Operationalising the concept of intrinsic capacity in clinical settings

Islene Araujo de Carvalho, Finbarr C Martin, Matteo Cesari, Yuka Sumi, Jotheeswaran A Thiyagarajan, John Beard

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BACKGROUND PAPER, 1
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Background paper

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Objectives

This paper explores key issues relating to the clinical application of “intrinsic capacity”, a relatively new concept. Intrinsic capacity (IC) is a composite of all the physical and mental attributes on which an individual can draw, not only in older age, but across their lives. Healthy ageing of an individual (“the process of developing and maintaining the functional ability that enables wellbeing in older age”) depends upon their IC and their socio-economic and physical environments and the interactions between them.

We suggest that focusing upon intrinsic capacity for the identification of individuals who may benefit from interventions, as well as for clinical outcome measures, can reorient public health and clinical practice away from the disease-orientated approach and towards a more effective person centred approach based on functional evaluation, which will identify earlier opportunities for intervention.

We draw on several studies to propose key components of intrinsic capacity that might be the focus of clinical assessment. Firstly, we use data from the English Longitudinal Study of Ageing (ELSA) to identify risk factors for care dependency in a generally healthy community dwelling population. We then use data from the Toulouse Frailty Clinic (France) to identify factors associated with prevalent care dependency, and then further test the results using data from the Hertfordshire Ageing Study (UK). From these analyses, we propose key domains of intrinsic capacity that may be relevant to detect important changes and transitions in functioning useful in clinical practice to predict and prevent care dependence.

We then discuss the requirements of the potential measures for each domain which might be suitable for use in a systematic approach to identify individual older people with levels of intrinsic capacity that are below, or declining faster than, age norms for the purpose of collaborative care planning which could include interventions to arrest or reverse declines in intrinsic capacity. These measures should be of value to health professionals in clinical practice and to policy makers when designing public health strategies intended to enable the maintenance of functional ability into older age.

Finally, the scope of the strategy and links with the long term management of NCDs and to long term care and support for people with care dependency, will be described. This will illustrate the potential added value of intrinsic capacity for these established pillars of health and social care of older people.
Introduction: the key role of intrinsic capacity

Healthy Ageing has been defined by WHO as “the process of developing and maintaining the functional ability that enables wellbeing in older age”. However, a hallmark of ageing is the exceptionally wide range of functional ability. At any given chronological age, some individuals remain active and independent, others need help to carry out essential everyday activities. (ADLs) Healthy ageing depends upon an individuals’ IC, their environment and the interactions between the two. The focus on IC has the potential to help clinicians better understand the biology of the person and to design personalised interventions to improve the health of individuals and the population as a whole.

Intrinsic Capacity (IC) is the composite of all the physical and mental capacities that an individual can draw upon at any point in their life. Figure 1 is a schematic that illustrates the range of capacity at different ages in the second half of life. At a population level, there is a general tendency for IC to decline from mid-adulthood onwards, although for most individuals this trend will not be smooth, but reflect multiple setbacks and potential recoveries. In populations where death usually occurs in older age, then towards the end of life, most people experience significant losses in IC. Preservation of mental and/or physical capacities in some 80 year olds means they have an overall IC more often associated with much younger people. Thus chronological age is inadequate for defining a person as at risk of negative events,

This variation in residual IC results from differences between individuals in their conditions of growth, development and aging. Furthermore, whilst declines in IC occur in the absence of diagnosed diseases (eg. NCDs) their presence may explain some of the variation in it, either temporarily or longer term. (1) Lifestyle, injuries, events and but also health or social interventions at different points across the life course will be major influences on trajectories of IC. This holistic perspective offers an entry point for the public health response to population ageing.

Limitations of the traditional response to functional decline in older people

Observable inability to undertake various activities of daily living (ADL) without assistance is a critical indicator of significant loss of intrinsic capacity. In clinical practice, the period of life
when functional losses become manifest, has traditionally been the domain of geriatricians. Clinical practice during this period has often been guided by a comprehensive geriatric assessment, and this approach has been shown to be more effective than standard care in reducing negative outcomes such as care dependence.

*Fig 2: Traditional way to address functional decline in older age*

Taking a more holistic life course approach, the WHO model of Healthy Ageing proposes that this period of significant loss of capacity is often preceded by earlier, more robust, health states. Any population of older people is likely to therefore also include sub populations with high and stable capacity or with capacity levels that are declining, but not yet at the point of requiring care and support. Individual trajectories between these states may not be smooth. Some individuals may never experience a high stable state: others may never experience a significant decline before death. In ageing populations however, many individuals will experience a significant decline, associated with functional limitations, before death.

The health and social needs of ageing populations are often complex and ongoing, spanning a range of areas of functioning, and waxing and waning over time. Traditional care models for people in later life are fragmented and inefficient. Even in countries with reasonably well developed health and social care provision, responses to challenges such as sensory deficits, incident diseases and difficulty with ADLs generally operate independently from each other. This can be reinforced by healthcare for people with several conditions (multi-morbidity) being provided in specialist silos. To meet these complex needs there must be fundamental changes to the focus of clinical care for older people. Instead of trying to manage an array of diseases and treat specific symptoms in a disjointed fashion, interventions should be prioritized in ways that optimize trajectories of older people’s physical and mental capacities.

The health and social needs of ageing populations are often complex and ongoing, spanning a range of areas of functioning, and waxing and waning over time. Traditional care models for
people in later life are fragmented and inefficient. Even in countries with reasonably well developed health and social care provision, responses to the complex clinical challenges brought by older persons remain inadequate because they fail to organize such complexity in an organized and person-tailored plan of action.

In contrast, an integrated person centered approach aims to offer a coordinated response. We propose that IC provides a unifying focus to understand their inter-relationships. The advantage of the IC concept is that it can incorporate the notion of frailty and the impact of diseases but is not defined by them: rather, these states are conceptualised as contributing at any point to an individual’s continuous trajectory of intrinsic capacity, which is the more proximal cause of functional decline. Services that starts with this holistic entry point and where effectiveness is assessed in terms of impact on these trajectories, are likely to provide much more integrated care than those that respond reactively to individual conditions.

