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Biochemical measures and frailty in people with intellectual disabilities

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Abstract

Introduction: People with intellectual disabilities (ID) are earlier frail than people in the general population. Although this may be explained by lifelong unfavourable social, psychological and clinical causes, underlying physiological pathways might be considered too. Biological measures can help identify pathophysiological pathways. Therefore, we examined the association between frailty and a range of serum markers on inflammation, anaemia, the metabolic system, micronutrients and renal functioning.
Methods: Participants ($n = 757$) with borderline to severe ID (50+) were recruited from three Dutch ID care and support services.
Results: Frailty was measured with a frailty index, a measure based on the accumulation of deficits. Linear regression analyses were performed to identify associations between frailty and biochemical measures independent of age, gender, level of ID and the presence of Down syndrome. Frailty appears associated with inflammation (IL-6 and CRP), anaemia, metabolic markers (glucose, cholesterol and albumin) and renal functioning (cystatin-C and creatinine).
Discussion: These results are in line with results observed in the general population. Future research needs to investigate the causal relation between biochemical measures and frailty, with a special focus on inflammation and nutrition. Furthermore, the possibility to screen for frailty using biochemical measures needs to be used.

Keywords: *frailty, people with intellectual disability, physiological measures, inflammation, nutritional status, older people*

Introduction

Although people with Down syndrome and people with severe intellectual disabilities (ID) have shorter life expectancies than the general population, the average life expectancy of people with ID is increasing [1]. As a result, frailty, a state in which older people are prone to negative health outcomes including disability, hospitalisation,

institutionalisation and premature death [2], can become a major problem. In people with ID, early onset and high levels of frailty were observed [3], but the underlying pathways leading to the early onset of frailty in this population have not yet been investigated.

Frailty is a complex cascade that involves several physiological alterations, eventually leading to loss of function and failure to respond to stressor events [2]. The physiological mechanisms underlying the onset and development of frailty remain complicated and poorly understood. Even so, frailty has been associated with dysregulation in several physiological systems including the inflammatory system, the endocrine system, musculoskeletal functioning, metabolism and specific diseases including cardiovascular diseases and renal failure [2]. Biomarkers involved in these mechanisms have been associated with the prevalence [4] and incidence of frailty [5, 6, 7]. Although several biochemical measures show strong associations with frailty, there is not yet one biomarker that can adequately identify frailty [8]. Nevertheless, information on biochemical measures can provide useful information on underlying physiological processes leading to frailty. For example, nutritional deficiencies could reflect insufficient (micro)nutrient intake, problems with the gastrointestinal tract or an increased utilisation. Knowledge about the relation between (micro)nutrient status and frailty could promote interventions to limit (micro)nutrient deficiencies. In addition, eventually biochemical measures can help to screen and identify those at high risk to develop frailty (Figure 1).

Knowledge about dysregulation in physiological systems and its association with frailty has not yet been investigated in people with ID. Information from the general population might not be applicable to the ID population, because the development of frailty and its relation with biochemical processes may be different in this population because of lifelong unfavourable chronic conditions, environmental factors, life style and genetic factors (Figure 1). Previously, Carmeli *et al.* [9] found high inflammatory markers in healthy adults with unspecified ID compared with those without ID, but it has not yet been studied whether these high inflammatory markers are associated with overall health status. Therefore, in the present, explorative study, we aimed at assessing the association between frailty (in terms of deficit accumulation) and physiological processes in older people with ID.

Materials and methods

Subjects and study design

This study was part of the 'Healthy aging and intellectual disabilities' study (HA-ID) [10]. In this observational study, information was collected on the general health status of older people with ID using formal care in the Netherlands. Three Dutch care provider services for people with ID offering a broad spectrum of care, ranging from ambulatory support to residential care, collaborated in this study. Together they provided care to 2,322 clients with borderline to profound ID aged 50 and over, who were all invited to participate. Eventually, 1,050 clients participated in the HA-ID study, forming a study population nearly representative for the Dutch population of adults aged 50 and above with ID who receive formal care. Those capable of understanding the available information signed the consent form themselves. Legal representatives were approached for those not able to make this decision. Details about recruitment, design, inclusion criteria and representativeness have been published elsewhere [10]. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC-2008-234) and the ethics committees of the participating care organisations approved this study. Data collection included body measurements, physical fitness tests, questionnaires and laboratory tests in

