audio scope/ audiogram (35, 83, 107, 112)
Digit/Letter/symbol Substitution Test (Processing speed) (28, 70, 102)	One leg stand (OLS) test (70, 77)	Insulin-like growth factor 1 (IGF-1) (20)	little interest or pleasure in doing things (ICOPE item) (58, 76, 83, 91, 108, 110, 114-117)	Weber and Rinne test of hearing loss (32)
Trail making (part-A processing speed) (70)	Timed up and go test (TUG) (7, 30, 69, 113)	Exhaustion (23, 30, 111)	Goldberg anxiety scale (25)	Hearing/Vision impairment diagnosed by a physician (95, 97, 100)
Trail making (part-B executive function) (70)	B-POMA (7, 74, 79)	Appendicular skeletal muscle mass (ASM) (24, 85)	EURO-D depression scale (65, 85, 87, 111)	
SPMSQ (26, 75, 76, 106, 110)	Frail scale (modified. i.e. used resistance & Ambulation among 5) (22, 82)	Mid-upper arm circumference (65, 87)	World Mental Health CIDI (6)	
Reasoning (96)	Knee extension strength (7)	Adiposity to muscle ratio (66, 86, 98)	PHQ-9 (32, 80)	
Language function test (96)	Mobility aid use (75, 94)	FRAIL Scale (5 components) (31)	Mood (90)	
AMTS)/Modified (22, 81, 82, 90)	Physical fitness in back scratch test (77)	ENIGMA (7)	HADS-A-7 (28)	
CSI-D (65, 87)	Chair-sit-and-reach test (77)	Nutritional screening initiative (NSI) assessment tool (7)	Mastery (Pearlin Mastery Scale) (28)	
MoCA (31, 32, 105, 111)	6-minute walk test (24, 85)	Modified SF-12 QoL scale (7)	GSES-12 (28)	
Forward and backward digit span (6)	Steadiness (31)	Two-minute step-in-place test (TMS) (77)	Self-reported exhaustion (16, 17)	
Intact mental status test (67)	Stair climbing (94)	Phase angle (25)	GDS-4 (100)	
Episodic memory (23, 71)	Barthel index (BI) (95)	Poor Endurance (23)		
Semantic memory (23)		Waist circumference (55)		
Clifton Assessment schedule (94)	Difficulty in lifting and carrying 10 pounds (22)			
Mini-cog (55, 80, 100)	Chronic musculoskeletal pain (self-reported) (111)			
Hasegawa dementia scale revised (HDS-R) (113)	Incontinence (111)			
Neuropsychological assessment battery (NAB) (112)	Fatigue (112)			

Abbreviations: CES-D – center for epidemiological studies depression score, FEV1 – Forced expiratory volume in one second, MMSE-Mini mental state examination, GDS- Geriatric depression sale, MNA- Mini nutritional assessment, ADL-Activities of daily living, QoL – quality of life, ICOPE- integrated care for older people, AMTS-Abbreviated mental test score, SPMSQ- short portable mental state questionnaire, PHQ-9 -Patient health questionnaire, CSI-D – Community screening instrument for dementia, CIDI -composite international diagnostic interview, PEF- Peak expiratory flow, BMI – body mass index, GAD-7 – Generalized anxiety disorder-7, B-POMA –Tinetti's balance subscale of performance-oriented mobility assessment, ENIGMA - Elderly nutritional indicators for geriatric malnutrition assessment, MoCA - Montreal cognitive assessment, GSES- General self-efficacy scale, HADS-A-7 - anxiety sub-scale of hospital anxiety and depression Scale

IC index has shown cross-sectional associations with quality of life (7), medication adherence (89), sleep health (21), nursing home-acquired pneumonia (90), polypharmacy (82), hypertension status (32), hospitalization (90), presence of chronic neurological illness (69), low self-rated health (82) and various health conditions, such as insomnia, memory loss, constipation, slowness, chronic obstructive pulmonary disease, and osteoarthritis (64).

Functional ability with IC

IC predicted functional difficulty parameters, including the future incidence of ADL (20, 24, 27, 35, 74-81), IADL (20, 24, 27, 31, 66, 74, 76, 78, 82, 83), Frailty (24, 84-88), disability/ functional decline/dependence (6, 28, 65, 75), and have shown cross-sectional associations with ADL (7, 23, 25, 69), frailty (7, 25, 63) and IADL (7, 23, 25, 63). Moreover, IC was associated with fragility fracture (99), nursing home stay (35), life-space mobility (30), falls (24), incontinence (64, 82), and sarcopenia (18).