Towards public health and clinical approaches incorporating intrinsic capacity

At present, the predominant public health paradigm involves health promotion, population wide preventative interventions such as vaccination, age-selective screening for occult disease (e.g. cervical cancer) assessments of risk factors for NCDs (e.g. lipids and blood pressure). Responses are based on these findings plus clinical manifestations. The initial innovation of geriatric medicine was to seek disease based explanations for functional decline. More recently, geriatric medicine has progressed to focus on geriatric syndromes and non-disease based assessments.

We propose that the next advance will be to systematically place assessments and responses to declines in intrinsic capacity as the central focus, augmented as necessary with explanatory from disease diagnoses and geriatric syndromes. For this, a longitudinal approach is required to monitor physiological and functional declines on both an individual and a population level. Determining the best and most cost-effective time to start monitoring characteristics, such as usual or fast gait, is challenging. Detecting an abnormal rate of decline is important since it is associated with a high risk of premature hospitalisation and/or death. If it were possible to identify the critical period when intrinsic capacity starts to fall before a clinical or functional threshold is reached, it might be feasible to invest in interventions that maintain intrinsic capacity. The determination of normative values for IC might also promote the idea that prevention against age-related limitations should not be confined to older ages, but start in adulthood. Research into factors that influence the timing and rate of declining capacities as well as the cost and efficacy of interventions is required to determine the optimal approach to preserving IC. It will also be necessary to detect, and measure the effects of, compensatory mechanisms that a person utilizes to overcome declining physical or mental capacities.

Figure 3 illustrates a theoretical model which could be used to monitor, maintain and maximize IC. The details of the domains etc are provisional. IC monitoring in combination with clinical assessments would be used to create a Comprehensive Health Care Plan. The implementation of evidence based, multidimensional IC programmes combined with the treatment of any underlying causes/diseases should result in the maximal IC possible for each individual as he/she moves from mid-life into older age.
Figure 3: How to monitor, maintain and maximize IC

In this model, interventions are person-centred and provided on an integrated care basis. Ideally, most could be delivered in the community within a primary healthcare setting by a multidisciplinary team.

The key for maintaining IC is that everyone can have access to the ‘comprehensive health assessment plus’. The ‘comprehensive health assessment plus’ includes assessment of intrinsic capacity and identification of associated underlining causes/diseases, as well as social care and support needs. These will inform a comprehensive care plan aimed to deliver multicomponent interventions to prevent or maintain intrinsic capacity, management and treatment of underlining diseases and address long term care and support needs.

The care plan therefore has several components; management of the changes in the trajectory of intrinsic capacity which includes interventions to prevent, slow or stop declines in IC. This is supported by treatments of specific conditions and, where needed, support to compensate for functional losses. What we are looking as the end goal is to maintain intrinsic capacity, not specifically to cure disease.

Remember that this is not for a traditional geriatric population, this is for people in the middle of the curve.

Strategies to implement these principles can be many, and will depend on the available human resources and level of development of national health systems. For example in some countries monitoring of intrinsic capacity can be undertaken daily, using self-management approaches and with help of mobile technologies. In other settings, community based strategies combining...
screening and incidental case finding could be more feasible as an approach to monitor trajectories of intrinsic capacity and identify the people most in need of care.

We have undertaken research looking into the operationalization of IC in two scenarios:

- The English Longitudinal Study of Ageing (ELSA) was used for presenting an example of IC operationalization in earlier phases of adulthood;
- The clinical database of the Frailty Clinic of the Centre Hospitalier Universitaire de Toulouse was used for operationalizing IC in older people at risk of care dependence.

The following sections will present a summary of the main results of these two studies and their implications for metrics and monitoring.

Full report of the two studies can be made available upon request.

**Clinical operationalization of intrinsic capacity during earlier phases of the adult life course – findings from the ELSA Study (the English Longitudinal Study of Ageing) ([https://www.elsa-project.ac.uk/](https://www.elsa-project.ac.uk/))**

While a significant body of research has explored the impact of a range of interventions on specific components of capacity as an outcome (for example physical capacity), fewer studies have examined how monitoring of the more comprehensive construct of IC might be used to improve clinical practice.

To fill this gap, we examined data from ELSA to assess whether a range of biomarkers and theory-driven capacity constructs might provide useful information on Healthy Ageing trajectories. We examined whether the ELSA data were consistent with the Healthy Ageing model, whether commonly used measures might provide a useful representation of intrinsic capacity in relatively robust individuals, and whether these IC indicators (alone or clustered) were predictive of subsequent loss of IADLs. We examined the factor structure of the individual variables and used structural equation modelling to assess longitudinally the direct and indirect relationships of a biomarker score, theory-driven constructs, personal characteristics and multimorbidity with subsequent IADL loss.

**Use of ELSA biomarkers as indicators of intrinsic capacity**

We limited analysis to ELSA participants who reported no losses of IADLs or ADLs at baseline. In an effort to explore parameters which might support detection of early changes in IC before the overt manifestation of clinical disease, we considered all objective biomarkers used in the study as potential indicators of the intrinsic capacity of the participant. We used factor analysis to identify if, and how, the biomarkers clustered, and derived a weighted aggregate score, which we interpreted as an estimate of intrinsic capacity. We tested longitudinally whether this overall measure, and the subdomains identified in factor analysis, predicted incident loss of activities of daily living.

We then considered these various characteristics in a structural equation model based on the WHO model of Healthy Ageing and examined the direct and indirect relationships of total intrinsic capacity score (and subdomains of intrinsic capacity) and other key factors including personal characteristics and multimorbidity on subsequent loss of IADLs.

It is important to note that the biomarkers included in the ELSA study are neither complete nor random. They were chosen by the ELSA investigators to inform specific research questions of...
interest, not to create the best overall measure of IC. Since these questions largely drew on existing knowledge and research priorities, they cover most domains that might be conceptualised within the notion of intrinsic capacity. However, some potential components cannot currently be measured objectively (for example mood or energy levels) and are lacking from the factor analysis. Nor is it likely that all the biomarkers included in ELSA operate at the same level. For example, some may be underlying drivers of capacity while others may directly reflect capacity. The biomarker set considered in this analysis can therefore be considered to be only relatively complete, but limited in its ability to measure some aspects of IC. The analyses presented can nevertheless be considered as an example to show the methodological approach and feasibility for the assessment of IC.