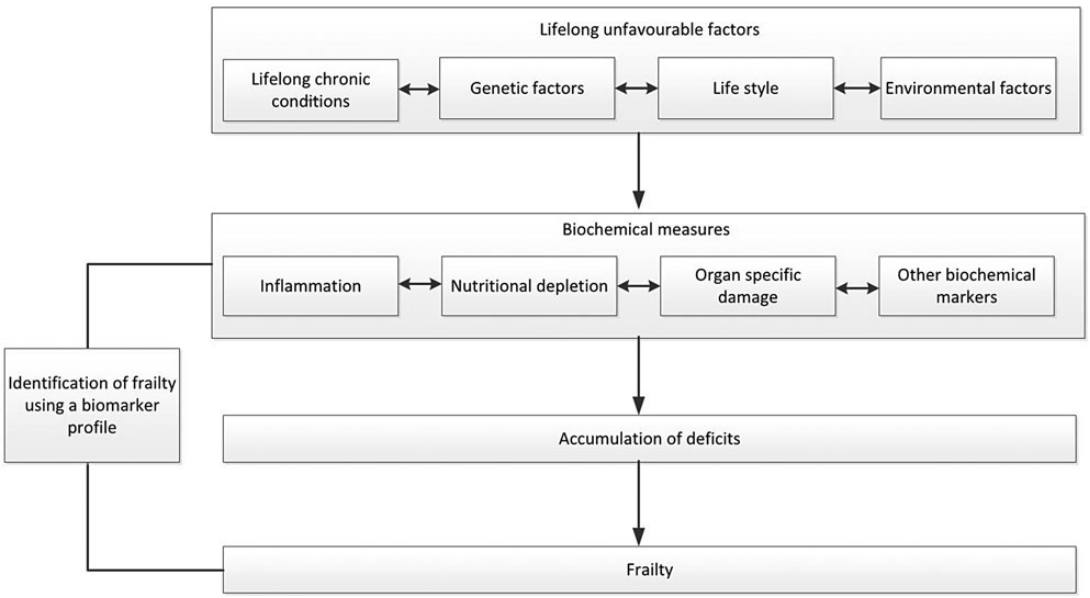

Figure 1. Schematic representation of the pathway of frailty and the role of biochemical measures.

addition to file records. Data on age, gender and residential status were retrieved from the administrative systems. Residential status was categorised as centralised setting, community-based setting and living independently or with relatives with ambulatory support. Level of ID was obtained from the records of behavioural therapists and psychologists and was classified as borderline (intelligence quotient (IQ) 70–80), mild (IQ 55–70), moderate (IQ 35–55), severe (IQ 25–35) or profound (IQ < 25).The presence of Down syndrome was retrieved from the medical files. Medical files were used to determine the used medication. The following ATC codes were used to classify drugs that could interfere with the included biochemical values: A10 for glucose-lowering drugs, B03A for haemoglobin-related drugs, C10 for lipid-lowering drugs, A12A for calcium supplements, and A11CC and A11CB for vitamin D supplements.

Blood samples

Blood samples were drawn in Becton Dickinson collection tubes by a trained medical assistant in the morning following an 8 h overnight fast (November 2008–July 2010). The samples were centrifuged, and serum was stored at −80°C until the measurements. CRP, haemoglobin and all metabolic markers were analysed at the laboratory of the Erasmus Medical Center, which is a reference laboratory. Calcium was determined on a Beckman Coulter DxC analyser. Vitamin-D3 (25-OH vitamin-D) measurements were performed using an electrochemiluminescence immunoassay with polyclonal antibodies on a Cobas-E module (Roche Diagnostics®, 128 Penzberg, Germany). Creatinine and cystatin-C were measured using the Cobas 8000 Modular Analyzer from Roche Diagnostics AG (Rotkreuz, Switzerland). IL-6 was analysed for this study specifically. The level of IL-6 was quantified using a sensitive enzyme-linked immunosorbent assay (ELISA; Human IL6 Elisa Ready-SET-Go! cat no. 88-7066). The lower detection limit for IL-6 was 19.5 pg/ml.