Measurement and validation of IC and its domains

Various approaches have been utilized in the process of constructing IC, each involving a different number and type of domain. Although most studies (n=38; 45%) utilized the five domains methodology (6, 7, 24, 26-28, 30, 31, 55-57, 62, 64, 71, 74, 79, 81, 84, 85, 94, 96, 98, 103-107), seven studies utilized the bifactor structure (with one general domain (IC) and five sub-domains) (20, 22, 23, 35, 66, 67, 86). Five of these studies (20, 23, 35, 66, 67) comparing the goodness of fit when the bifactor approach was applied instead of the correlated factors and hierarchical model options found that the bifactor structure has better model fit statistics. Eight other studies adopted the six domains construct by dividing the sensory domain into two components, namely hearing and vision (21, 33, 75, 83, 87, 89, 91, 108), whereas eleven studies considered only four domains by excluding the sensory domain (34, 59-61, 70, 73, 77, 88, 90, 93, 102) and another two studies used four domains excluding the cognition domain (16, 17). Three studies utilized other methods, including seven domains (65), eight domains (78), and no domain but summing up indicators directly (5).

Studies comparing the traditional (correlated factors) method, the bifactor method, and the hierarchical method consistently demonstrate that the bifactor model provides a superior fit compared to both the hierarchical model and the correlated factors models (20, 23, 35, 66, 67). In measuring IC, various methods have been used, ranging from simple approaches involving a single variable to complex composite assessments. Details of all methods used to operationalize each domain under the reviewed articles are shown in Table 2 (Table 2).

Computation of IC scores

Sixty-seven articles have created IC composite scores. Standard methods for constructing IC composite scores involve using factor analysis or principal component analysis (7, 25, 73), in line with original research relating to IC (20). Out of the nine studies utilizing factor analysis methods, two employed the traditional correlated five-factors approach (30, 98), while the remaining seven utilized the bifactor method, incorporating five specific factors and one general factor (20, 22, 23, 35, 66, 67, 86).

However, the majority 32 (47.8%) papers calculated the IC score by summing individual IC domains scores without weighting, using either a two-point scale (0-impaired/bad and 1-unimpaired/good) or a three-point scale (0-impaired, 1-slightly impaired, or 2-unimpaired) (18, 19, 21, 24, 32, 33, 55-58, 61-64, 68, 69, 71, 74, 75, 80, 82-85, 94, 95, 97, 100, 106, 109, 113, 114). Other ways employed to compute IC were averaging the z-scores of the domains (70, 72, 81, 90, 93, 96, 102), direct summation of the values of indicators (5, 16, 17, 88, 101, 115), the latent growth modeling (LGM) method (31), weighted linear combination of indicators with loading greater than 0.3 (78), direct summation of indicators associated with domains in the regression model (26, 65, 79), averaging the domains' average values (28, 59, 60), and a 2-parameter domains item response theory (IRT) which refers to direct categorization of IC as "0" for impairment in any domain and "1" for no impairment in any of the domains (6, 27).

Discussion

Some eight years since the WHO redefined Healthy Aging, there has been an exponential growth in research relating to IC, with almost all publications in the last 2 years and the majority (61%) leveraging data from Asia. Whilst studies have explored the association and predictive ability of IC with inflammatory, lifestyle, health, and socio-economic factors, research relating to genes and IC is rare. Many methods have been used to assess and score IC, making it vital that a consensus is reached globally.

While specific studies estimating the heritability of IC are currently lacking, evidence based on the five IC domains suggests a heritability range of 20-85%; specifically, genetic factors contribute to the variability in cognitive 50-70% (37-39), sensory 20-30% (40-43), locomotor 30-85% (44-47), vitality 25– 65% (48-50) and psychological 35–70% (51-54) domains. There has been one attempt, through a candidate gene study approach, to identify genes associated with the broader IC domain. This particular study showed a significant association of IC with ApoE carriage (26). Understanding the interaction between genes and environment (including lifestyle factors) and IC is important. Before this, it is essential to identify genetic markers associated with IC. Such research may confirm the benefits of lifestyle or behavioral changes in helping people age well, including allowing the personalization of this intervention to the individual.