The best fit in the factor analysis for these biomarkers was achieved with a 7 factor structure that comprised the following domains: Strength, Sensory, Hypertension, Metabolism, Inflammation, Cognition, and Locomotion (Table 1). Total biomarker score and all sub domains except hypertension demonstrated a strong predictive validity for subsequent negative outcomes, even after accounting for the number of coexistent diseases in each participant (Table 2.). This suggests that this aggregate biomarker measure of intrinsic capacity provides additional information beyond that derived from traditional disease based assessments and provides support for our notion of the validity and potential utility of IC separate from multimorbidity.

**Table 1. Factor structure of biomarkers in ELSA**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Strength</th>
<th>Sensory</th>
<th>Cardiovascular</th>
<th>Metabolic</th>
<th>Inflammatory</th>
<th>Cognitive</th>
<th>Locomotor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait speed</td>
<td>0.2419</td>
<td>0.1960</td>
<td>0.0053</td>
<td>0.0660</td>
<td>-0.1546</td>
<td>0.1936</td>
<td>0.4068</td>
</tr>
<tr>
<td>Chair stand</td>
<td>0.1871</td>
<td>0.0796</td>
<td>0.0117</td>
<td>0.0734</td>
<td>-0.0791</td>
<td>0.1707</td>
<td>0.5288</td>
</tr>
<tr>
<td>Grip strength</td>
<td>0.7741</td>
<td>0.0472</td>
<td>-0.0178</td>
<td>0.0899</td>
<td>0.1694</td>
<td>0.0392</td>
<td>0.1588</td>
</tr>
<tr>
<td>Forced Expiratory Volume</td>
<td>0.6636</td>
<td>0.0523</td>
<td>0.0644</td>
<td>0.1388</td>
<td>-0.0317</td>
<td>0.0953</td>
<td>0.1056</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>-0.4841</td>
<td>-0.0047</td>
<td>-0.1056</td>
<td>0.5478</td>
<td>-0.0157</td>
<td>-0.1121</td>
<td>-0.1342</td>
</tr>
<tr>
<td>DHEAS</td>
<td>0.3996</td>
<td>0.0019</td>
<td>0.0351</td>
<td>-0.0514</td>
<td>0.0150</td>
<td>-0.0588</td>
<td>-0.0801</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.5378</td>
<td>-0.0021</td>
<td>0.1869</td>
<td>-0.0287</td>
<td>-0.0454</td>
<td>-0.0168</td>
<td>-0.0340</td>
</tr>
<tr>
<td>Average systolic BP</td>
<td>0.0098</td>
<td>-0.0012</td>
<td>0.6398</td>
<td>0.0082</td>
<td>-0.0669</td>
<td>0.0740</td>
<td>0.0184</td>
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<tr>
<td>Average Diastolic BP</td>
<td>-0.1570</td>
<td>-0.0497</td>
<td>0.9399</td>
<td>0.0115</td>
<td>0.1087</td>
<td>-0.0963</td>
<td>-0.0212</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.0311</td>
<td>0.0243</td>
<td>-0.2293</td>
<td>0.448</td>
<td>-0.1023</td>
<td>0.0684</td>
<td>-0.1416</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.2783</td>
<td>0.0206</td>
<td>-0.0333</td>
<td>0.4998</td>
<td>0.1101</td>
<td>0.0776</td>
<td>0.0865</td>
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<tr>
<td>LDL</td>
<td>-0.0082</td>
<td>-0.0529</td>
<td>0.1132</td>
<td>-0.3527</td>
<td>0.0136</td>
<td>-0.1088</td>
<td>-0.0170</td>
</tr>
<tr>
<td>HbA1C</td>
<td>-0.1417</td>
<td>-0.0355</td>
<td>0.0015</td>
<td>0.4631</td>
<td>-0.0882</td>
<td>-0.0194</td>
<td>0.0273</td>
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<tr>
<td>Fibrinogen</td>
<td>0.0330</td>
<td>0.0262</td>
<td>-0.0081</td>
<td>-0.0391</td>
<td>0.9967</td>
<td>0.0217</td>
<td>0.0604</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.0581</td>
<td>0.0145</td>
<td>0.0293</td>
<td>-0.1616</td>
<td>0.4622</td>
<td>0.0323</td>
<td>0.0524</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.1481</td>
<td>0.0760</td>
<td>0.0106</td>
<td>0.0223</td>
<td>-0.0444</td>
<td>0.5165</td>
<td>0.1712</td>
</tr>
<tr>
<td>Memory</td>
<td>0.0623</td>
<td>0.0590</td>
<td>-0.0049</td>
<td>0.0263</td>
<td>-0.1249</td>
<td>0.7662</td>
<td>0.0887</td>
</tr>
<tr>
<td>Near vision</td>
<td>0.0642</td>
<td>0.8509</td>
<td>-0.0084</td>
<td>0.0269</td>
<td>-0.0193</td>
<td>0.0305</td>
<td>0.0185</td>
</tr>
<tr>
<td>Distance vision</td>
<td>0.1175</td>
<td>0.8874</td>
<td>0.0183</td>
<td>-0.0004</td>
<td>0.0037</td>
<td>0.0255</td>
<td>0.0811</td>
</tr>
<tr>
<td>Hearing</td>
<td>-0.1464</td>
<td>0.3321</td>
<td>-0.0649</td>
<td>0.0204</td>
<td>-0.0999</td>
<td>0.1311</td>
<td>0.1318</td>
</tr>
</tbody>
</table>
### Table 2. Predictive Validity of Intrinsic Capacity (Biomarker Score) and Adverse Outcomes