Constructing the frailty index

Frailty was measured with a frailty index (FI), an operationalisation of frailty that focuses on the quantity, rather than on the nature of health problems [11]. It captures physical, psychological and social health and has been shown to predict negative health outcomes in several clinical and community-dwelling populations [2, 11]. Following a standardised procedure [12], we developed an FI with data collected in the HA-ID study. The index consisted of 51 deficits that were all (i) related to health, (ii) positively associated with age, (iii) frequently but not too often present in the population (>5%, <80%) and (iv) no more than 30% of the outcomes values were missing. Furthermore, the deficits did not correlate too strongly with each other ($r < 0.7$), and together, they covered different health aspects. All deficits were re-coded to a score between 0 (deficit absent) and 1 (deficit present). An FI score was calculated by the number of present deficits divided by the total number of measurements, resulting in a score ranging from zero (lowest level of frailty) to one (highest level of frailty). A complete list of the deficits, used measurements and cut-off values has been presented elsewhere [3]. Cholesterol, glucose and haemoglobin were originally included in the FI. Therefore, per definition, these measures are somewhat correlated with the FI. To eliminate this correlation, the index was recomposed without the item of interest for each biochemical measure.

Statistical analysis

First, to test for selection bias, participants for whom blood samples were available were compared with non-participants using Pearson χ^2 tests (categorical variables) and *t*-tests (continuous variables). Second, regression analyses were performed with the biochemical measures as dependent variables and the FI as independent variable. Linearity between biochemical measures and frailty could not be assumed. Therefore, a curve estimation procedure was used to find the best fit of the model for each biochemical measure and if required a polynomial effect was added to the model. The physiological measures were incorporated into the models on a continuous scale, with an exception for IL-6, which was dichotomised at the detection limit (19.5 pg/ml). Three different linear regression models were created. The first analysed the unadjusted association between the biochemical measures and frailty (to aid interpretation, multiplied by 100). Participant's characteristics (gender, age, level of ID and Down syndrome) were entered into a second model. Dummy variables were composed for Down syndrome (the presence of Down syndrome or unknown status versus no Down syndrome) and for the level of ID (moderate or severe/profound versus borderline/mild). Furthermore, potential confounders were entered per biochemical measure: vitamin D was adjusted for vitamin D supplementation and the period (summer/winter) of blood collection, calcium for calcium supplementation, anaemia for iron supplementation, glucose for glucose-lowering drugs and cholesterol/HDL/triglycerides for lipid-lowering drugs. The third model incorporated all biochemical measures from the same functional category and the baseline characteristics. The following functional categories were defined: inflammation (CRP and IL-6), anaemia (haemoglobin), micronutrients (vitamin-D and calcium), metabolic markers (glucose, triglycerides, cholesterol and albumin) and renal functioning (creatinine and cystatine-c). SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Results were considered statistically significant if the *P* value was <0.05.

Results

Baseline characteristics

For 757 out of 1,050 of the HA-ID participants, at least one biochemical measure was available; 293 participants were excluded, because they had no information on biochemical measures. The included participants did not show significant differences with regard to gender, level of ID, age and the presence of Down syndrome (Table 1). Those who were