As outlined in the results section, our scoping review introduces new elements beyond those explored in the initial review addressing adverse health outcomes associated with IC. In addition to investigating biological and inflammatory biomarkers which are new, this review also identifies additional

factors previously unexplored, which are related to socio-economic (such as educational status, economic standing, marital status, ethnicity, residence, housing index, and social engagement); functional ability (such as fragility fracture, life-space mobility, nursing home stay, incontinence, and sarcopenia are also assessed); morbidity and mortality (such as multimorbidity, medication adherence, polypharmacy, hospitalization and its associated complications, sleep health, cardiovascular diseases mortality, and respiratory diseases mortality which were not addressed in the previous review) and behavioral and lifestyle-related factors (such as exercise, alcohol consumption, smoking, eating habits, and dietary patterns).

In the context of developing IC indices, no consistent method has been used thus far. New indicators for IC domains continue to be used, often without goodness of fit testing. Goodness of fit tests must be done while new indicators are used to determine whether those indicators are appropriate (118). Similarly, some studies used quick and direct tools, and others employed more complex and time-consuming composite measures. Balancing the precision of variable measurement with tool simplicity is crucial, and in the realm of measurement science, it is recommended to utilize straightforward yet robust instruments to assess variables like IC (119, 120). Studies also reveal that the bifactor method correlates with the five factors method and performs better than the correlated factors and hierarchical methods (20, 23, 35, 66, 67). There is also evidence of better explanatory power of the bifactor model when compared to the other two methods (121-123). Whilst evidence supports that the bifactor method results have better conceptual clarity and fit than the other structures, the lack of standardization may introduce bias (128).

Furthermore, there needs to be an effort to reach a consensus in defining indicators for individual domains. Consensus about the indicators and methods is necessary to inform the planning of future cohort studies. Planned cohort studies, as opposed to leveraging already collected data, may have the advantage of enabling the collection of appropriate indicators to measure IC. Two primary approaches are being applied to compute the IC composite score: the CFA (20, 22, 23, 30, 66, 67, 86, 96) and the arithmetic sum/average of the values of the domains (19, 24, 32, 55-58, 62-64, 71, 74, 75, 82, 84, 85, 94, 106, 114). Both have demonstrated good construct and predictive validity. Concerning the approaches for measurement, the reflective versus formative nature of the IC measurement (i.e. whether IC should be considered as an underlying latent trait of all capacities or an aggregate summary measure of the subdomain capacities) shall also be considered in future studies (124).

Limitations and Strengths

The major strength of this review is that we followed a rigorous and stepwise screening process with the involvement of independent assessors. The findings were reported following the JBI's PRISMA guideline extension for scoping review (PRISMA-ScR). The scope of the literature search was limited to peer-reviewed articles, and as a result, unpublished studies and organizational reports were not included. Due to logistic limitations, only articles published in the English language were reviewed, although studies published in other languages may have provided information on the external validity of IC tools in a multicultural setting.

Conclusion and recommendations

Since the introduction of IC for defining healthy aging and functional capacity, extensive research has been conducted to measure these indices and validate them, as well as to assess their relevance in medical, social, and behavioral sciences. This review identifies that there is a knowledge gap (no evidence) when it comes to our understanding of the genetics of IC. Such understanding can be improved by leveraging existing longitudinal studies but there is also a need for planned cohort studies where IC measurements are collected prospectively, and genetic data is also available. This review highlights the current difficulties in comparing existing studies given the lack of standardization in defining indicators that ought to be collected for each IC domain and how best to assess and score IC. Reaching such consensus is imperative because it will not only define the approach for the use of already collected data but will also support the planning and conduct of new longitudinal studies focused on IC and functional ability. The pooling of data globally to advance our understanding collectively would also be more likely through a standardized approach.

Acknowledgments: MB Beyene is Ph.D. student with scholarship support from University of Adelaide (The University Adelaide Research Scholarship).

Funding: AT Amare is currently supported by the National Health and Medical Research Council (NHMRC) Emerging Leadership (EL1) Investigator Grant (APP2008000). Open Access funding enabled and organized by CAUL and The University of Adelaide.

Conflicts of interest: Professor Renuka Visvanathan is a member of the WHO Clinical Consortium in Healthy Aging, but the work presented in this manuscript does not represent the views of the consortium.

Ethical standards: This review was conducted in accordance with established ethical procedures and standards.

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How to cite this article: M.B. Beyene, R. Visvanathan, A.T. Amare. Intrinsic Capacity and Its Biological Basis: A Scoping Review. J Frailty Aging 2024;13(3)193-202; http://dx.doi.org/10.14283/jfa.2024.30