<table>
<thead>
<tr>
<th>Predictors</th>
<th>ADL difficulties (RR)</th>
<th>IADL difficulties (RR)</th>
<th>Frailty index score (coefficient)</th>
<th>Frailty: phenotype 3 or more (RR)</th>
<th>Subjective health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0**</td>
<td>1.0**</td>
<td>0.1**</td>
<td>1.1**</td>
<td>1.0</td>
</tr>
<tr>
<td>IC Composite score</td>
<td>1.1***</td>
<td>1.2***</td>
<td>0.3**</td>
<td>1.2**</td>
<td>1.2**</td>
</tr>
<tr>
<td>Factor 1 (strength)</td>
<td>1.4*</td>
<td>1.3*</td>
<td>0.74**</td>
<td>N/A</td>
<td>1.2**</td>
</tr>
<tr>
<td>Factor 2 (sensory)</td>
<td>1.1**</td>
<td>1.2*</td>
<td>N/A</td>
<td>0.8**</td>
<td>0.8*</td>
</tr>
<tr>
<td>Factor 3 (vascular)</td>
<td>1.0</td>
<td>1.1*</td>
<td>-0.1</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Factor 4 (metabolic)</td>
<td>1.2*</td>
<td>1.1</td>
<td>0.56**</td>
<td>1.2**</td>
<td>1.4**</td>
</tr>
<tr>
<td>Factor 5 (inflammatory)</td>
<td>1.2 ***</td>
<td>1.1*</td>
<td>0.62**</td>
<td>1.9**</td>
<td>1.2**</td>
</tr>
<tr>
<td>Factor 6 (cognitive)</td>
<td>1.4 ***</td>
<td>2.1***</td>
<td>0.67**</td>
<td>1.5**</td>
<td>1.5**</td>
</tr>
<tr>
<td>Factor 7 (locomotive)</td>
<td>1.2 ***</td>
<td>1.4**</td>
<td>2.51**</td>
<td>N/A</td>
<td>1.8**</td>
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<tr>
<td>Number of chronic diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Ref</td>
<td>Ref</td>
<td>-</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>1</td>
<td>1.7</td>
<td>1.7***</td>
<td>-</td>
<td>2.7*</td>
<td>1.5*</td>
</tr>
<tr>
<td>2</td>
<td>2.2*</td>
<td>2.1***</td>
<td>-</td>
<td>2.5*</td>
<td>3.2**</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3.1**</td>
<td>3.1***</td>
<td>-</td>
<td>4.1*</td>
<td>8.1**</td>
</tr>
</tbody>
</table>

*** p value <0.001 ** p value <0.01 * p value <0.05

We further examined the predictive utility of these biomarker scores through structural equation modelling to examine the direct and indirect interactions of key characteristics derived from the WHO Healthy Ageing model. We included personal characteristics (sex, age, wealth, level of education and physical activity), total biomarker score (or set of sub domains), number of current health conditions, and assessed the relationship between these characteristics and the incident
development of IADLs in a later study wave (Figures 4 and 5). These models suggested that as hypothesised by the Healthy Ageing model, personal characteristics are strongly associated with the biomarker score (interpreted here as an indicator of intrinsic capacity), and that biomarker score was a significant predictor of subsequent outcomes after accounting for multimorbidity. In contrast to the Healthy Ageing model, multimorbidity was also found to independently predict outcomes, and some of the effect of biomarker score operated indirectly through multimorbidity.

Notably, chronological age was not directly associated with the incident loss of IADL’s, but operated through multimorbidity or the biomarker IC scores.

Figure 4. Direct and Indirect Relations between Personal Characteristics, IC and Incident Loss of IADLs
To test the predictive value of these biomarkers in the subpopulation of older people in more robust health, we limited the sample to participants with a total biomarker score within the top 75th percentile. The findings were consistent with those obtained from the total population.

This analysis suggests that a range of widely used biomarkers can provide objective measures of the new concept intrinsic capacity, independent of the health status of the individual. Both the total biomarker score as well as the clustering-generated subdomains provided information on subsequent health trajectories beyond what could be gained by a disease based assessment, and the relationships and interactions between the multiple characteristics examined in this analysis were generally consistent with the WHO Healthy Ageing model.

**Assessment of the theory based structure of IC for clinical operationalization**

While the biomarker based analysis described above points to the added value that information on intrinsic capacity and trajectories of capacity may provide to clinicians, the specific biomarkers included in the analysis were not selected on the basis of existing theory. Therefore, we undertook a similar, but theory driven, analysis of the same data set, drawing partially on the findings of the separate later section of this paper on biological theory and intrinsic capacity. This section proposes that intrinsic capacity might be considered in five domains: cognition, psychosocial, locomotion, sensory, and energy/metabolism related.

We therefore identified several variables within the ELSA dataset that might best capture these domains in order to conduct confirmatory factor analysis. The locomotion, cognition and sensory subdomains identified in the biomarker analysis were very consistent with this theory driven
framework and we retained these and the biomarkers within them in their previous structure. For the energy/metabolism domain we merged the biomarker subdomains of strength, metabolic and endocrine biomarkers, excluding HDL, LDL, BMI, hip to waist ratio and HbA1c as these do not fit the theoretical criteria for a component of capacity. We also excluded high and low blood pressure and inflammatory measures (which we similarly interpreted as drivers of change rather than measures of capacity). For the not previously clustered ew psychosocial domain, we included the score on the Geriatric Depression Scale (a subjectively reported but rigorous measure of mood) as well as psychological measures of control, autonomy, pleasure and self-realisation.

The factor frame for this second order confirmatory factor analysis is shown in Figure 6.

*Figure 6 Second Order Confirmatory Factor Analysis*

We used structural equation modelling to examine the relationships of these factors with the same variables that we considered for the biomarker analysis (personal, multimorbidity and incident IADL loss). Consistent with the previous analysis, low IC score had a significant direct relationship with subsequent loss of IADLs (Figure 7). Three factors (locomotion, cognition and sensory) had a
significant direct relationship with the incident loss of IADL as well as operating indirectly through multimorbidity (Figure 8). The other two (vitality and psychosocial) operated indirectly through either the other factors or through multimorbidity. The specific estimates for these relationships is shown in Table 3. When the outcome was changed from IADL to ADL loss, results were similar, but the psychosocial factor showed a significant predictive association with the outcome, whereas the link with the cognition factor became indirect.