Table 1. Baseline descriptive characteristics of the HA-ID study

	Included	Excluded	All	Statistics	
				Test	*P* value
n	757	293	1,050		
Age (mean (SD))	61.7 (8.0)	61.6 (8.3)	61.6 (8.0)	0.43	0.93
Gender (%)				0.55	0.46
Male	394	145	539		
Female	363	148	511		
Level of ID (%)				4.86	0.30
Borderline	19	12	31		
Mild	154	69	223		
Moderate	373	133	506		
Severe	128	44	172		
Profound	70	21	91		
Unknown	13	14	27		
Down syndrome (%)				0.03	0.87
Yes	111	38	149		
No	544	180	724		
Unknown	202	75	177		
FI score (mean (SD))	0.28 (0.12)	0.26 (0.14)	0.27 (0.13)	2.10	0.036
Residential status				33.5	<0.001
Central setting	430	127	557		
Community based	296	137	433		
Ambulatory support	30	20	50		
Unknown	1	9	10		
Biochemical measures	*n*	mean (SD)/number of abnormal values (%)			
CRP (mg/l)	723	6.84 (18.0)			
IL-6 (%, >19.5 pg/ml)	622	63 (10)			
Haemoglobin (mmol, Fe/l)	735	8.74 (0.83)			
Vitamin D (nmol/l)	618	63.3 (33.4)			
Calcium (mmol/l)	585	2.22 (0.12)			
Glucose (mmol/l)	724	5.01 (2.6)			
HDL (mmol/l)	724	1.25 (0.38)			
Triglycerides (mmol/l)	724	1.43 (0.76)			
Cholesterol (mmol/l)	723	5.29 (1.04)			
Albumin (g/l)	724	42.2 (3.83)			
Creatinine (μmol/l)	634	75.2 (19.9)			
Cystatin-C (mg/l)	634	1.05 (0.26)			

SD, standard deviation; ID, intellectual disability, the total number of included biochemical measurements depended on the availability and successfulness of the laboratory measurements.

excluded showed slightly lower mean FI scores and were more often living in the community compared with the included participants.

Association between frailty and available biochemical measures

Unadjusted and adjusted for age, gender, level of ID and Down syndrome, higher FI scores were associated with higher levels of IL-6, CRP and cystatin-C and with lower levels of haemoglobin, cholesterol, glucose and albumin (Table 2; Models 1 and 2), although the associations between cholesterol and IL-6 weakened after adjusting for other biochemical measures from the same system (Table 2; Model 3). Calcium and creatinine showed a non-linear association with the FI score; either a high or a low calcium/creatinine level was associated with higher FI scores.

Discussion

For the first time, we showed associations between frailty and biochemical measures in a large, nearly representative, population of older people with ID (50 years and over) receiving specialised support or care. Frailty was associated with inflammation, anaemia, metabolic markers and renal functioning.

Chronic inflammation can result in organ damage, muscle waste and chronic diseases, which all contribute to frailty [2]. The other way around, inflammation arises as a consequence of chronic diseases such as atherosclerosis, Alzheimer dementia and type 2 diabetes [13]. For years, IL-6 has been called the cytokine for gerontologists [14], and IL-6, CRP and other inflammatory markers have frequently been associated with both ageing and frailty [15, 16]. In line, we found that elevated levels of IL-6 and CRP were associated with higher FI scores.

The consequences of low levels of haemoglobin (e.g. fatigue, low muscle strength, cognitive decline) are frequently

Table 2. The unstandardised and standardised regression coefficient (β) with 95% CI, for the predictive value of biochemical measures for frailty