*Figure 7. Structural Equation Model of Theory Derived Factor Score and Incident loss of IADL*
Figure 8 Structural equation modelling of IC factors with incident IADL loss
Table 3 Regression Weights: (Group number 1 - Default model)

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>S.E.</th>
<th>C.R.</th>
<th>P</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosocial &lt;- Wealth</td>
<td>.036</td>
<td>.003</td>
<td>13.019</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>Psychosocial &lt;- Education</td>
<td>.082</td>
<td>.010</td>
<td>8.088</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>Psychosocial &lt;- Age</td>
<td>-.017</td>
<td>.001</td>
<td>-16.597</td>
<td>***</td>
<td></td>
</tr>
<tr>
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<td>.274</td>
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<td>14.697</td>
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Implications for metrics and monitoring

The WHO Healthy Ageing model proposes that intrinsic capacity peaks in early adulthood and tends to decline from midlife. This decline is highly variable between individuals and within the same person over time, and between domains. This analysis suggests that assessment of intrinsic capacity, or biomarkers for it, may help understand where an individual sits at any point in time compared to...
the general population, and can serve as a predictor of functional issues in the future. The predictive value is independent of chronological age and multimorbidity.

A recent meeting convened by WHO on intrinsic capacity and frailty suggested that measures of capacity would have more clinical utility if they could be separated into specific domains that may have clinical relevance. In the present analyses, we developed a theory derived factor structure and a data driven structure and both had significant predictive value. Furthermore, there was great complementarity between the two approaches with three subdomains being entirely consistent between the two models, and one theory based domain comprising the aggregation of three data driven domains. The final theory based domain (psychosocial) could only be measured by subjective reporting and so was excluded from the data driven analysis.

While the five theory driven domains are certainly not final in their conceptualisation, they do therefore appear to be largely supported by the data. However, the biomarkers used in this analysis were chosen opportunistically, as they were present in the ELSA data, and the specific measures/biomarkers used to assess these 5 domains require further consideration.

It is also worth noting that in our analyses, the presence of disease was independently predictive of poor functional outcome. This suggests that the most informative clinical assessment would involve information on both IC and disease diagnoses, although the latter is not feasible in many settings. However, it also suggests that a systematic and comprehensive approach to measurement of IC should be included in comprehensive geriatric assessments (CGA). At present this is inconsistent and measures for some domains are often only capable of detecting advanced losses. The main focus of our analysis has been on older people with relative high levels of intrinsic capacity, with some analyses excluding participants who had already lost one IADL. Conventional CGA might render these people more homogenous than would be the case with improved tools to measure IC. This has two implications. Firstly it suggests it is likely to be of value to monitor intrinsic capacity from at least midlife. This may become more feasible as personalised medicine becomes more widespread. On the other hand, when capacity falls to a significant degree, the risk of experiencing an array of non-disease health states becomes high. These include frailty, incontinence, high risk of falls. We have not assessed these within this study, but it may be that once capacity falls to a certain point, information on these, too, should be collected. Monitoring of health state would therefore include consideration of capacity, disease and these geriatric syndromes.

Clinical operationalization in older people at risk of care dependence in later phases of the adult life course

Physiological changes and declines in multiple organs affect IC and are responsible for declines that generally start at mid-life. However, it is usually only at older ages that the physiological reserves and adaptation mechanisms are depleted to the point they become manifest as overt losses of capacity. As previously stated, traditional health assessments do not comprehensively capture these changes of IC. The period of life when (Instrumental) ADL losses become manifest may be preceded by a state of transition, often conceptualised as frailty, when loss of system reserve leads to weakness in the face of stressors.

In the next phase of our exploration of the potential operationalisation of the IC construct, we examined the findings from the Frailty Clinic of the Centre Hospitalier Universitaire de Toulouse. This clinic was established in 2011 to assess individuals aged 65 years and older identified as frail by their primary care physicians. The aims of this innovative service were to multidimensionally assess frailty in order to identify the underlying causes and develop personalised interventions against functional loss (2).
The Frailty Clinic dataset

This clinical database includes included sociodemographic, anthropometric and clinical characteristics plus simple and practicable means of measuring IC domains. Height and weight were measured to ascertain adiposity (BMI) and any unintentional weight loss in the previous three months was noted. The following were also assessed: grip strength; physical function using the Short Physical Performance Battery (comprising tests for balance, gait speed and chair stands)\(^3\); self-reported hearing impairment (Hearing Handicap Inventory for the Elderly – Screening (HHIES))\(^4, 5\); and self-reported urinary incontinence (Initial Standard Incontinence Screening Form)\(^6\). Measures of patients’ mental capacity and well-being included their cognitive function (Mini Mental State Examination (MMSE))\(^7\) and any depressive symptoms (Geriatric Depression Scale (GDS))\(^8\). Questionnaires were used to assess disability in Activities of Daily Living (ADL)\(^9\) and Instrumental ADL (IADL)\(^10\) and so to derive the outcome variables.

These data provided an opportunity to observe the specific assessment variables that were feasible in practice and to investigate the relationships between these and prevalent functional ability.

Analyses

Complete data were available for 1,057 participants. Predictors and outcomes were dichotomised. Predictors included: obesity (BMI ≥ 30kg/m\(^2\)); unintentional weight loss in the previous three months; low cognition (MMSE ≤ 24); depressive symptoms (GDS ≥ 6); weak grip strength (<26kg [men], <16kg [women]); slow gait speed; hearing impairment (HHIES > 8); and urinary incontinence (incontinence score>1). Outcomes were impaired ADL (score ≤ 5) and impaired IADL (score ≤ 3).

The associations between each predictor and the risk of functional impairments were examined using Poisson regression models with a robust variance estimator to yield relative risks. Predictors significantly associated with impaired ADL were then included in a mutually-adjusted model, along with gender and age. Internal construct validity was evaluated using principal component analysis and cluster analysis. The performance of a summary score, derived using predictors significant in mutually adjusted models for impaired ADL and IADL, was characterised using receiver operator characteristic (ROC) analysis.

Results

Slow gait speed and low cognition were associated with increased risk of both impaired ADL and IADL in mutually-adjusted analyses. Obesity and incontinence were additional indicators of impaired ADL, and weak grip strength was an additional indicator of impairment in IADL. ROC analysis of these mutually-adjusted models resulted in an area under curve (AUC) of 0.82 for ADL (95% CI 0.80-0.85) and 0.81 for IADL (95% CI 0.78-0.85).

A score based on the number of these five adverse characteristics was strongly associated with risk of ADL and IADL impairment and prediction models based only on this score had high AUC values for these outcomes in ROC analyses. PCA analyses and cluster analyses separated individuals into two groups. One group had good health regarding most of these five attributes and the other group had poorer health.
Figure 9: Indicators associated with limitations in functioning

Relative risk of impairment in ADL/IADL

- Obesity
- Unintentional weight loss
- Low cognition (MMSE < 24)
- Mild-severe depression (GDS > 6)
- Weak grip strength
- Slow gait speed (≥ 0.8 m/s)
- Poor hearing
- Incontinence
- Age (SD change)
- Gender (female)

ROC (95% CI):
- ADL: 0.62 (0.50, 0.75)
- IADL: 0.92 (0.78, 0.95)

Figure 10: Indicators associated with limitations in functioning, score based analysis

Principal component analysis of binary predictors

<table>
<thead>
<tr>
<th>Binary predictors</th>
<th>First component coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese (BMI ≥ 30 kg/m²)</td>
<td>0.05</td>
</tr>
<tr>
<td>Unintentional weight loss</td>
<td>0.20</td>
</tr>
<tr>
<td>Low cognition (MMSE &lt; 24)</td>
<td>0.38</td>
</tr>
<tr>
<td>Mild-severe depression (GDS &gt; 6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Slow gait speed (≥ 0.8 m/s)</td>
<td>0.54</td>
</tr>
<tr>
<td>Weak grip (&lt;26 kg [M], &lt;16 kg [F])</td>
<td>0.48</td>
</tr>
<tr>
<td>Hearing impairment (HIES &gt; 0)</td>
<td>0.23</td>
</tr>
<tr>
<td>Incontinence score ≥ 1</td>
<td>0.36</td>
</tr>
</tbody>
</table>

PCA was based on the tetrahedral correlation matrix of binary predictors

Variance explained by first component 27%

- For each participant, the coefficients for the presence of the above characteristics can be summed to obtain a score
- Higher scores would be assigned to participants with poorer health states
- Analysis replicated slow gait speed, reduced grip strength and low cognition as most influential contributors to summary score
Testing these indicators in the Hertfordshire Ageing Study:

We used datasets from the Hertfordshire Ageing Study to ascertain whether the indicators derived from associations with prevalent functional losses were predictive of incident loss in function. The Hertfordshire Ageing Study (HAS) has been described previously (11). In brief, 292 men and women born in Hertfordshire between 1920 and 1930 and still living there were invited in 2003/5 to attend a research clinic for detailed characterisation of their health behaviours and sociodemographic and clinical characteristics. Data on birth weight and weight at one year were extracted from historical ledgers maintained by health visitors in the 1930s.

A nurse-administered home interview was used to elicit information on: cognitive and physical frailty (Strawbridge questionnaire)(12); cognitive function (Mini-Mental State Examination) (13); and depressive symptoms (Hospital Anxiety and Depression Scale (HAD-D)) (14). Details of all prescribed and over-the-counter medications were obtained and coded according to the British National Formulary, and then used to determine the number of systems medicated as a marker of comorbidity.

Participants subsequently attended a research clinic for the measurement of: height and weight (used to ascertain BMI); grip strength (using a Jamar dynamometer and standardised protocol) (15); gait speed (on a 3m walk); and hearing threshold (by standardised audiology tests in both ears).

Analyses

Predictors for the analyses included: adiposity (BMI); cognition (MMSE); depression score (HAD-D); grip strength; gait speed; hearing impairment (Worse Hearing Threshold); multimorbidity (number of systems medicated); birth weight; weight at one year; and conditional infant weight gain. Outcome variables were deficiency in the Strawbridge physical domain, and deficiency in the Strawbridge cognitive domain.

When the score derived in the Toulouse dataset analysis was replicated in the Hertfordshire Ageing Study, it was strongly associated with Strawbridge physical domain but its association with cognitive domain was much weaker. Although significant univariate predictors of physical and cognitive impairments were similar to the predictors of IADL and ADL found in the Frailty Clinic database, significant mutually-adjusted associations differed between the two studies.

The significant predictors of functional decline (Strawbridge physical and cognitive deficits) in mutually-adjusted analysis found in the Hertfordshire data-set were: Physical: increased adiposity, higher depression scores, slower gait speed, weaker grip strength, increased multimorbidity and higher conditional infant weight. With cognition: only depression and multimorbidity showed significantly associations.

Implications for metrics and monitoring

The IC score (derived in the same manner as used in the Toulouse Frailty Clinic analysis) was strongly predictive of subsequent declines in the Strawbridge physical domain. This suggests that an operational definition of intrinsic capacity using measures of cognition, gait speed, grip strength, BMI, urinary incontinence and depressive symptoms may be useful in identifying older people with, or at high risk of, care dependence. All of these assessments can take place at a primary care level.

All the proposed elements are consistent with previous literature and theoretical models, except urinary incontinence. This may be an overlooked component of IC, or an underlying cause of
declining IC (for example leading to depression or lower levels of physical activity) or be a marker of other physiologic losses that are captured by other IC tests (for example neurological function). Changes in energy expenditure brought by the ageing process expressed as exhaustion and fatigue could likely be part of the construct and needs to be further investigated.

Clinical research evidence for domains supporting the construct of intrinsic capacity

An extensive literature review was undertaken to both inform these analyses and to ascertain whether the indicators/predictors and domains identified by the Toulouse Frailty Clinic and ELSA analysis for the operationalization of intrinsic capacity in clinical settings were supported by existing evidence.

Identification of the domains defining intrinsic capacity

In 1999, Stuck and colleagues (16) conducted a systematic review of the literature aimed at measuring the strength of evidence linking different risk factors to the transition to care dependence in older persons. The study is considered a seminal paper for geriatric medicine, and subsequently informed the preparation of an evidence review by the WHO Regional Office for Europe (17). From the list of risk factors identified by Stuck and colleagues (16), mood (i.e., depressive symptoms), cognition, physical performance, energy expenditure (i.e., weight loss, abnormal body mass index), and vision (i.e., reduced visual acuity) were indicated as strongly associated to incident declines in function. These results were confirmed by subsequent systematic reviews (18), even when the analysis of literature was restricted to data coming from low-and-medium-income countries (19).