System	Biochemical measure	*n*	Model 1		Model 2		Model 3	
			B (95% CI)	β	*B* (95% CI)	β	*B* (95% CI)	β
Inflammation	IL-6 <19.5 pg/ml	594	**4.73 (1.42 to 8.04)**	**0.11**	**3.57 (0.76 to 6.39)**	**0.09**	2.50 (−0.37 to 5.38)	0.06
	CRP	685	**0.14 (0.09 to 0.20)***	**0.20**	**0.09 (0.05 to 0.14)***	**0.14**	**0.08 (0.03 to 0.12)**	**0.11**
Anaemia	Haemoglobin	691	**−5.24 (−6.31 to −4.17)***	**−0.35**	**−3.66 (−4.69 to −2.63)***	**−0.24**	NA	NA
Micronutrients	Vitamin D	589	**0.04 (0.01 to 0.07)**	**0.11**	0.002 (−0.03 to 0.03)	0.01	−0.001 (−0.04 to 0.03)	−0.004
	Calcium	559	**−300 (−478.6 to −122.1)**	**−2.94**	−132.3 (−284.3 to −19.67)	−1.30	−137.3 (−289.1 to 14.4)	−1.35
	Calcium^2	559	**66.9 (27.0 to 106.7)**	**2.93**	30.85 (−3.06 to 64.75)	1.35	31.15 (−2.71 to 65.0)	1.37
Metabolic markers	Glucose	673	**−0.42 (−0.78 to −0.06)**	**−0.09**	**−0.36 (−0.66 to −0.05)**	**−0.08**	−0.21 (−0.50 to 0.08)	−0.04
	HDL	673	−1.20 (−3.79 to 1.39)	−0.04	−0.90 (−3.10 to 1.31)	−0.03	−0.24 (−2.78 to 2.32)	−0.01
	Triglycerides	673	−0.42 (−1.67 to 0.83)	−0.03	0.06 (−0.99 to 1.10)	0.00	0.52 (−0.77 to 1.81)	0.03
	Cholesterol	672	**−2.02 (−2.94 to −1.10)***	**−0.17**	**−1.37 (−2.20 to −0.53)**	**−0.11**	−0.30 (−1.25 to 0.66)	−0.25
	Albumin	686	**−1.21 (−1.44 to −0.98)***	**−0.37**	**−0.79 (−1.01 to −0.57)***	**−0.24**	**0.73 (−0.97 to −0.49)***	**0.12**
Renal functioning	Creatinine	606	**−0.37 (0.56 to −0.18)***	**−0.58**	**−0.30 (0.47 to −0.14)***	**−0.48**	**−0.37 (−0.52 to −0.21)***	**−0.57**
	Creatinine^2	606	**0.002 (0.001 to 0.003)***	**0.54**	**0.001 (0.001 to 0.002)**	**0.45**	**0.001 (0.00 to 0.002)**	**0.12**
	Cystatin-C	606	**12.6 (8.87 to 16.3)***	**0.26**	**9.53 (5.85 to 13.22)***	**0.20**	**17.6 (13.03 to 22.3)***	**0.37**

Model 1: unadjusted; Model 2: adjusted for gender, age, level of ID, Down syndrome and drug/supplement use; Model 3: adjusted for gender, age, level of ID, Down syndrome and all system measures mentioned in the table; Bold text = *P* value <0.005.
**P* values <0.001.

observed in frail individuals [17], which could explain the association we found. The scarce amount of literature on the association between frailty and haemoglobin shows inconsistent results [18].

In contrast to most results observed in the general population [4, 6, 7], we were unable to find an inverse association between vitamin D and frailty. Even though we adjusted for supplements prescribed by the physician, we were unable to adjust for over-the-counter-drugs that may have included vitamin D supplementation. This could have interfered with our results.

Serum albumin is the most abundant blood protein in human beings, and low levels are associated with malnutrition, disease and inflammation. Therefore, alteration in serum albumin can reflect complications in multiple systems. Not surprisingly, frailty, related to failure in several organs and systems, was found to have a strong inverse association with albumin in the general population [4, 15]. In accordance with these studies, we found that low albumin concentrations were associated with higher FI scores. We found an association between low levels of glucose and cholesterol and frailty, but this association disappeared if adjusted for albumin. Nevertheless, these results suggest that a poor nutritional status is associated with higher frailty.

Last, we found a rather strong association between creatinine, cystatin-C and frailty. In the general population, a higher prevalence and incidence of frailty was observed for participants with lower levels of kidney functioning measured with cystatin-C [19]. The consequences of kidney failure could result in a higher prevalence of frailty [20]. Additionally, cystatin-C has frequently shown to predict cardiovascular outcomes [21]. Alternatively, cystatin-C may be associated with a chronic inflammatory state in frail individuals [22].