In a recent study published by Chaudhry and colleagues (20), several age-related impairments (again, mainly identified from the Stuck and colleagues’ review (16)) were explored for their capacity to predict functional declines. Impairments in muscle strength, mobility, cognition, vision, hearing, and mood were all associated with an increased risk of incident mobility disability (defined as severe difficulty or inability to climb 10 steps or walk ¼ of mile). Consistent results (except for a non-statistically significant result for hearing impairment) were reported for incident loss of ADL.

Taking into account this and other evidence, five different domains are proposed as of primary interest for framing the biological background of intrinsic capacity: 1) cognition, 2) mood 3) sensory 4) vitality/energy balance, and 5) locomotion.
The domain of cognition
Among individuals, cognitive function undergoes extremely heterogeneous patterns of modification with increasing age. Cognitive subdomains show moderate correlations in their rate of age-related changes, suggesting that the diversity of trajectories is primarily explained by the specific characteristics of the individual(21). Moreover, it has been shown that people experiencing steeper declines in cognitive function have a higher risk of negative health-related outcomes(22). Thus, cognitive function may be an important component of an age-independent, individual-specific, and dynamic risk profile.

The relationship between cognitive and physical capacity is very strong. Analyses conducted in the Canadian Study of Health and Aging showed that the severity of cognitive decline is associated with a hierarchy of functional loss(23). Cano and colleagues(24) showed that decreasing levels of cognitive performance are directly associated with increasing severity of frailty (i.e., a condition of extreme vulnerability to exogenous and endogenous stressors, responsible for exposing the individual at increased risk of negative health-related outcomes(25)). Consistently, it has been reported that older people with poorer cognitive function present more rapid decline of gait speed over time compared to individuals with normal cognition(26). Cognitive and physical impairments have shown to independently contribute to the risk of care dependence(27).

The domain of mood
Frailty was originally conceived by Fried and Walston as a vicious cycle, predominantly characterized by physical risk factors for functional loss and dependence(28). It has been argued that model may capture a biased and partial subpopulation of frail individuals (characterized by “physical” issues), and not adequately consider the influence that mood and cognition may play in the disabling cascade(29). Indeed, as for cognition, mood has a strong and close relationship with the functional status of the individual and there is also a close relationship between mood and cognition themselves.. Depressive symptoms may represent an independent risk factor for severe loss in capacity, or synergistically act with other conditions in the determination of the functional loss(30).
In the Established Populations for Epidemiologic Studies of the Elderly (EPESE), the severity of depressive symptoms experienced by the participants showed a gradient of risk for subsequent physical decline (31). The results were confirmed even after analyses were restricted to individuals with no ADL or mobility disability at the baseline. These findings suggest that mood assessment may support strategies for the early identification of individuals at risk of transitioning to functional losses. Also noteworthy is the close relationship of depressive symptoms with other risk conditions threatening the healthy aging of the individual, such as the poor emotional vitality (32), fatigue (33), and pain (34).

### The domain of sensory functions

Sensory impairments (e.g. poor vision and hearing capacity) have important implications for the health status and functioning of the individual (35). In 2015, sense organ disorders represented the second leading cause of years lived with disability and counted for more than 68 million disability-adjusted life-years (DALY) (36).

The prevalence of vision impairment significantly increases with age (37), and such trend is reported worldwide (38). Vision impairment may increase the risk of subsequent care dependence (37) by acting on/enhancing different clinical mediators (e.g., depression (39), mobility impairment (40), and falls 28). Visual impairment may also limit physical activity and social engagement. Interestingly, the prevalence of vision impairment has been decreasing over the last twenty years in high- as well as in low- and medium-income countries (38), indicating the great potentialities for improving the populations’ health status by intervening on this condition (36).

Hearing impairment results in an even greater burden of disease in older populations, (1) although a weaker association has been reported between hearing loss and declines in physical capacity (37). Nevertheless, studies have shown that hearing impairment may still play an important role in the onset of negative health-related outcomes (e.g., incident care dependence and institutionalization), perhaps following a gender-specific pattern (41). Systematic reviews and meta-analyses have also demonstrated that amplification is beneficial in individuals with untreated sensorineural hearing loss in terms of quality of life by acting on the reduction of psychological, social, and emotional burdens of the condition (42, 43).

### The domain of energy balance

Modifications occurring in energy expenditure and metabolism have been repeatedly indicated as directly involved in the process of aging. A decline of energy expenditure (due to the parallel reductions of resting metabolic rate and activity energy expenditure) occurs with age across species (44). At the same time, inadequate diet may determine an altered intake of nutrients and energy, disrupting the metabolic homeostasis and exposing the individual to the risk of malnutrition. Obesity is also associated with incident disability. Markers of malnutrition such as weight loss and low or high body mass index, are frequently indicated as targets of intervention for preventing functional decline (16, 45).

It should be acknowledged that nutrition per se does not completely fit with the model of intrinsic capacity, which is focused on the intrinsic attributes that enable an individual to perform. Nevertheless, the capacity of the organism to receive and elaborate dietary nutrients may still define a special body function able to affect the individual’s functioning and wellness. It is also noteworthy how the mechanisms related to the diet consumption, absorption, and processing constitute a complex network of body functions mirroring the health status of the individual. In fact, malnutrition may be caused by social issues (e.g., isolation, poverty), but also by physiological (e.g.,...
gastrointestinal conditions, oro-nasal conditions) and psychological (e.g., depression) conditions affecting the eating process.

Diseases also affect energy homeostasis through various mechanisms impacting the quantity and quality of food intake, malabsorption, changed metabolic mechanisms and protein-energy requirements etc. Malnutrition may play a role in the development of sarcopenia, including sarcopenic obesity. Studies have speculated that measures of malnutrition may adequately serve as surrogate tools for the frailty assessment. Finally, nutritional interventions are able to positively change body composition, intrinsic capacity notably strength and delay care dependency.

**The domain of mobility and muscle strength (locomotion)**

Mobility is strongly associated with health status across species. In older age, measures of mobility, such as the gait speed, present a linear relationship with the risk of negative health-related outcomes. In pooled analyses of 9 cohort studies, Studenski and colleagues demonstrated that it is possible to accurately estimate the life expectancy of an individual aged 65 years or older by simply knowing age, sex, and gait speed. In this study, nomograms of gait speed were also provided with the aim of supporting clinical decisions. Consistent findings have also been reported for other outcomes, including incident disability and dependence.

Data like these indicate that measures of mobility may indeed capture something more than muscle functioning, and rather represent comprehensive markers of wellbeing. In this context, a large body of evidence demonstrates the relationship between measures of mobility with subclinical pathophysiological changes, such as increased atherosclerotic formation, decreased aerobic capacity, or inflammatory status.

Age- and sex-dependent trajectories have been described for muscle strength. The rapid increase of muscle strength during the first decades of life and its gradual decline after the age of 40 have been consistently shown in literature, independently of the world regions. At the same time, muscle strength is a strong predictor of negative outcomes (including care dependence), even over the long term.

In recent years, measures of muscle strength and mobility have been combined in algorithms defining age-related conditions, such as sarcopenia. In other words, these markers have been considered as the clinical manifestation of physiological declines occurring in systems necessary for the proper functioning of the individual. It is noteworthy that the physical decline of the individual (in terms of increasing muscle weakness and poor mobility) has been repeatedly evoked as an “additional vital sign” for older persons, a key component of the CGA, and/or the lever for overcoming obsolete paradigms of traditional medicine (e.g., the concept of disease as the center of medical activities).

**Implications for metrics and monitoring**

There is extensive evidence supporting several domains of health status that may be considered in the development of the intrinsic capacity construct. Cognition, mood/depressive symptoms, mobility and muscle strength, sensory, and energy utilization seem the most robust candidates corroborated (at this time) by a larger body of evidence.

**Measurements for identifying people with declining capacity in the selected domains**
Systematic rapid reviews were carried out to determine the validity and reliability of the more commonly studied and better validated screening and diagnostic measurements for: malnutrition, cognitive impairment, depressive symptoms, mobility impairment (i.e. low gait speed and poor grip strength), vision impairment and hearing impairment. The main objective of the commissioned reviews was to assess the psychometric properties of valid screening tests. The review was limited to studies investigating the use of these instruments in a primary care or community setting, rather than in specialist medical practice.

We report here on the diagnostic accuracy and capability of the measures/tools to classify older persons correctly as having or not having declines in physical and mental capacities. In each case the cut-off for the categorical definition was determined by the studies according to their reference condition (e.g., GDS depressive symptoms in relation to diagnosis of clinical depression). The analysis of the instruments also comments briefly on their feasibility and acceptability in the clinical setting. For more details on methods and results see ANNEX 1.

Table 4 summarizes the main results of the review:

<table>
<thead>
<tr>
<th>Domain parameter</th>
<th>Putative measures of physical and mental capacities for ICOPE Screening tool</th>
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<tbody>
<tr>
<td>Screening tool</td>
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<td>Source of information</td>
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<td>Setting</td>
<td>Primary care</td>
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</table>
These instruments are used in the context of screening for conditions that are associated with declines of intrinsic capacity on people at risk of care dependence, as per previous discussion in this paper. These current tests and tools have not being used on mild-life adults or for monitoring purposes, and we believe that they would be inappropriate for that use.

New performance tests will need to be developed for younger older adults, to capture initial loss in capacity, for example gait speed test may need to be replace by stress performance tests in mid-life adult populations.

### Concluding remarks and provisional recommendations for metrics and monitoring

Key points arising from this paper include:

1. Assessment of intrinsic capacity appears to have clinically relevant predictive value beyond that provided by traditional disease based assessments.
2. For clinical utility, IC needs to be decomposed into sub domains that can inform clinical responses. A review of past research and our own analysis supports a subdomain structure including locomotor, cognitive, sensory, psychosocial and vitality/energy domains.
3. The instruments used to measure these domains may need to be tailored to specific levels of IC. Traditional geriatric instruments may be of most value for those with significant losses of capacity, while more subtle biomarkers may be most informative for those with relatively high levels of capacity.
4. For individuals with overt losses of capacity, a final set of six screening instruments that showed adequate accuracy and predictive ability for measuring six proposed domains of intrinsic capacity:
   - Mobility: SPPB (73)
   - Vitality/Energy balance - measure of malnutrition: MNA-SF (69)
   - Psychosocial - measure of depressive symptoms: GDS-15 (68)
Cognitive: MMSE (70)
Sensory - Hearing: WVT (71), Vision: PEEK (72)

The multiple analyses described in this paper have provided support for the potential value of measuring intrinsic capacity (in addition to more traditional disease based assessments) in clinical practice. Further, studies of relatively healthy “young old” populations and older populations at the point of transitioning to care dependency have identified a reasonably consistent set of key components of intrinsic capacity associated with incident or prevalent poorer health states (ie. losses of the “functional ability that enables wellbeing in older age”). Developing a composite measure of IC that encompasses all of the factors that affect IC is likely to be very challenging and may involve weighted scoring systems. It may be that individual older people vary in the importance they ascribe to declines of capacity in the various domains. Whether this refinement should be built into the composite score, or individual preferences better considered at the stage of collaborative care planning needs some consideration.

Hard endpoints should be selected to determine the cost effectiveness of long term monitoring of IC; potential endpoints include hospitalisation, care dependency, and fractures. The relationships between IC, functional ability and quality of life (QoL) in older people should also be investigated.

**Implementation**

At present, people are familiar with going to a healthcare facility as patients because of specific symptoms or for routine diagnostic tests rather than for a general assessment of their health. In low and middle income countries (LAMICs), community based healthcare workers and volunteers could be trained to monitor older people using a similar approach to that utilised by maternal-child healthcare workers. In high income countries (HICs), self-operated computerized systems can be used to carry out routine tests, thus minimising the need for human resources. Good algorithms are needed to analyse health metadata from these systems, smart phones and wearable devices, so that the interpretation of the information is as simple as possible and can be used to advise people about how to enhance their IC and functional ability. The reliability and accuracy of data obtained from these devices must be evaluated.
References


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