These results provide an important basis for future research into both the understanding of frailty in people with ID and the possibility to the identification of frail individuals. Special focus should be given to inflammation. Ageing is characterised by a low-grade chronic inflammatory status, termed 'inflammaging'. Inflammaging is associated with and predictive for several chronic diseases and adverse health outcomes [23]. Although the exact aetiology needs to be further investigated, we showed, in line with others, an association between inflammation and frailty. Carmeli *et al.* [9] showed that overall, people with unspecified ID ($n = 15$) have an increased inflammatory state. These results imply that a chronic inflammatory state in people with ID could partly explain the early onset of frailty. We included only 12 biochemical measures, but many more are known to be associated with frailty (e.g. TNF, oxidative stress). Similarly, because frailty is characterised by abnormalities across different systems, a combination of biochemical measures rather than a single biomarker is likely to be required to measure frailty [24, 25].

Our study has several limitations. First and most important, the cross-sectional design is not suited to study causal effects. It is therefore unknown whether alterations in the studied biochemical measures contributed to the incidence of frailty, or that being frail affects physical processes leading to deviated biochemical measures. Second, people of whom no blood sample was available had slightly lower FI scores and were more often living in the community, leading to an over-representation of people living at central settings. Last, contrary to most studies, we used an FI to measure frailty instead of the clinical frailty phenotype, in which frailty is defined as the presence of three or more of the following characteristics: weight loss, exhaustion, weakness, slow walking speed and low physical activity [26]. Even so, Hubbard *et al.* [16] showed that the associations between biochemical markers and frailty are consistent across the two frailty measures. In addition, the FI seems to be a more suitable measure for people with ID (Schoufour *et al.*, submitted) and has shown predictive validity in this group [27, 28].

In conclusion, we showed associations between frailty and biochemical measures in people with ID. In line with the literature, we found associations between frailty and inflammation, metabolic markers, haemoglobin and kidney functioning. We suggest that future research focuses on the possible effect of inflammaging on frailty in people with ID, using prospective study designs. In addition, the effect of a poor nutritional status and frailty needs further examination. This knowledge may not only lead to interventions but also to a possible biomarkers that may be used to screen for frailty in a population with difficulties using general frailty screening measures (e.g. self-report questionnaires or physical performance tests). Previously, we showed that the consequences of frailty in people with ID are severe: high frailty scores are related to mortality, increased disability, decreased mobility, diseases and higher care intensity. It is very important to prevent frailty as early as possible. Studies from the general population show that frailty is difficult to treat if scores are already high. Biochemical measures can help to early identify frail individuals and provide information on possible pathways involved in the early onset of frailty in people with ID.

Key points

- People with ID show signs of early frailty.
- Frailty is associated with inflammation.
- Frailty is associated with nutritional status.

Conflicts of interest

None of the authors has any financial, personal, or potential conflict of interest.

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Observational cohort study: deprivation and access to anti-dementia drugs in the UK

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Abstract

Background: UK National Dementia Strategies prioritise fair access to dementia treatments for the whole population. We investigated for the first time inequalities in NHS national dementia prescribing and how they have varied between UK countries and over time.
Method: we investigated the association between Townsend deprivation score and anti-dementia drug prescribing in 77,045 dementia patients from UK primary care records from 2002 to 2013.
Results: we included 77,045 patients with recorded dementia diagnosis or anti-dementia drug prescription. Least deprived patients were 25% more likely to be initiated on anti-dementia drugs than the most deprived (adjusted incidence rate ratio 1.25, 95% confidence interval 1.19–1.31). This was driven by data from English practices where prescribing rates were consistently lower in more deprived patients compared with Scotland, Northern Ireland and Wales, where prescribing was not related to deprivation quintile. Compared with English practices, anti-dementia medication was prescribed more often in Northern Irish (1.81, 1.41–2.34) and less in Welsh practices (0.68, 0.55–0.82), with a trend towards more prescribing in Scottish practices (1.14, 0.98–1.32). Drug initiation rates were also higher in younger people and men.
Conclusion: four years after the English National Dementia Strategy, there is no evidence that the Strategy's key objective of reducing treatment inequalities is being achieved. Higher overall anti-dementia drug prescribing in Scottish and Northern Irish practices, and differing clinical guidelines in Scotland from other UK countries might explain greater equality in prescribing in these countries. Strategies to offer treatment to more deprived people with dementia in England are needed.

Keywords: *dementia, healthcare disparities, cholinesterase inhibitor, older people*